1 Appendix D: Evidence Tables – Treatment of active TB (RQs I, K, L, M, & P)

1.1 RQ I: In children and young people with active TB receiving drug treatment, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

1.1.1 Kansoy et al, 1998

Bibliographic reference	Kansoy S, Kurtas N, Aksit S et al (1996) Superiority of Intermittent-Short Course Chemotherapy in Childhood Pulmonary Tuberculosis. Turkish Journal of Medical Sciences 26(1): 41-43
Study type	RCT
Study quality	The interventions did not differ in the two groups by dosing frequency alone: different treatment periods – daily + intermittent group received treatment for a total of 9 months; daily group received treatment for a total of 12 months note: this will not affect those outcomes that were measured at 6 months (i.e. number to show radiologic improvement, number to completely resolve and mean weight gain) nor the 'time-to' outcomes (i.e. therapy period for early clinical response) initial 3-drug phase was shorter in the daily + intermittent group (2 weeks) than in the daily group (1 month) The interventions do not use the 4 standard recommended drugs: the regimens contain streptomycin but are lacking ethambutol and pyrazinamide Randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were followed up for an equal length of time Treatment completion was not comparable and outcome data was not similarly available: daily + intermittent group: 3 of 18 excluded due to non-adherence, and outcome data was not provided for these daily group: 0 of 18 excluded due to non-adherence

	Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure) Did not follow the intent-to-treat principle
Number of patients	Randomised = 36 daily group = 18 daily + intermittent group = 18 Analysed / outcome data available for = 33 daily group = 15 daily + intermittent group = 18
Patient characteristics	*Inclusion* Ages 5 months to 13 years Pulmonary TB *Diagnostic criteria* Clinical: afternoon fever excessive sweating cough anorexia weight loss Epidemiologic direct contact with a tuberculous adult (bacillary positive or negative) Radiologic

<table>
<tr><td></td><td>
parenchymal or mediastinal lymph nodes in chest roentgenograms
Immunologic
tuberculin test positivity (PPD)
Histobacteriologic
acid-fast bacilli in the sputum, or gastric washings or in any histologic specimen
Exclusion
Poor “family compliance”
Baseline
<table>
<tr><th></th><th>Daily + intermittent
(n = 18)</th><th>Intermittent
(n = 15)</th></tr>
<tr><td>Male/female</td><td>12/6</td><td>10/5</td></tr>
<tr><td>Age (mean years ± SD)</td><td>7.6±3.9</td><td>7.7±4.0</td></tr>
<tr><td>Diagnostic criteria
clinical
epidemiologic
immunologic
radiologic
histobacteriologic</td><td>
18
14
15
18
2</td><td>
15
12
12
15
2</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Daily regimen
1SRH$_7$/8RH$_7$/3R$_7$</td></tr>
</table>

	daily streptomycin, isoniazid and rifampicin 1 month daily isoniazid and rifampicin for 8 months daily rifampicin for 3 months Dosing: streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg All patients were treated on an outpatient basis
Comparison	Daily + intermittent regimen $0.5SRH_7/8.5RH_2$ daily streptomycin, isoniazid and rifampicin for two weeks twice weekly isoniazid and rifampicin for 8.5 months Dosing: streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg All patients were treated on an outpatient basis
Length of follow up	12 months after treatment completion
Location	Izmir, Turkey
Outcomes measures and effect	**Response to treatment – disease resolution** Number to completely resolve (i.e. no radiologic remainder):

size	daily group = 9 of 15 daily + intermittent group = 8 of 18 p1 > 0.05 OR2 (95% CI) = 1.88 (0.47 to 7.53) i.e. not statistically significant
	Response to treatment – radiologic improvement Number to show radiologic improvement: daily group = 15 of 15 daily + intermittent group = 18 of 18 OR2 (95% CI) = 0.84 (0.12 to 44.73) i.e. not statistically significant
	Response to treatment – time to clinical response Mean therapy period (days ± SD) for early clinical response: daily group (n = 15) = 23.0±7.0 daily + intermittent group (n = 18) = 24.6±7.5 p1 > 0.05 MD3 (95% CI) = -1.6 (-6.56 to 3.36) i.e. not statistically significant
	Symptom improvement – weight gain Mean weight gain (kg ± SD): daily group (n = 15) = 3.91±1.83

	daily + intermittent group (n = 18) = 3.82±1.78 p1 > 0.05 MD3 (95% CI) = 0.09 (-1.15 to 1.33) i.e. not statistically significant
	Relapse Number to relapse (based on clinical or radiologic recurrence) in 12 months after treatment completion: daily group = 0 of 15 daily + intermittent group = 0 of 18 OR2 (95% CI) = 1.19 (0.02 to 63.73) i.e. not statistically significant
	Adverse events – hepatotoxicity Defined as elevated serum aspartate aminotransferase and alanine aminotransferase (note: thresholds not given) Number to experience hepatotoxicity: daily group = 1 of 15 daily + intermittent group = 0 of 18 OR2 (95% CI) = 3.83 (0.14 to 101.08) i.e. not statistically significant
	Adherence Number excluded due to “poor compliance” (note: definition not provided): daily group = 3 of 18 daily + intermittent group = 0 of 18

	p1 > 0.05 OR2 (95% CI) = 8.35 (0.40 to 174.51) i.e. not statistically significant
Source of funding	Details not given
Comments	The interventions did not differ in the two groups by dosing frequency alone: different treatment periods – daily + intermittent group received treatment for a total of 9 months; daily group received treatment for a total of 12 months note: this will not affect those outcomes that were measured at 6 months (i.e. number to show radiologic improvement, number to completely resolve and mean weight gain) nor the 'time-to' outcomes (i.e. therapy period for early clinical response) initial 3-drug phase was shorter in the daily + intermittent group (2 weeks) than in the daily group (1 month) The interventions do not use the 4 standard recommended drugs: the regimens contain streptomycin but are lacking ethambutol and pyrazinamide Because the interventions vary by treatment duration in addition to dosing frequency, this study is also considered for possible inclusion in review question M
1 Calculated by authors using the chi-square test or student's t-test; p < 0.05 was taken as significant 2 Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer 3 Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence intervals; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis	

1.1.2 Kumar et al, 1990

Bibliographic reference	Kumar L, Dhand R, Singhi PD et al (1990) A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatric Infectious Disease Journal 9: 802-6

Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: do not use the 4 standard recommended drugs: the regimens are lacking ethambutol Randomisation: any currency note available was taken from each participant and its number noted; even numbers were assigned to the intermittent regimen, odd numbers to the daily + intermittent regimen Allocation concealment and blinding is unclear By the limited characteristics reported (sex and outcomes of diagnostic tests), the groups were comparable at baseline The two arms received different care with regards to setting in which treatment was taken: intermittent regimen – took doses in the clinic daily + intermittent regimen – given a weekly supply to take at home Groups were comparable with regards to treatment completion and availability of outcome data Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure)
Number of patients	n = 76 intermittent regimen = 37 daily + intermittent regimen = 39 By site Tuberculous lymphadenopathy = 27 intermittent regimen = 15 daily + intermittent regimen = 12 – note: one case was subsequently shown to be M. Avium intracellulare complex and excluded (i.e. n = 11) Pulmonary tuberculosis = 43 intermittent regimen = 20

	daily + intermittent regimen = 23 Disseminated tuberculosis = 6 intermittent regimen = 2 daily + intermittent regimen = 4
Patient characteristics	Inclusion Newly diagnosed patients of either sex Ages 1 to 15 years Pulmonary, lymph node or disseminated TB Diagnostic criteria Tuberculous lymphadenopathy enlargement of lymph nodes either regionally or generalised positive Mantoux reaction (10 mm or more at 72 hours after 1 tuberculin unit of purified protein derivative S) caseous granulomata on histopathology presence of acid-fast bacilli in histopathologic sections or smears prepared from lymph node aspirates stained with Ziehl-Neelson and cultured on Lowenstein Jensen slants as well as liquid media Pulmonary tuberculosis history of fever, cough, sputum production (older children), chest pain or hemoptysis, along with malaise, fatigue, weakness and weight loss evidence of consolidation, cavitation, fibrosis, hilar lymph node enlargement, collapse, pleural effusion or pneumothorax on chest roentgenogram positive Mantoux reaction gastric lavage, deep laryngeal swab or sputum (older children) positive for acid-fast bacilli in smears and/or positive culture

Disseminated tuberculosis

involvement of multiple organs

miliary mottling on chest roentgenogram either alone or in addition to radiologic features consistent with diagnosis of tuberculosis in an extrapulmonary site

histopathologic evidence of tuberculosis in the form of caseous granulomata in biopsies of lymph nodes or liver

demonstration of acid-fast bacilli in gastric lavage, sputum or tissue biopsies and/or positive culture

Mantoux test was not taken as a diagnostic criterion for this group as it is known to be negative in a significant proportion of disseminated TB cases, particularly those with severe malnutrition; however, when positive it was considered additional evidence of tubercular infection

Exclusion

Children aged less than a year

Children who were thought to have only primary complex in the lung

Tuberculous meningitis

Those who had received earlier treatment

Abnormal renal, hepatic or cardiac status

Baseline

	Intermittent (n = 37)	**Daily + intermittent** (n = 39)
Sex		
Male	23	23
Female	13	17
Positive Mantoux test	35	36

<table>
<tr><td></td><td>
<table>
<tr><td>Positive chest roentgenogram</td><td>24</td><td>28</td></tr>
<tr><td>Smear from sputum, or gastric lavage or any discharge</td><td>15</td><td>12</td></tr>
<tr><td>Positive culture</td><td>4</td><td>3</td></tr>
<tr><td>Compatible histopathology</td><td>14</td><td>15</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Intermittent regimen
$2HRZ_2/4HR_2$:
twice weekly isoniazid, rifampicin and pyrazinamide for two months
twice weekly isoniazid and rifampicin for 4 months
total doses = 52
Dosing:
isoniazid: 20 to 30 mg/kg body weight/dose
rifampicin: 10 to 15 mg/kg body weight/dose
pyrazinamide: 50 to 60 mg/kg body weight/dose
Doses taken in the clinic</td></tr>
<tr><td>Comparison</td><td>Daily + intermittent regimen
$2HRZ_7/4HR_2$:
daily isoniazid, rifampicin and pyrazinamide for two months
twice weekly isoniazid and rifampicin for 4 months
total doses = 94</td></tr>
</table>

<table>
<tr><td></td><td>Dosing:
isoniazid: 10 to 15 mg/kg body weight/dose
rifampicin: 10 to 15 mg/kg body weight/dose
pyrazinamide: 20 to 30 mg/kg body weight/dose
During the daily phase, a weekly supply of treatment was provided for patients to take at home
During intermittent phase, doses taken in the clinic</td></tr>
<tr><td>Length of follow up</td><td>All followed up for at least the full treatment period, though total follow-up varied:
<table>
<tr><th rowspan="2">Group</th><th rowspan="2">Regimen</th><th colspan="6">Number of patients / period after cessation of treatment</th></tr>
<tr><th>< 12 months</th><th>12 months</th><th>15 months</th><th>18 months</th><th>21 months</th><th>24 months</th></tr>
<tr><td rowspan="2">Tuberculous lymphadenopathy</td><td>intermittent</td><td></td><td></td><td></td><td>3</td><td></td><td>12</td></tr>
<tr><td>daily + intermittent</td><td></td><td></td><td>1</td><td>3</td><td>2</td><td>5</td></tr>
<tr><td rowspan="2">Pulmonary tuberculosis</td><td>intermittent</td><td>1</td><td></td><td>7</td><td></td><td>4</td><td>3</td></tr>
<tr><td>daily + intermittent</td><td></td><td>1</td><td>2</td><td>3</td><td>3</td><td>7</td></tr>
<tr><td rowspan="2">Disseminated tuberculosis</td><td>intermittent</td><td></td><td></td><td></td><td>1</td><td>1</td><td></td></tr>
<tr><td>daily + intermittent</td><td>1</td><td></td><td></td><td></td><td></td><td>3</td></tr>
</table></td></tr>
<tr><td>Location</td><td>Paediatric outpatient department, India</td></tr>
<tr><td>Outcomes</td><td>Mortality</td></tr>
</table>

measures and effect size	Cross-site1 Intermittent regimen = 1 of 37 Daily + intermittent regimen = 1 of 39 OR2 (95% CI) = 1.06 (0.06 to 17.52) i.e. not statistically significant Tuberculous lymphadenopathy Intermittent regimen = 0 of 15 Daily + intermittent regimen = 0 of 12 OR2 (95% CI) = 0.81 (0.01 to 43.60) i.e. not statistically significant Pulmonary tuberculosis Intermittent regimen = 1 of 20 Daily + intermittent regimen = 1 of 23 OR2 (95% CI) = 1.16 (0.07 to 19.80) i.e. not statistically significant Disseminated tuberculosis Intermittent regimen = 0 of 2 Daily + intermittent regimen = 0 of 4 OR2 (95% CI) = 1.80 (0.03 to 121.71) i.e. not statistically significant
	Response to treatment

	Criteria for grading response to treatment General improvement normalisation of body temperature improvement in appetite weight gain Tuberculous lymphadenopathy ‘Marked’ Reduction in lymph node size within 3 to 4 months and no appearance of new lymph node enlargement, plus improvement in general condition ‘Moderate’ Reduction in lymph node size later than 3 to 4 months and no appearance of new lymph node enlargement, plus improvement in general condition ‘Poor’ Increase in lymph node size or sinus formation and appearance of new lymph node enlargement, not responding to therapy Pulmonary tuberculosis ‘Marked’ General improvement, disappearance of cough, radiologic clearance of pulmonary lesions within 3 months of therapy and no appearance of new lesions ‘Moderate’ General improvement, partial radiologic clearance of pulmonary lesions within 3 months of therapy and no appearance of new lesions ‘Poor’

	No significant general improvement and no radiologic clearance, or increase in size of pulmonary lesions or appearance of new lesions Disseminated tuberculosis 'Marked' General improvement, disappearance of cough, radiologic clearance of pulmonary lesions within 3 months of therapy, no appearance of new lesions, and regression in size of enlarged organs within 3 to 4 months 'Moderate' General improvement, partial radiologic clearance of pulmonary lesions within 3 months of therapy , no appearance of new lesions, and partial regression in size of enlarged organs 'Poor' No significant general improvement and no radiologic clearance, failure of regression of organomegaly, or increase in size of pulmonary lesions or appearance of new lesions *Results* Cross-site1 Marked: intermittent regimen = 25 of 37 daily + intermittent regimen = 28 of 39 OR2 (95% CI) = 0.82 (0.31 to 2.18) i.e. not statistically significant Moderate: intermittent regimen = 11 of 37 daily + intermittent regimen = 3 of 39 **OR2 (95% CI) = 5.08 (1.29 to 20.03)**

	i.e. statistically significant Poor: intermittent regimen = 1 of 37 daily + intermittent regimen = 1 of 39 OR2 (95% CI) = 1.06 (0.06 to 17.52) i.e. not statistically significant Tuberculous lymphadenopathy Marked: intermittent regimen = 10 of 15 daily + intermittent regimen = 8 of 12 OR2 (95% CI) = 1.00 (0.20 to 5.00) i.e. not statistically significant Moderate: intermittent regimen = 5 of 15 daily + intermittent regimen = 3 of 12 OR2 (95% CI) = 1.50 (0.28 to 8.14) i.e. not statistically significant Poor: intermittent regimen = 0 of 15 daily + intermittent regimen = 1 of 12 note: this patient was later found to have M. Avium intracellulare complex

	OR2 (95% CI) = 0.25 (0.01 to 6.64) i.e. not statistically significant Pulmonary tuberculosis note: 4 dropouts and 1 death in intermittent group, and 6 dropouts and 1 death in daily + intermittent group Marked: intermittent regimen = 13 of 20 daily + intermittent regimen = 16 of 23 OR2,3 (95% CI) = 0.81 (0.23 to 2.92) i.e. not statistically significant Moderate: intermittent regimen = 1 of 20 daily + intermittent regimen = 0 of 23 OR2,3 (95% CI) = 3.62 (0.14 to 93.85) i.e. not statistically significant Poor: intermittent regimen = 1 of 20 daily + intermittent regimen = 0 of 23 OR2,3 (95% CI) = 3.62 (0.14 to 93.85) i.e. not statistically significant Disseminated tuberculosis Marked:

	intermittent regimen = 2 of 2 daily + intermittent regimen = 4 of 4 OR2 (95% CI) = 0.56 (0.01 to 37.57) i.e. not statistically significant Moderate: intermittent regimen = 0 of 2 daily + intermittent regimen = 0 of 4 OR2 (95% CI) = 1.80 (0.03 to 121.71) i.e. not statistically significant Poor: intermittent regimen = 0 of 2 daily + intermittent regimen = 0 of 4 OR2 (95% CI) = 1.80 (0.03 to 121.71) i.e. not statistically significant
	Relapse Cross-site1 Intermittent regimen = 0 of 35 Daily + intermittent regimen = 0 of 35 OR2 (95% CI) = 1.00 (0.02 to 51.81) i.e. not statistically significant Tuberculous lymphadenopathy

	Intermittent regimen = 0 of 15 Daily + intermittent regimen = 0 of 12 OR2 (95% CI) = 0.81 (0.01 to 43.60) i.e. not statistically significant Pulmonary tuberculosis Intermittent regimen = 0 of 20 Daily + intermittent regimen = 0 of 23 OR2 (95% CI) = 1.15 (0.02 to 60.41) i.e. not statistically significant Disseminated tuberculosis Not reported
	Adverse effects – adverse events requiring modification of treatment Cross-site Intermittent regimen = 0 of 37 Daily + intermittent regimen = 0 of 39 OR2 (95% CI) = 1.05 (0.02 to 54.45) i.e. not statistically significant
	Adverse effects – hypersensitivity reactions Cross-site Intermittent regimen = 0 of 37 Daily + intermittent regimen = 0 of 39

	OR2 (95% CI) = 1.05 (0.02 to 54.45) i.e. not statistically significant
	Adverse effects – hematologic effects Cross-site Intermittent regimen = 0 of 37 Daily + intermittent regimen = 0 of 39 OR2 (95% CI) = 1.05 (0.02 to 54.45) i.e. not statistically significant
Source of funding	Indian Council of Medical Research
Comments	Intervention does not exactly match the intervention of interest: do not use the 4 standard recommended drugs: the regimens are lacking ethambutol
1 Data for each site pooled by reviewer 2 Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer 3 Calculated according to the intent-to-treat principle (i.e. those that were lost to follow-up or died are included in the analysis) Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide	

1.1.3 Ramachandran et al, 1998 / Swaminathan et al, 2005

Study type	RCT
Study quality	The interventions did not differ in the two groups by dosing frequency alone: different treatment periods – daily group received treatment for a total of 9 months; intermittent group received treatment for a total of 6 months different frameworks – daily group received 2 drugs on a daily basis throughout; intermittent group regimen was

	divided into an initial phase (3 drugs taken 3 times a week) and a continuation phase (2 drugs taken twice a week) The interventions do not use the 4 standard recommended drugs: the regimens both lack ethambutol, and daily regimen also lacks pyrazinamide Randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline, although more patients in the intermittent group had cavitatory disease at baseline, a sign that the disease in this group may have been more severe at treatment initiation than in the daily group Groups did not receive the same care apart from the interventions studied – therapy was supervised in the intermittent group, whilst the daily group attended the clinic once a week to collect their drugs Groups were followed up for an equal length of time It is unclear if the groups were comparable for treatment completion or availability of outcome data Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure) Unclear if the intent-to-treat principle was followed
Number of patients	Admitted to study = 141 Analysed at 24 months = 137 daily group = 68 intermittent group = 69 Analysed at 60 months = 133 daily group = 67 intermittent group = 66
Patient characteristics	Inclusion Ages 1 to 12 years presenting with respiratory complaints Pulmonary tuberculosis assessed clinically and by chest radiograph

	No more than 2 weeks of previous anti-tuberculosis treatment No evidence of renal or hepatic disease Patients with associated lymphadenitis and minimal pleural effusion not warranting a pleural tap were also considered eligible Diagnostic criteria A tuberculin skin test with 1 TU PPD RT23 was placed on all children and read at 48 to 72 hours; an induration of .10 mm was taken as a positive test Bacteriological confirmation of infection was obtained where possible by gastric lavage or sputum smear and culture, or lymph node biopsies for histopathological examination and culture in those with enlarged superficial lymph nodes Most probably TB (category A): patients with a primary focus plus hilar adenitis, mediastinal adenitis, miliary tuberculosis and progressive primary complex these patients were started on anti-tuberculosis drugs Probably TB (category B): patients with a doubtful radiological abnormality these patients were started on antibiotics alone and a repeat chest radiograph taken at the end of 2 weeks; if the abnormality persisted, they were admitted to the study. Treatment groups were stratified according to category of disease Exclusion Massive pleural effusion Extrapulmonary tuberculosis other than pleural Isolated bronchiectasis Baseline

	Daily (n = 68)	**Intermittent** (n = 69)
Age < 5 years	41	36
Tuberculin test > 10 mm	50	49
Contact with TB	54	53
BCG scar present	43	35
Gastric lavage / sputum culture positive	19	21
Lymph node culture / histopathologically positive	4	3
Confirmation of TB	24	23
Parenchymal lesions on x-ray	35	33
Adenitis (mediastinal, hilar or both)	17	17
Parenchymal lesion and adenitis	14	11
Cavity	2	8

Intervention	Daily regimen $9HR_7$ daily isoniazid and rifampicin for 9 months Dosing: isoniazid: 6 mg/kg body weight/dose, up to 150 mg rifampicin: 12 mg/kg body weight/dose, up to 300 mg

	As far as possible, patients were hospitalised for a minimum period of 2 weeks and more, if necessary. Subsequent to discharge, patients attended the clinic once a week to collect their drugs; they were given the drugs under supervision on the days they attended
Comparison	Intermittent regimen $2HRZ_3/4HR_2$ 3 times weekly isoniazid, rifampicin and pyrazinamide for 2 months twice weekly isoniazid and rifampicin for 4 months Dosing: isoniazid: 15 mg/kg body weight/dose, up to 300 mg rifampicin: 12 mg/kg body weight/dose, up to 300 mg pyrazinamide: 45 mg/kg body weight/dose, up to 1 g As far as possible, patients were hospitalised for a minimum period of 2 weeks and more, if necessary. Subsequent to discharge, patients attended thrice a week for the first 2 months followed by twice a week for the next 4 months for supervised chemotherapy
Location	Chennai, India
Source of funding	Details not given
Bibliographic reference	Ramachandran P, Kripasankar AS & Duraipandian M (1998) Short course chemotherapy for pulmonary tuberculosis in children. Indian Journal of Tuberculosis 45: 83-7
Length of follow up	24 months after treatment completion
Outcomes measures and effect size	**Mortality** Number of deaths during treatment: daily group = 1 of 68 intermittent group = 2 of 69

	OR1 (95% CI) = 0.50 (0.04 to 5.65) i.e. not statistically significant
	Response to treatment – disease resolution Number to require treatment extension due to incomplete resolution: daily group = 5 of 68 intermittent group = 4 of 69 OR1 (95% CI) = 1.29 (0.33 to 5.02) i.e. not statistically significant
	Adverse events – hepatotoxicity Number to experience hepatotoxicity: daily group = 2 of 68 1 patient experienced jaundice, 1 patient experienced hepatitis B intermittent group = 1 of 69 1 patient experienced jaundice OR1 (95% CI) = 2.06 (0.18 to 23.27) i.e. not statistically significant
Bibliographic reference	Swaminathan S, Raghavan A, Duraipandian M et al (2005) Short-course chemotherapy for paediatric respiratory tuberculosis: 5-year report. International Journal of Tuberculosis and Lung Disease 9(6): 693-6
Length of follow up	60 months Of 134 children available for follow-up, 11 were not available at the time of final follow-up (60 months), including one who died in an accident at 48 months; the last available radiographs were considered for evaluation in these cases (eight at 48 months, two at 36 months and one at 24 months)

Outcomes measures and effect size	**Response to treatment – disease resolution** % with normal chest radiograph at treatment completion: daily group (n = 67) = 61% intermittent group (n = 67) = 48% OR1 (95% CI) = 1.69 (0.97 to 2.97) i.e. not statistically significant % with normal chest radiograph at 60 months: daily group (n = 67) = 82% intermittent group (n = 66) = 89.5% OR1 (95% CI) = 0.54 (0.20 to 1.48) i.e. not statistically significant % with residual lesions at treatment completion: daily group (n = 67) = 39% intermittent group (n = 67) = 49% OR1 (95% CI) = 0.67 (0.38 to 1.17) i.e. not statistically significant % with residual lesions at 60 months: daily group (n = 67) = 15% intermittent group (n = 66) = 1.5% p < 0.01 **OR[1] (95% CI) = 11.40 (1.42 to 91.85)**

	i.e. **statistically significant**
	Relapse Number of patients in whom relapse was observed during the 60-month follow-up period: daily group = 1 of 67 intermittent group = 0 of 66 OR[1] (95% CI) = 3.00 (0.12 to 74.98) i.e. not statistically significant
Comments	The interventions did not differ in the two groups by dosing frequency alone: different treatment periods – daily group received treatment for a total of 9 months; intermittent group received treatment for a total of 6 months different frameworks – daily group received 2 drugs on a daily basis throughout; intermittent group regimen was divided into an initial phase (3 drugs taken 3 times a week) and a continuation phase (2 drugs taken twice a week) The interventions do not use the 4 standard recommended drugs: the regimens both lack ethambutol, and daily regimen also lacks pyrazinamide Because the interventions vary by treatment duration in addition to dosing frequency, this study is also considered for possible inclusion in review question M
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer [2] Calculated by authors using the chi-square test; $p < 0.01$ was taken as significant Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide	

1.1.4 Te Water Naude et al, 2000

Bibliographic reference	Te Water Naude JM, Donald PR, Hussey GD et al (2000) Twice weekly vs. daily chemotherapy for childhood tuberculosis. Pediatric Infectious Disease Journal 19: 405-10
Study type	RCT

Study quality	The interventions did not differ in the two groups by dosing frequency alone: intermittent group receive 3 drugs for the first two months, and only two drugs for the remaining 4 months; daily group received 3 drugs for the full 6 months treatment period was 26 weeks in intermittent group, and 24 weeks in the daily group; however, intermittent group received less mg of medication per kg of body weight each week do not use the 4 standard recommended drugs: the regimens are lacking ethambutol Randomisation: random number tables by household unit (to avoid confusion in the event of more than one child from a particular household being enrolled note: not analysed at the level of the randomisation unit (analysed by individuals, not by household unit), nor is sufficient data available to correct for this – i.e. unit-of-analysis error Allocation concealment unclear Participants and individuals administering care were not blinded; unclear if investigators were blinded, but given that the trial was 'open' the suspicion is that they were not Groups were comparable at the baseline, except for: weight for age – significantly lower in the intermittent group number who were culture positive – significantly lower in the intermittent group These differences may indicate that the intermittent group were less likely to have tuberculosis, or that their tuberculosis was less severe than the daily group. Groups received the same care apart from the interventions studied Groups were followed up for an equal length of time, treatment completion was comparable and outcome data was similarly available Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure) Did not follow the intent-to-treat principle

Number of patients	Randomised = 314 daily group = 161 intermittent group = 153 Received treatment (exclusion criteria applied after randomisation i.e. number = randomised minus exclusions) = 213 daily group = 118 intermittent group = 95 Analysed = 206 daily group = 117 intermittent group = 89
Patient characteristics	Inclusion Ages < 14 years Referral to clinic for TB screening Exclusion Extrathoracic TB Previous treatment for TB > 30 days hospital treatment before referral for clinic management Home address in a rural area *Diagnostic criteria* Suspect cases: suspicious chest radiograph – perihilar opacification with or without parenchymal lesions, and suggestive clinical features – cough for > 2 weeks, wheeze for > 2 weeks or weight under 80th centile

Probable cases:

diagnostic chest radiographs – hilar adenopathy with or without parenchymal lesions, a miliary pattern or pleural effusion, or

suspicious chest radiograph – perihilar opacification with or without parenchymal lesions – with close household contact with an adult with pulmonary TB or with a tine test where two or more papules were confluent (considered equivalent to a Mantoux test of ≥ 15 mm induration)

Confirmed cases:

positive sputum or gastric washing culture for M. Tuberculosis

Parenchymal disease:

segmental opacification, with or without hilar adenopathy, cavitation, bronchopneumonic spread or miliary disease

Baseline

	Intermittent (n = 95)	**Daily** (n = 118)	**p**1
Female/male	46/49	61/57	0.68
Age (median months (interquartile range))	24.9 (13.4 – 40.5)	27.9 (16.9 – 43.2)	0.58
Cough reported	72	94	0.64
Wheeze reported	39	53	0.74
Weight (kg)	11.5 (9.0 – 14.0)	12.1 (10.0 – 14.4)	0.23
Weight under 80th centile	17	16	0.39
Weight for age (median % (interquartile range))	**89.6 (82.4 – 100.7)**	**96.6 (86.1 – 104.0)**	**0.015**
Height (cm) (n = 187)	83.6 (74.0 – 95.0)	86.0 (76.0 – 94.5)	0.37

	<table><tr><td>Height for age (median % (interquartile range))</td><td>95.0 (92.6 – 99.3)</td><td>96.2 (93.2 – 100.8)</td><td>0.09</td></tr><tr><td>Household contacts with pulmonary TB (n = 205)</td><td>78</td><td>74</td><td>0.003</td></tr><tr><td>Smear-positive</td><td>44</td><td>41</td><td>0.12</td></tr><tr><td>Culture-positive</td><td>38</td><td>66</td><td>0.03</td></tr></table>
Intervention	Daily regimen $6HRZ_{5\ (Monday\ to\ Friday)}$: daily isoniazid, rifampicin and pyrazinamide for six months (Monday to Friday only) Dosing: isoniazid: 10 mg/kg body weight/dose rifampicin: 10 mg/kg body weight/dose pyrazinamide: 25 mg/kg body weight/dose Doses taken in the clinic under supervision of nursing personnel, or when this was not feasible parents or guardians collected the treatment weekly from the clinic
Comparison	Intermittent regimen $2HRZ_2/4HR_2$: twice weekly isoniazid, rifampicin and pyrazinamide for two months twice weekly isoniazid and rifampicin for 4 months Dosing: isoniazid: 15 mg/kg body weight/dose rifampicin: 15 mg/kg body weight/dose

<table>
<tr><td></td><td>pyrazinamide: 55 mg/kg body weight/dose
Doses taken in the clinic under supervision of nursing personnel, or when this was not feasible parents or guardians collected the treatment weekly from the clinic</td></tr>
<tr><td>Length of follow up</td><td>30 months after the initiation of treatment</td></tr>
<tr><td>Location</td><td>Local authority clinic, Western Cape Province of South Africa</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Response to treatment
Composite measure, assessed as follows:
<table>
<tr><th>Criterion</th><th>-1</th><th>0</th><th>+1</th><th>+2</th></tr>
<tr><td>Parent’s assessment</td><td>Worse</td><td>Not better</td><td>Better</td><td>Much better</td></tr>
<tr><td>Clinical symptoms</td><td>Worse</td><td>Unchanged</td><td>Better</td><td>Much better</td></tr>
<tr><td>Weight gain</td><td>Lost weight</td><td>Unchanged</td><td>Gained weight
(ipsi-centile)</td><td>Significant gain
(crossing centiles)</td></tr>
<tr><td>Chest radiograph</td><td>Worse</td><td>Unchanged</td><td>Some clearing</td><td>Definite clearing</td></tr>
</table>
Possible combined score range: -4 to +8
Median scores (interquartile range) 3 months after treatment initiation:
daily group (n = 89) = 5 (4 – 7)
intermittent group (n = 70) = 5 (4 – 6)
p1 = 0.24
i.e. not statistically significant
difference in the medians2 = 0
Median scores (interquartile range) 6 months after treatment initiation i.e. end of treatment period:</td></tr>
</table>

	daily group (n = 93) = 6 (5 – 7) intermittent group (n = 70) = 6 (5 – 7) p1 = 0.90 i.e. not statistically significant difference in the medians2 = 0 Median scores (interquartile range) 12 months after treatment initiation i.e. 6 months after treatment end: daily group (n = 74) = 5 (4 – 6) intermittent group (n = 65) = 4 (3 – 5) p1 = 0.068 i.e. not statistically significant difference in the medians2 = 1 Median scores (interquartile range) 18-30 months after treatment initiation i.e. 12-24 months after treatment end: daily group (n = 74) = 4 (3 – 5) intermittent group (n = 71) = 4 (3 – 5) p1 = 0.949 i.e. not statistically significant difference in the medians2 = 0
	Symptom improvement – weight gain Median weight gain on completion of treatment (interquartile range): daily group = 1.75 kg (1.2 – 2.3 kg) intermittent group = 1.5 kg (1.0 – 2.1 kg)

	p1 = 0.21 i.e. not statistically significant difference in the medians2 = 0.25 kg
	Relapse Judged by an independent paediatric pulmonologist according to: clinical findings – respiratory signs, weight loss chest radiography – serial deterioration despite exclusion of other conditions Number considered a relapse: daily group = 0 of 117 intermittent group = 1 of 89 OR3 (95% CI) = 0.25 (0.01 to 6.24) i.e. not statistically significant
	Adverse events No significant side effects were documented in either of the regimens (no further details provided)
	Treatment completion Number completing on schedule: daily group = 114 of 117 intermittent group = 85 of 89 OR3 (95% CI) = 1.79 (0.39 to 8.20) i.e. not statistically significant
	Adherence

	Measured by nurses – dose counting Number of children adherent (defined as taking 75% or more of doses prescribed) daily group = 90 of 117 intermittent group = 70 of 89 p1 = 0.29 OR3 (95% CI) = 0.90 (0.47 to 1.76) i.e. not statistically significant Number of partial adherers (defined as taking 75% or more of doses prescribed, but less than 75% during any single 4-week period) daily group = 30 of 117 intermittent group = 21 of 89 p1 = 0.69 OR3 (95% CI) = 1.12 (0.59 to 2.12) i.e. not statistically significant Median days to default by non-adherers (interquartile range) daily group (n = 117) = 42 (33 – 69) intermittent group (n = 89) = 72 (44 – 93) p1 = 0.08 i.e. not statistically significant difference in the medians2 = -30 days Median days to default by partial adherers (interquartile range)

	daily group (n = 117) = 101 (40 – 132) intermittent group (n = 89) = 124 (74 – 144) $p^1 = 0.17$ i.e. not statistically significant difference in the medians[2] = -23 days Median % of prescribed doses taken (interquartile range) daily group = 91% (77 – 97) intermittent group = 93% (75 – 100) $p^1 = 0.29$ i.e. not statistically significant difference in the medians[2] = -2%
Source of funding	South African Medical Research Council
Comments	The interventions did not differ in the two groups by dosing frequency alone: intermittent group receive 3 drugs for the first two months, and only two drugs for the remaining 4 months; daily group received 3 drugs for the full 6 months treatment period was 26 weeks in intermittent group, and 24 weeks in the daily group; however, intermittent group received less mg of medication per kg of body weight each week The interventions do not use the 4 standard recommended drugs: the regimens are lacking ethambutol

[1] Calculated by authors using the chi-square test; $p < 0.05$ was taken as significant

[2] Difference in the medians not provided by authors; calculated by reviewer as ($median_{intermittent} - median_{daily}$)

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

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; TB, tuberculosis; Z,

pyrazinamide

1.2 RQK: How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active respiratory and non-respiratory TB?

1.2.1 People coinfected with tuberculosis and HIV

1.2.1.1 Jindani et al 2004

Bibliographic reference	Jindani A, Nunn AJ & Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51
Study type	Randomised controlled trial
Study quality	Appropriate method of randomisation used? • yes – randomised allocation sequence was generated by computer Allocation concealment used? • yes – computer operated by an independent person based at the International Union Against Tuberculosis and Lung Disease; participating centres were supplied with a batch of sealed and serially numbered opaque envelopes each containing the treatment card of the allocated regimen (these were regularly checked during site visits to ensure that they had not been tampered with Blinding used? • no – no attempt to conceal treatment allocation after randomisation from patients, researchers, or healthcare staff Groups comparable at baseline? • unclear – baseline characteristics not reported by HIV status Groups received the same care apart from the intervention(s) studied? • yes, although details provided limited Groups followed up for an equal and appropriate length of time? • yes – 12 months after treatment completion Groups comparable for treatment completion and availability of outcome data? • yes, although attrition rate was high in both groups Study used precise definitions and reliable measures of outcome? • yes Population studied is the same as the population of interest? • possibly some drug resistance at baseline, although unclear as baseline characteristics not reported by HIV status Intervention used is the same as the intervention of interest?

Bibliographic reference	Jindani A, Nunn AJ & Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51
	• intervention varies by more than the combination of antituberculosis drugs – regimens with an E-continuation phase were 2 months longer than those with an R-continuation phase, and some patients receiving an E-continuation phase had an initial dosing schedule of 3-times weekly and some had a daily dosing schedule, whereas all Have substitute outcomes been used instead of the patient-important outcomes of interest? • response to treatment
Number of patients	n = 127 (HIV subgroup only) • E-continuation phase, daily initial phase = 45 • E-continuation phase, intermittent initial phase = 45 • R-continuation phase = 37 Data available 12 months after treatment completion = 68 (HIV subgroup only) • E-continuation phase = 49 • R-continuation phase = 19
Patient characteristics	Inclusion criteria • age 15–65 years • two sputum samples positive for tubercle bacilli on direct smear microscopy • less than a month of previous antituberculous chemotherapy Only data for HIV subgroup was extracted Exclusion criteria • patients were not eligible if they were so ill they were thought unlikely to survive the initial weeks of treatment • extrapulmonary tuberculosis • other diseases likely to prejudice the response to, or assessment of, treatment, including: diabetes, liver disease, nephritis, blood disorders, epilepsy, peripheral neuritis • pregnancy • psychiatric illness • alcoholism
Intervention	E-continuation phase regimen – $2HRZE_7/6HE_7$ or $2HRZE_3/6HE_7$ • daily ethambutol, isoniazid, rifampicin, and pyrazinamide for 2 months, followed by daily ethambutol and isoniazid for a further 6 months; or • ethambutol, isoniazid, rifampicin, and pyrazinamide three times weekly for 2 months followed by daily ethambutol and isoniazid for 6 months Doses were according to World Health Organisation and International Union Against Tuberculosis and Lung Disease recommendations:

<table>
<tr><th>Bibliographic reference</th><th>Jindani A, Nunn AJ & Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51</th></tr>
<tr><td></td><td>
<table>
<tr><th rowspan="2"></th><th colspan="3">Number of tablets</th></tr>
<tr><th>25-39 kg</th><th>40-55 kg</th><th>>55 kg</th></tr>
<tr><td colspan="4">Daily intensive phase, 2HRZE$_7$</td></tr>
<tr><td>R (150 mg) and H (100 mg) combined tablet</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>E (400 mg)</td><td>1.5</td><td>2</td><td>3</td></tr>
<tr><td>Z (400 mg)</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td colspan="4">Intermittent intensive phase, 2HRZE$_3$</td></tr>
<tr><td>R (150 mg) and H (100 mg) combined tablet</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>H (100 mg)</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td>E (400 mg)</td><td>1.5</td><td>2</td><td>3</td></tr>
<tr><td>Z (400 mg)</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td colspan="4">E-continuation phase, 6HE$_7$</td></tr>
<tr><td>E (400 mg) and H (100 mg) combined tablet</td><td>1.5</td><td>2</td><td>3</td></tr>
</table>
Patients were admitted to hospital or attended the treatment facility daily so that ingestion of the drugs could be directly observed for the first 2 months; thereafter, the patient was given a month’s supply of the drugs to be taken under the supervision of a relative or other person who was designated the treatment monitor and who had agreed to undertake this function</td></tr>
<tr><td>Comparison</td><td>R-continuation phase regimen – 2HRZE$_7$/4HR$_7$
• daily ethambutol, isoniazid, rifampicin, and pyrazinamide for 2 months followed by daily rifampicin and isoniazid for 4 months
Doses were according to World Health Organisation and International Union Against Tuberculosis and Lung Disease recommendations:
<table>
<tr><th rowspan="2"></th><th colspan="3">Number of tablets</th></tr>
<tr><th>25-39 kg</th><th>40-55 kg</th><th>>55 kg</th></tr>
<tr><td colspan="4">Daily intensive phase, 2HRZE$_7$</td></tr>
<tr><td>R (150 mg) and H (100 mg) combined tablet</td><td>2</td><td>3</td><td>4</td></tr>
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</table>
</td></tr>
</table>

Bibliographic reference	**Jindani A, Nunn AJ & Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51**
	<table><tr><td>Z (400 mg)</td><td>2</td><td>3</td><td>4</td></tr><tr><td colspan="4">R-continuation phase, 4HR$_7$</td></tr><tr><td>R (150 mg) and H (100 mg) combined tablet</td><td>2</td><td>3</td><td>4</td></tr></table> Patients were admitted to hospital or attended the treatment facility daily so that ingestion of the drugs could be directly observed for the first 2 months; thereafter, the patient was given a month's supply of the drugs to be taken under the supervision of a relative or other person who was designated the treatment monitor and who had agreed to undertake this function
Length of follow up	12 months after treatment completion
Location	Multinational study; all HIV patients in African clinics
Outcomes measures and effect size	Mortality Number of deaths • E-continuation phase, daily initial phase = 10 of 45 • E-continuation phase, intermittent initial phase = 3 of 45 • R-continuation phase = 4 of 37 *E-continuation phase compared with R-continuation phase (any dosing schedule)* • OR[a] (95% CI) = 1.39 (0.42 to 4.59) i.e. not statistically significant *E-continuation phase compared with R-continuation phase (daily dosing only)* • OR[a] (95% CI) = 2.36 (0.67 to 8.25) i.e. not statistically significant
	Response to treatment – unfavourable outcome Number of patients to have an unfavourable outcome, defined as failure[b] or relapse[c], at the end of follow-up • E-continuation phase = 13 of 90 • R-continuation phase = 1 of 37 *E-continuation phase compared with R-continuation phase (any dosing schedule)* • OR[a] (95% CI) = 6.08 (0.77 to 48.27) i.e. not statistically significant
Source of funding	Substantial amounts of the drugs were donated by Hoechst Marion Roussel, Italy; FATOL, Arzneimittel, Germany; and BRACCO, SpA, Italy Funding in cash or kind was obtained from Ministère des Affaires Etrangères, Direction du Développement et de la Coopération Technique, France; the Norwegian Heart and Lung Association; Norwegian Agency for Development

Bibliographic reference	Jindani A, Nunn AJ & Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51
	Cooperation; US Agency for International Development; Trustees of the Royal Free Hospital, London, UK; and the Kuratorium Tuberkulose in der Welt e.V. None of these organisations had any influence on the design or interpretation of the trial, writing of the report, or the decision to submit it for publication
Comments	

(a) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer
(b) Failure was defined as a culture of 20 or more colonies at month 6 or 8, or a change of treatment by the local investigator owing to treatment failure
(c) Relapse was defined as a culture of 20 or more colonies at any point after the end of treatment or, in the absence of culture confirmation, initiation by the local investigator of treatment for relapse

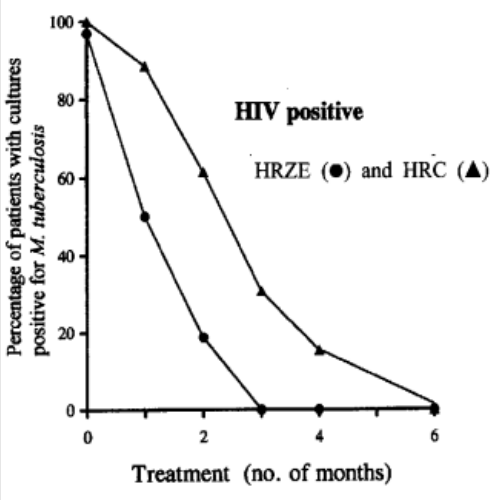
Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide

1.2.1.2 Kennedy et al 1996

Bibliographic reference	Kennedy N, Berger L, Curram J et al (1996) Randomised controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. Clinical Infectious Diseases 22: 827-33
Study type	Randomised controlled trial
Study quality	Appropriate method of randomisation used? • yes – randomisation scheme was generated by a computer program with use of a block size of 10 patients, such that five patients received each treatment regimen per block Allocation concealment used? • yes – treatment instructions were contained within sealed envelopes Blinding used? • no Groups comparable at baseline? • unclear Groups received the same care apart from the intervention(s) studied? • unclear – details provided were limited Groups followed up for an equal and appropriate length of time? • yes – 12 months (6 months after treatment completion) Groups comparable for treatment completion and availability of outcome data? • unclear Study used precise definitions and reliable measures of outcome? • precise definition and reliable measure used for response to treatment, but not for relapse Population studied is the same as the population of interest?

Bibliographic reference	Kennedy N, Berger L, Curram J et al (1996) Randomised controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. Clinical Infectious Diseases 22: 827-33
	• 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? • response to treatment
Number of patients	n = 58 (HIV subgroup only) • HRC group = 26 • HRZE group = 32
Patient characteristics	Inclusion criteria • clinical and radiological presentations were consistent with pulmonary tuberculosis • acid-fast bacilli present in the sputum on direct fluorescent microscopy • over 18 years of age Only data for HIV subgroup was extracted Exclusion criteria • patients with a history of treatment for tuberculosisor of other exposures to any of the study drugs • patients with cultures positive for mycobacteria other than M. tuberculosis • patients with isolates of M. tuberculosis that were resistant to any of the study drugs • severe renal disease • hepatic disease • cardiovascular disease • pregnancy or lactation • a history of adverse reaction to one of the study drugs • epilepsy • concomitant treatment with theophylline • patients with severe tuberculosis who were considered unlikely to survive despite treatment
Intervention	4HRC/2HR • 300 mg of isoniazid • 600 mg of rifampicin • 750 mg of ciprofloxacin • all drugs were given orally once a day in the morning
Comparison	2HRZE/2HRZ/2HR • 300 mg of isoniazid

Bibliographic reference	**Kennedy N, Berger L, Curram J et al (1996) Randomised controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. Clinical Infectious Diseases 22: 827-33**
	• 600 mg of rifampicin • 25 mg/kg of bodyweight of pyrazinamide • 15 mg/kg of bodyweight of ethambutol • all drugs were given orally once a day in the morning
Length of follow up	12 months (6 months after treatment completion)
Location	Kilimanjaro, Tanzania
Outcomes measures and effect size	Relapse Number of patients to experience culture-confirmed relapse • HRC group = 4 of 26 • HRZE group = 0 of 32 • OR[a] (95% CI) = 13.00 (0.67 to 253.61) i.e. not statistically significant
	Response to treatment – culture conversion Time to first negative test results (mean, median (range) (months)) • HRC group (n = 26) = 2.5, 2 (1–6) • HRZE group (n = 32) = 1.6, 1 (1–3) • MD[b] = 0.9 **• p = 0.0003** **i.e. statistically significant**

Bibliographic reference	Kennedy N, Berger L, Curram J et al (1996) Randomised controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. Clinical Infectious Diseases 22: 827-33
	
Source of funding	Bayer
Comments	

(d) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer
(e) Mean difference not provided by authors; calculated by reviewer

Abbreviations: C, ciprofloxacin; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide

1.2.1.3 Schwander et al, 1995

Bibliographic reference	Schwander S, Rüsch-Gerdes S, Mateega A et al (1995) A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. Tubercle and Lung Disease 76: 210-8
Study type	Randomised controlled trial
Study quality	Appropriate method of randomisation used? • yes – random selection of numbered envelopes Allocation concealment used? • yes – use of opaque envelopes Blinding used? • patients were able to see the different shapes of tablets, but they were not informed about their content; study nurses and physicians were advised not to request information about medication from patients and remained blind to treatment throughout the study; the only individuals administering care not to be blinded were the drug dispensers

Bibliographic reference	Schwander S, Rüsch-Gerdes S, Mateega A et al (1995) A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. Tubercle and Lung Disease 76: 210-8
	Groups comparable at baseline? • age, sex, BCG scar presence and other clinical and laboratory parameters were comparable between the 2 groups Groups received the same care apart from the intervention(s) studied? • yes Groups followed up for an equal and appropriate length of time? • both groups followed for 6 months Groups comparable for treatment completion and availability of outcome data? • groups comparable for availability of outcome data, and unclear if groups comparable for treatment completion Study used precise definitions and reliable measures of outcome? • yes Population studied is the same as the population of interest? • no Intervention used is the same as the intervention of interest? • no Have substitute outcomes been used instead of the patient-important outcomes of interest? • response to treatment
Number of patients	n = 50 • rifabutin group = 25 • rifampicin group = 25 Data available = 49 • rifabutin group = 24 • rifampicin group = 25
Patient characteristics	Inclusion criteria • chest x-ray suggestive of pulmonary tuberculosis • sputum positive for acid-fast bacilli • HIV-1 seropositive • ≥15 years of age • use of contraceptive method Exclusion criteria • uric acid >24 mg/dl for men, and >18 mg/dl for women • ALT >78 U/l • total bilirubin >2.5 mg/dl

Bibliographic reference	**Schwander S, Rüsch-Gerdes S, Mateega A et al (1995) A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. Tubercle and Lung Disease 76: 210-8**
	• creatinine >1.5 mg/dl • alcohol abuse • pregnancy or lactation Baseline characteristics

	Rifabutin group	Rifampicin group	p-value
Sex, M:F	16:8	17:8	>0.05
BCG scar present, n(%)	15 (63%)	13 (52%)	>0.05
Cavitatory disease, n(%)	18 (72%)	22 (88%)	>0.05
Age (women), mean±SD (years)	25±3.8	28.8±5.2	>0.05
Age (men), mean±SD (years)	30.8±12.5	30.4±6.0	>0.05
Body weight, mean±SD (kg)	52.8±8.0	51.0±7.0	>0.05
Karnofsky score, mean±SD	63.0±15.0	67.0±15.0	>0.05
Temperature, mean±SD (°C)	38.0±0.9	37.7±1.0	>0.05
Tuberculin skin test, mean±SD (mm)	11.0±10.5	15.6±9.5	>0.05
Erythrocyte sedimentation rate, mean±SD (mm)	108±29	104±21	>0.05
Lymphocytes, mean±SD (10^3/µl)	1.5±0.8	1.8±0.7	>0.05
Neutrophils, mean±SD (10^3/µl)	4.1±2.5	5.0±2.3	>0.05
CD4 count, mean±SD (/µl)	318±249	360±259	>0.05
ALT, mean±SD (U/l)	24±26	21±11	>0.05
Uric acid, mean±SD (mg/dl)	4.8±1.9	5.5±1.8	>0.05

Intervention	Rifabutin group – 2HRbZE/4HRb • daily intake of rifabutin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifabutin and isoniazid for a further 4 months • treatment regimens were adapted and modified according to the World Health Organisation guidelines for tuberculosis treatment in adults Dosing • rifabutin: 150 mg/day for those <50 kg, and 300 mg/day for those ≥50kg • isoniazid: 300 mg/day • pyrazinamide: 1500 mg/day for those <50 kg, and 2000 mg/day for those ≥50kg

Bibliographic reference	Schwander S, Rüsch-Gerdes S, Mateega A et al (1995) A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. Tubercle and Lung Disease 76: 210-8
	• ethambutol: 80 mg/day for those <50 kg, and 1200 mg/day for those ≥50kg
Comparison	Rifampicin group – 2HRZE/4HR • daily intake of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for a further 4 months • treatment regimens were adapted and modified according to the World Health Organisation guidelines for tuberculosis treatment in adults Dosing • rifampicin: 450 mg/day for those <50 kg, and 600 mg/day for those ≥50kg • isoniazid: 300 mg/day • pyrazinamide: 1500 mg/day for those <50 kg, and 2000 mg/day for those ≥50kg • ethambutol: 80 mg/day for those <50 kg, and 1200 mg/day for those ≥50kg
Length of follow up	6 months
Location	Kampala, Uganda
Outcomes measures and effect size	Mortality Number of deaths during the study period • rifabutin group = 4 of 25 • rifampicin group = 2 of 25 • OR[a] (95% CI) = 2.19 (0.36 to 13.22) i.e. not statistically significant
	Changes in signs and symptoms – radiographic change Number of patients in whom radiographic improvement was observed • rifabutin group = 24 of 25 • rifampicin group = 25 of 25 • OR[a] (95% CI) = 0.32 (0.01 to 8.25) i.e. not statistically significant
	Response to treatment – sputum conversion Number of patients to undergo sputum conversion, defined as 3 consecutive negative sputum smears and cultures from the initiation of therapy or a negative smear followed by a consistent absence of sputum production • rifabutin group = 22 of 25 • rifampicin group = 22 of 25 • OR[a] (95% CI) = 1.00 (0.18 to 5.51) i.e. not statistically significant

Bibliographic reference	Schwander S, Rüsch-Gerdes S, Mateega A et al (1995) A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. Tubercle and Lung Disease 76: 210-8
	Time to sputum conversion (median, days)[b], defined as the time to the first of 3 consecutive negative sputum smears and cultures from the initiation of therapy or a negative smear followed by a consistent absence of sputum production • rifabutin group (n = 25) = Not reported • rifampicin group (n = 25) = Not reported Difference in the medians[c] = Not reported
Source of funding	Study partially supported by Farmitalia Carlo Erba, Freiburg, Germany
Comments	

(f) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer
(g) Not provided by authors; read off Kaplan-Meier plot by reviewer
(h) Difference not provided by authors; calculated by reviewer

Abbreviations: ALT, alanine aminotransferase; BCG, Bacillus Calmette-Guérin vaccine; CI, confidence interval; E, ethambutol; F, female; H, isoniazid; M, male; OR, odds ratio; R, rifampicin; Rb, rifabutin; SD, standard deviation; Z, pyrazinamide

1.2.1.4 HIV/TB Study Writing Group, 2009

Bibliographic reference	HIV/TB Study Writing Group (2009) Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. AIDS 23: 2485-95
Study type	Prospective cohort
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? • yes, in the multivariate analysis – Kaplan-Meier estimation and Cox proportional hazards regression models were used to estimate the probability of death; the model was adjusted for the following a priori chosen variables: region of residence, age, sex, country of birth, risk factors for HIV and TB acquisition, HIV diagnosis preceding the date of TB diagnosis, CD4 cell count, prior AIDS, initiation of cART, date of TB diagnosis, previous TB, symptoms duration, type of anti-TB treatment, resistance to anti-TB drugs, and TB location Groups comparable at baseline? • unclear Groups received the same care apart from the intervention(s) studied? • unclear – details of treatment and other care received were limited Groups followed up for an equal and appropriate length of time?

Bibliographic reference	HIV/TB Study Writing Group (2009) Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. AIDS 23: 2485-95
	• yes – 1 year 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 drug resistance was present at baseline (7% of patients in Central/Northern Europe, 13% in Southern Europe and 50% in Eastern Europe) Intervention used is the same as the intervention of interest? • unclear – details of treatment and other care received were limited Have substitute outcomes been used instead of the patient-important outcomes of interest? • no
Number of patients	n = 784 • non-rifampicin group = 117 • rifampicin group = 667
Patient characteristics	Inclusion criteria • initiation of antituberculosis therapy between January 2004 and December 2006 • known to be infected with HIV at diagnosis of tuberculosis, or diagnosed with HIV infection within 6 months of tuberculosis diagnosis • aged 16 years or older Diagnosis of tuberculosis • confirmed tuberculosis = M. tuberculosis cultured or M. tuberculosis DNA demonstrated by PCR • probable tuberculosis = acid-fast bacilli or granulomatous inflammation present • presumptive tuberculosis = antituberculosis therapy initiated in the absence of supportive microbiological or histological evidence and diagnosis of tuberculosis not subsequently ruled out
Intervention	Non-rifampicin group • regimens contained at least isoniazid and pyrazinamide, but not rifampicin
Comparison	Rifampicin group • regimens contained at least rifampicin (or any other rifamycin), isoniazid and pyrazinamide
Length of follow up	1 year
Location	Argentina, Italy, Spain, Denmark, France, Switzerland, Belarus, Latvia, Romania, Russia, Ukraine and the UK
Outcomes measures and	Mortality – univariate analysis

Bibliographic reference	HIV/TB Study Writing Group (2009) Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. AIDS 23: 2485-95
effect size	RR (95% CI) (non-rifampicin compared to rifampicin group) = 1.82 (1.17 to 2.84); p = 0.0079 i.e. statistically significant Mortality – multivariate analysis[a] RR (95% CI) (non-rifampicin compared to rifampicin group) = 1.21 (0.74 to 1.97); p = 0.447 i.e. not statistically significant
Source of funding	Data collection in Eastern Europe (Belarus, Latvia, Russia, Ukraine) and Argentina was funded by the Copenhagen HIV Programme and the EuroSIDA study Primary support for EuroSIDA is provided by the European Commission BIOMED 1, BIOMED 2, the 5th Framework and the 6th Framework Current support also includes unrestricted grants from Bristol-Myers Squibb, GlaxoSmithKline, Roche, Gilead, Pfizer, Merck and Co, Tibotec, and Boehringer-Ingelheim The participation of centres from Switzerland was supported by a grant from the Swiss Federal Office for Education and Science Data collection in Western Europe was self-funded by the participating cohorts as follows: Aquitaine Cohort, France; Danish HIV Cohort, Denmark; SWISS HIV Cohort, Switzerland; Mortimer Market Hospital and King's College Hospital in London, UK In Spain, the study was funded by Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spanish Network for the AIDS Research, Madrid, Spain, and Agencia de Salud Pública de Barcelona
Comments	

(i) Model was adjusted for the following a priori chosen variables: region of residence, age, sex, country of birth, risk factors for HIV and TB acquisition, HIV diagnosis preceding the date of TB diagnosis, CD4 cell count, prior AIDS, initiation of cART, date of TB diagnosis, previous TB, symptoms duration, resistance to anti-TB drugs, and TB location

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction; RR, relative risk

1.2.1.5 Okwera et al, 2006

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44
Study type	Prospective cohort
Study quality	Method of allocation to treatment groups unrelated to potential confounding factors? • allocation was based on the time of treatment Blinding used? • unclear, though unlikely Attempts made within the design or analysis to balance the groups for potential confounders? • no

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44
	Groups comparable at baseline? • no – 2HRZE/4HR group were significantly older, 2HRZE/6HR group had significantly higher levels of haemoglobin, and 2HRZE/6HE group had significantly higher total white blood cell counts Groups received the same care apart from the intervention(s) studied? • no – rifampicin regimens (2HRZE/4HR and 2HRZE/6HR) were self-administered, non-rifampicin regimen (2HRZE/6HE) was directly observed Groups followed up for an equal and appropriate length of time? • no – median follow-up in the 2HRZE/4HR group was 512 days, 533 days in the 2HRZE/6HR group, and 661 days in the 2HRZE/6HE group Groups comparable for treatment completion and availability of outcome data? • no – 83% completed treatment in the 2HRZE/4HR group, 73% completed treatment in the 2HRZE/6HR group, and 65% completed treatment in the 2HRZE/6HE group Study used precise definitions and reliable measures of outcome? • no definitions provided for culture-negative at 2 months, treatment failure or treatment completion Population studied is the same as the population of interest? • population appears to match the population of interest, although unclear if there was any drug resistance at baseline Intervention used is the same as the intervention of interest? • no – interventions varied by more than the combination of drugs used (also varied by dosing frequency and the use of DOT, as well as the duration of treatment with regards to the 2HRZE/4HR group) Have substitute outcomes been used instead of the patient-important outcomes of interest? • culture-negative at 2 months – an indicator of response to treatment, a surrogate for cure
Number of patients	n = 549 • 2HRZE/6HE group = 136 • 2HRZE/6HR group = 266 • 2HRZE/4HR group = 147
Patient characteristics	Inclusion criteria • adults with initial episodes of smear-positive pulmonary tuberculosis • HIV-positive Diagnosis of tuberculosis • acid-fast bacilli smear-positive • at least one sputum culture-positive for M. tuberculosis • chest X-ray findings consistent with tuberculosis Exclusion criteria

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44

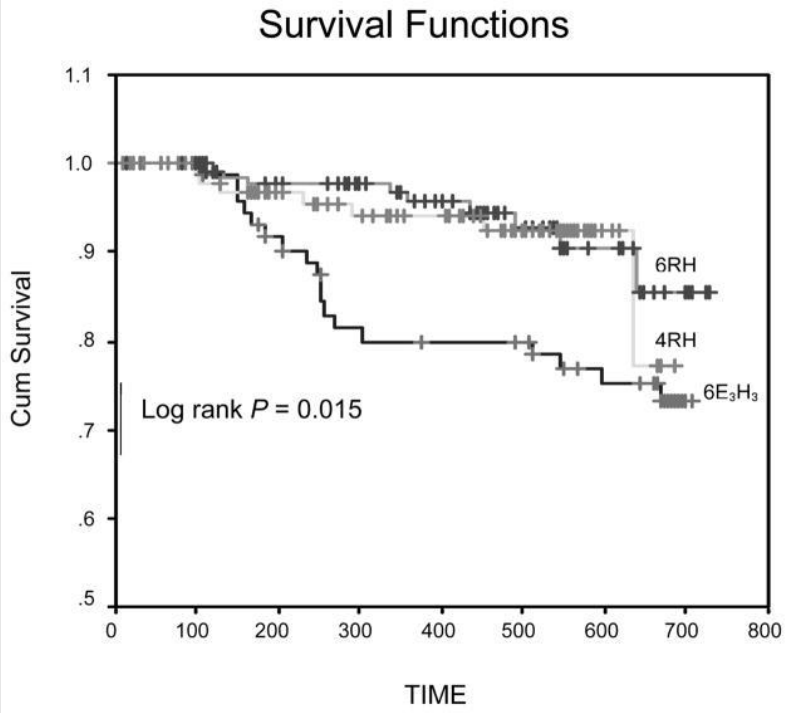
• suspected miliary and meningeal tuberculosis
• previous treatment of tuberculosis
• pregnant women
• no antiretroviral therapy during the course of the study

Baseline characteristics

	2HRZE/6HE group	2HRZE/6HR group	2HRZE/4HR group	p-value
Sex, (% male)	70 (51%)	128 (48%)	77 (52%)	0.666
Age (mean±SD, years)	28.2±6.4	29.2±6.2	33.3±7.7	0.0001
BMI (mean±SD, kg/m^2)	18.9±2.5	19.1±2.7	19.2±2.3	0.69
Karnofsky scale score (mean±SD)	80±7.1	82±6.7	81±8.2	0.018
Weight (mean±SD, kg)	50.3±7.3	50.9±7.6	52.1±7.0	0.297
Haemoglobin (mean±SD, gm/dl)	10.8±1.9	13.4±2.3	11.1±2.9	0.001
Total white blood cell count (mean±SD, mm^3)	7.2±3.5	5.4±1.7	6.3±2.4	0.001
Tuberculin skin test (mean±SD, mm)	15.3±6.9	14.5±6.8	13.1±6.0	0.0241
Chest X-ray findings (extent of disease) (n(%))				
– normal	1 (0.7%)	1 (0.4%)	4 (3.0%)	0.229

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44				
	─ minimal disease	10 (7.4%)	33 (12.5%)	16 (11.0%)	
	─ moderately advanced disease	48 (36.0%)	89 (33.6%)	55 (37.0%)	
	─ far advanced disease	76 (56.0%)	142 (53.5%)	72 (49.0%)	
	─ cavitatory disease	82 (61.0%)	148 (56.0%)	69 (47.0%)	0.057
Intervention	Ethambutol-containing continuation phase - 2HRZE/6HE • isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months • followed by isoniazid and ethambutol 3 times a week for 6 months Dosing: • 900 mg isoniazid • 1800 mg ethambutol • no dosing information given for rifampicin and pyrazinamide Directly observed therapy				
Comparison	Rifampicin-containing continuation phase - 2HRZE/4HR or 2HRZE/6HR • isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months • followed by isoniazid and rifampicin daily for 4 or 6 months Dosing: • 300 mg isoniazid • 600 mg ethambutol • no dosing information given for pyrazinamide and ethambutol Self-administered therapy				
Length of follow up	Median follow-up: • 2HRZE/6HE group = 661 days • 2HRZE/6HR group = 533 days • 2HRZE/4HR group = 512 days				
Location	Kampala, Uganda				
Outcomes measures and	Mortality				

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44
effect size	Number of people to die within 2 years • 2HRZE/6HE group = 27 of 136 • 2HRZE/6HR group = 62 of 266 • 2HRZE/4HR group = 51 of 147 • OR[a] (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.66 (0.41 to 1.06) i.e. not statistically significant • OR[a] (95% CI) (6-month E-containing continuation phase compared to 6-month R-containing continuation phase) = 0.82 (0.49 to 1.35) i.e. not statistically significant
	Treatment failure Number of patients to experience treatment failure • 2HRZE/6HE group = 8 of 136 • 2HRZE/6HR group = 7 of 266 • 2HRZE/4HR group = 5 of 147 • OR[a] (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 2.09 (0.84 to 5.22) i.e. not statistically significant • OR[a] (95% CI) (6-month E-containing continuation phase compared to 6-month R-containing continuation phase) = 2.31 (0.82 to 6.52) i.e. not statistically significant
	Relapse Number of patients to experience relapse, defined as the development of active tuberculosis after successful completion of an initial course of treatment during 24 months of follow-up after cure • 2HRZE/6HE group = 23 of 136 • 2HRZE/6HR group = 14 of 266 • 2HRZE/4HR group = 16 of 147 **• OR[a] (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 2.60 (1.45 to 4.65)** **i.e. statistically significant** **• OR[a] (95% CI) (6-month E-containing continuation phase compared to 6-month R-containing continuation phase) = 3.66 (1.82 to 7.38)** **i.e. statistically significant**

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44
	 Kaplan Meier curve showing time to relapse of patients in the three cohorts; '$6E_3H_3$' = 2HRZE/6HE group, '6RH' = 2HRZE/6HR group, '4RH' = 2HRZE/4HR group
	Response to treatment – culture conversion Number of patients to be culture-negative after 2 months of treatment • 2HRZE/6HE group = 101 of 136 • 2HRZE/6HR group = 238 of 266 • 2HRZE/4HR group = 126 of 147 **• OR[a] (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.39 (0.24 to 0.63) i.e. statistically significant**
	Adherence – treatment completion Number of patients to complete therapy • 2HRZE/6HE group = 89 of 136

Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. International Journal of Tuberculosis and Lung Disease 10(1): 39-44
	• 2HRZE/6HR group = 195 of 266 • 2HRZE/4HR group = 122 of 147 **• OR[a] (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.57 (0.39 to 0.87) i.e. statistically significant** • OR[a] (95% CI) (6-month E-containing continuation phase compared to 6-month rifampicin-containing continuation phase) = 0.69 (0.44 to 1.08) i.e. not statistically significant
Source of funding	No details provided
Comments	

(j) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer

Abbreviations: BMI, body mass index; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; SD, standard deviation; Z, pyrazinamide

1.2.2 People with tuberculosis and liver disease

1.2.2.1 Saigal et al, 2001

Bibliographic reference	Saigal S, Agarwal SR, Nandeesh HP et al (2001) Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. Journal of Gastroenterology and Hepatology 16: 1028-32
Study type	Randomised controlled trial
Study quality	Appropriate method of randomisation used? • yes – random number table Allocation concealment used? • unclear Blinding used? • no Groups comparable at baseline? • no – ofloxacin group had a significantly lower level of albumin and a greater prolongation of prothrombin time, which indicates that the underlying liver disease may have been more severe in this group; additionally, the aetiologies of the liver disease were not comparable in the 2 groups Groups received the same care apart from the intervention(s) studied? • unclear – limited details provided

Bibliographic reference	Saigal S, Agarwal SR, Nandeesh HP et al (2001) Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. Journal of Gastroenterology and Hepatology 16: 1028-32
	Groups followed up for an equal and appropriate length of time? • yes – 3 months after treatment was stopped 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? • no – 2 interventions varied by more than the combination of antituberculosis drugs used (regimens also varied by total duration of treatment); additionally, it is unclear if the doses used and the dosing frequencies were comparable in the 2 regimens Have substitute outcomes been used instead of the patient-important outcomes of interest? • no
Number of patients	n = 31 • ofloxacin group = 16 • rifampicin group = 15
Patient characteristics	Inclusion criteria • proven chronic liver disease • diagnosis of tuberculosis Screening for tuberculosis • fever • cough for >2 weeks • haemoptysis • unexplained weight loss • increasing ascites not responding to diuretics • unexplained bowel symptoms, such as diarrhoea, constipation or subacute intestinal obstructions • radiological lesions suggestive of tuberculosis • past or family history of tuberculosis Diagnosis of tuberculosis • based on a good clinical response to chemotherapy, and one or more of the following:

Bibliographic reference	Saigal S, Agarwal SR, Nandeesh HP et al (2001) Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. Journal of Gastroenterology and Hepatology 16: 1028-32
	─ histological evidence of caseating granulomas ─ sputum positivity for acid-fast bacilli ─ growth of M. tuberculosis on culture ─ positive PCR for M. tuberculosis in tissues • diagnosis of pleural or peritoneal tuberculosis was established if 3 of the following criteria were met: ─ raised ascite fluid cell count with lymphocyte predominance ─ raised ascetic fluid albumin (>2.5 g/dl) ─ raised adenosine deaminase (>33 U/l) ─ positive PCR for M. tuberculosis Exclusion criteria • serum bilirubin >5 mg/dl • baseline ALT/AST >200 IU/l • serum creatinine >2.5 mg/dl • increase in ALT/AST over 1 week prior to initiation of antituberculosis chemotherapy was >2-fold the baseline levels
Intervention	Ofloxacin group – 2HZEO/10HEO • isoniazid, pyrazinamide, ethambutol and ofloxacin for 2 months • followed by isoniazid, ethambutol and ofloxacin for a further 10 months Dosing: • ofloxacin was given in a dose of 400 mg once daily • no further dosing information provided
Comparison	Rifampicin group – 2HRE/7HR • isoniazid, rifampicin and ethambutol for 2 months • followed by isoniazid and rifampicin for a further 7 months Dosing: • no dosing information provided
Length of follow up	3 months after treatment was stopped
Location	New Delhi, India
Outcomes measures and effect size	Mortality – all cause Number of patients to die from any cause • ofloxacin group = 1 of 16[a] • rifampicin group = 0 of 15

Bibliographic reference	Saigal S, Agarwal SR, Nandeesh HP et al (2001) Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. Journal of Gastroenterology and Hepatology 16: 1028-32
	• OR[b] (95% CI) = 3.00 (0.11 to 79.50) i.e. not statistically significant
	Mortality – tuberculosis-related Number of tuberculosis-related deaths • ofloxacin group = 0 of 16 • rifampicin group = 0 of 15 • OR[b] (95% CI) = 0.94 (0.02 to 50.32) i.e. not statistically significant
	Mortality – hepatotoxicity-related Number of hepatotoxicity-related deaths • ofloxacin group = 0 of 16 • rifampicin group = 0 of 15 • OR[b] (95% CI) = 0.94 (0.02 to 50.32) i.e. not statistically significant
	Adverse events - hepatotoxicity Number of patients to experience hepatotoxicity, defined as ALT/AST levels >5-fold the baseline level or >400 IU/L, or if bilirubin increased by 2.5 mg/dl after exclusion of superimposed acute hepatitis • ofloxacin group = 0 of 16 • rifampicin group = 4 of 15 • OR[b] (95% CI) = 0.08 (0.00 to 1.58) i.e. not statistically significant
Source of funding	No details provided
Comments	

(k) Death resulted from intracranial bleeding unrelated to the antituberculosis chemotherapy during the follow-up
(l) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; E, ethambutol; H, isoniazid; O, ofloxacin; OR, odds ratio; PCR, polymerase chain reaction; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide

1.2.2.2 Pan et al, 2005

Bibliographic reference	Pan L, Jia Z-S, Chen L et al (2005) Effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus. World Journal of Gastroenterology 11(16): 2518-21

Bibliographic reference	Pan L, Jia Z-S, Chen L et al (2005) Effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus. World Journal of Gastroenterology 11(16): 2518-21
Study type	Prospective cohort
Study quality	Method of allocation to treatment groups unrelated to potential confounding factors? • unclear Blinding used? • unclear Attempts made within the design or analysis to balance the groups for potential confounders? • no Groups comparable at baseline? • yes – authors state that the 'general conditions of the 2 groups were not distinguishable ($p > 0.05$)', although no further details are provided Groups received the same care apart from the intervention(s) studied? • unclear – 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? • 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? • no – the regimens used vary by more than the combinations of drugs used (the 2 regimens used different dosing schedules; additionally, it is unclear if the total duration of treatment was comparable in the 2 groups) Have substitute outcomes been used instead of the patient-important outcomes of interest? • no
Number of patients	n = 47 • HRbAOL group = 23 • HRZS/E group = 24
Patient characteristics	Inclusion criteria • pulmonary tuberculosis • patients carrying HBV whose liver function was normal when they suffered from pulmonary tuberculosis; values of ALT were all <60 U/L before antituberculosis chemotherapy was initiated

Bibliographic reference	**Pan L, Jia Z-S, Chen L et al (2005) Effect of anti-tuberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus. World Journal of Gastroenterology 11(16): 2518-21**
	Diagnosis of tuberculosis • made by chest x-ray, medical history, acid-fast bacilli in the phlegm and tuberculosis PCR Exclusion criteria • infection with other hepatitis viruses • alcoholic liver ailment • other chronic liver ailment
Intervention	HRbAOL • 0.3 g isoniazid once a day • 0.6 g rifabutin once a week • 0.2 g amikacin twice a day • 0.2 g ofloxacin twice a day • 0.2 g levofloxacin twice a day
Comparison	HRZS/E • 0.3 g isoniazid once a day • 0.45 g rifampicin once a day • 1.0 g pyrazinamide once a day • 1.0 g ethambutol and/or 0.75 g streptomycin once a day
Length of follow up	Unclear
Location	Shaanxi Province, China
Outcomes measures and effect size	Adverse events – liver dysfunction Number of patients to experience liver dysfunction, defined as ALT >1336 IU/L 2-3 months after initiation of antituberculosis chemotherapy • HRbAOL group = 7 of 23 • HRZS/E group = 19 of 24 **• OR[a] (95% CI) = 0.12 (0.03 to 0.43)** **i.e. statistically significant**
Source of funding	No details provided
Comments	
(m) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer Abbreviations: A, amikacin; ALT, alanine aminotransferase; CI, confidence interval; E, ethambutol; H, isoniazid; HBV, hepatitis B virus; L, levofloxacin; O, ofloxacin; OR, odds ratio; PCR, polymerase chain reaction; R, rifampicin; Rb, rifabutin; S, streptomycin; Z, pyrazinamide	

1.2.3 People with tuberculosis and renal disease

No papers identified

1.2.4 People with tuberculosis and diabetes

No papers identified

1.2.5 People with tuberculosis and who are substance misusers

No papers identified

1.2.6 People with tuberculosis and impaired vision or eye disease

No papers identified

1.2.7 People with tuberculosis who are pregnant or breastfeeding

No papers identified

1.3 RQ L: In adults with drug susceptible, active respiratory TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

RQ L: duration of treatment in adults with respiratory tuberculosis

1.3.1 British Thoracic Society, 1975/80

Study type	RCT
Study quality	Population does not exactly match the population of interest: 3.4% drug resistance at baseline Intervention does not exactly match the intervention of interest: does not use all of or just the 4 standard recommended drugs: all regimens lacked pyrazinamide, some regimens lacked ethambutol, and some regimens contained streptomycin Method of randomisation, although allocation concealment was possible ("random allocations of treatment were made centrally by coordinators") Radiologists were blinded, although unclear if other investigators, patients or those administering care were blinded Groups were comparable at the baseline Unclear if groups received the same care apart from the interventions studied Groups were not followed up for an equal length of time: ‘follow-up’ was timed from treatment initiation; therefore,

	since treatment durations were of different duration, follow-up for outcomes that were measured after treatment completion was not equal Groups were statistically comparable for treatment completion, although this occurred in more patients in the 6M group Unclear if groups were comparable for availability of outcome data at 54 months (i.e. number to experience relapse and number to be considered 'alive and well'); information available was ambiguous
Number of patients	*Patients without cavities or no cavity >2 cm* Randomised = 431[1] 6-month regimens = 214[2] 12-month regimens = 217[3] Data available at treatment completion = 384 6-month regimens = 194[4] 12-month regimens = 190[5] Data available at 54 months after treatment initiation = 295[6] 6-month regimens = 144 12-month regimens = 151 *Patients with cavities >2 cm* Randomised = 381[1] 9-month regimens = 187[7] 18-month regimens = 194[8] Data available at treatment completion = 312 9-month regimens = 157[9] 18-month regimens = 155[10]

<table>
<tr><td></td><td>Data available at 54 months after treatment initiation = 253[6]
9-month regimens = 132
18-month regimens = 121</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Culture-positive pulmonary tuberculosis
Patients aged 15 to 70 years
Exclusion
Previous antituberculosis therapy for more than 2 weeks at any time
Pregnant
Impaired renal, hepatic or visual function
Baseline characteristics
Balanced in terms of mean age, sex and pretreatment radiographic characteristics
<table>
<tr><th colspan="7">Patients without cavities or no cavity >2 cm</th></tr>
<tr><td></td><td colspan="4">Age <60 years</td><td colspan="2">Age >60 years</td></tr>
<tr><td></td><td>6EHR</td><td>6SHR</td><td>12EHR</td><td>12SHR</td><td>6EHR</td><td>12EHR</td></tr>
<tr><td>Total</td><td>78</td><td>83</td><td>76</td><td>81</td><td>33</td><td>33</td></tr>
<tr><td>Mean age (years)</td><td>40</td><td>37</td><td>38</td><td>36</td><td>65</td><td>64</td></tr>
<tr><td>Sex</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>male</td><td>57</td><td>58</td><td>49</td><td>58</td><td>25</td><td>27</td></tr>
<tr><td>female</td><td>21</td><td>25</td><td>27</td><td>23</td><td>8</td><td>6</td></tr>
<tr><td>Radiographic extent of the</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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disease							
slight	16	22	17	16	8	6	
limited	36	42	35	33	12	14	
moderate	16	14	14	24	8	4	
extensive	9	5	8	7	5	7	
gross	1	0	2	1	0	2	
Radiographic extent of the disease							
nil	53	62	49	60	28	26	
slight	12	9	12	6	0	1	
moderate	12	9	10	11	3	4	
extensive	1	3	5	4	2	2	

Patients with cavities >2 cm						
	Age <60 years				Age >60 years	
	9EHR	**9SHR**	**18EHR**	**18SHR**	**9EHR**	**18EHR**
Total	65	72	67	62	20	26
Mean age (years)	38	38	40	39	65	64
Sex						
male	49	48	49	38	17	22
female	16	24	18	24	3	4
Radiographic extent of the						

	disease						
	slight	3	4	1	3	0	1
	limited	21	26	25	15	9	4
	moderate	19	20	21	21	3	11
	extensive	20	21	16	19	7	7
	gross	2	1	2	4	1	2
	Radiographic extent of the disease						
	nil	14	18	12	13	4	0
	slight	7	2	5	4	1	5
	moderate	15	25	21	18	7	7
	extensive	29	27	27	27	8	13

Intervention	**Patients without cavities or no cavity >2 cm: *6-month regimens*[11]** Patients aged less than 60 years – randomised to either: 6EHR: 6 months of ethambutol, isoniazid and rifampicin 6SHR: 6 months of streptomycin, isoniazid and rifampicin Patients aged more than 60 years – all received: 6EHR: 6 months of ethambutol, isoniazid and rifampicin **Patients with cavities >2 cm: *9-month regimens*[11]** Patients aged less than 60 years – randomised to either: 9EHR: 9 months of ethambutol, isoniazid and rifampicin

	9SHR: 9 months of streptomycin, isoniazid and rifampicin Patients aged more than 60 years – all received: 9EHR: 9 months of ethambutol, isoniazid and rifampicin Dosing: isoniazid: 300 mg/day, daily rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg, daily ethambutol: 25 mg/kg of body weight/day, daily streptomycin: 750 mg intramuscularly, 6 days/week Chemotherapy was administered on an outpatient or inpatient basis, according to the usual practice of the physician
Comparison	**Patients without cavities or no cavity >2 cm: *12-month regimens*[11]** Patients aged less than 60 years – randomised to either: 12EHR: 12 months of ethambutol, isoniazid and rifampicin 12SHR: 12 months of streptomycin, isoniazid and rifampicin Patients aged more than 60 years – all received: 12EHR: 12 months of ethambutol, isoniazid and rifampicin **Patients with cavities >2 cm: *18-month regimens*[11]** Patients aged less than 60 years – randomised to either: 18EHR: 18 months of ethambutol, isoniazid and rifampicin 18SHR: 18 months of streptomycin, isoniazid and rifampicin Patients aged more than 60 years – all received: 18EHR: 18 months of ethambutol, isoniazid and rifampicin

	Dosing: isoniazid: 300 mg/day, daily rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg, daily ethambutol: 25 mg/kg of body weight/day, daily streptomycin: 750 mg intramuscularly, 6 days/week Chemotherapy was administered on an outpatient or inpatient basis, according to the usual practice of the physician
Location	UK
Bibliographic reference	British Thoracic and Tuberculosis Association (1975) Short-course chemotherapy in pulmonary tuberculosis. A controlled trial by the British Thoracic and Tuberculosis Association. Lancet 305 (7899): 119-24
Length of follow up	Full treatment period
Outcomes measures and effect size	**Treatment failure** Defined as the presence of 2 or more positive cultures at different months during the last 3 months of treatment; the finding of 2 positive cultures in only 1 month in the last 3 months was not classed as a failure Number of participants without cavities or no cavity >2 cm to experience treatment failure 6-month regimens = 1 of 214 12-month regimens = 0 of 217 OR^{12} (95% CI) = 3.06 (0.12 to 75.45) i.e. not statistically significant Number of participants with cavities >2 cm to experience treatment failure 9-month regimens = 0 of 187 18-month regimens = 0 of 194 OR^{12} (95% CI) = 1.04 (0.02 to 52.55)

	i.e. not statistically significant
Bibliographic reference	British Thoracic Association (1980) Short-course chemotherapy in pulmonary tuberculosis. A controlled trial by the British Thoracic Association. Lancet 315(8179): 1182-3
Length of follow up	54 months after treatment initiation
Outcomes measures and effect size	**'Alive and well'** Number of participants without cavities or no cavity >2 cm to be considered 'alive and well' at 54 month of follow-up 6-month regimens = 129 of 214 12-month regimens = 140 of 217 OR[12] (95% CI) = 0.83 (0.57 to 1.23) i.e. not statistically significant Number of participants with cavities >2 cm to be considered 'alive and well' at 54 month of follow-up 9-month regimens = 116 of 187 18-month regimens = 108 of 194 OR[12] (95% CI) = 1.30 (0.86 to 1.96) i.e. not statistically significant
	Relapse Number of participants without cavities or no cavity >2 cm to experience relapse during the 54 month of follow-up 6-month regimens = 9 of 214 12-month regimens = 2 of 217 **OR[12] (95% CI) = 4.72 (1.01 to 22.11)** **i.e. statistically significant**

	Number of participants with cavities >2 cm to experience relapse during the 54 month of follow-up 9-month regimens = 0 of 187 18-month regimens = 0 of 194 OR[12] (95% CI) = 1.04 (0.02 to 52.55) i.e. not statistically significant
Source of funding	Ciba Laboratories and Lepetit Pharmaceuticals provided financial support
Comments	Population does not exactly match the population of interest: 3.4% drug resistance at baseline Intervention does not exactly match the intervention of interest: does not use all of or just the 4 standard recommended drugs: all regimens lacked pyrazinamide, some regimens lacked ethambutol, and some regimens contained streptomycin

[1] Reviewer calculated number randomised by adding together those who did not complete allocated treatment to the number remaining for analysis

[2] 6EHR (age < 60 years) = 86; 6SHR (age < 60 years) = 92; 6EHR (age > 60 years) = 36

[3] 12EHR (age < 60 years) = 90; 12SHR (age < 60 years) = 90; 12EHR (age > 60 years) = 37

[4] 9EHR (age < 60 years) = 77; 9SHR (age < 60 years) = 84; 9EHR (age > 60 years) = 26

[5] 18EHR (age < 60 years) = 78; 18SHR (age < 60 years) = 84; 18EHR (age > 60 years) = 32

[6] Reviewer included patients that “absconded/emigrated”; authors ‘analysed’: 6-month regimens = 130; 12-month regimens = 140; 9-month regimens = 116; 18-month regimens = 108

[7] 6EHR (age < 60 years) = 78; 6SHR (age < 60 years) = 83; 6EHR (age > 60 years) = 33

[8] 12EHR (age < 60 years) = 76; 12SHR (age < 60 years) = 81; 12EHR (age > 60 years) = 33

[9] 9EHR (age < 60 years) = 65; 9SHR (age < 60 years) = 72; 9EHR (age > 60 years) = 20

[10] 18EHR (age < 60 years) = 67; 18SHR (age < 60 years) = 62; 18EHR (age > 60 years) = 26

[11] Data for regimens of the same length were pooled by the reviewer

[12] Odds ratio and confidence interval calculated by reviewer

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

1.3.2 British Thoracic Society, 1981/2/4

Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: varies by more than duration: different combinations in each arm; 6-month arms have a 4-drug initial phase, whereas 9-month arm has a 3-drug initial phase does not use the 4 standard recommended drugs: 1 of the 6-month arms uses streptomycin instead of ethambutol, 9-month arm is missing pyrazinamide Method of randomisation was unclear Allocation concealment unclear, although allocation 'was made centrally 2 coordinators' Blinding was unclear, although radiographs were read by an observer without knowledge of the regimen allocated to the patients Groups were comparable at the baseline Unclear if groups received the same care apart from the interventions studied Unclear if groups were comparable for treatment completion, but there was a high attrition rate in terms of the number of patients for whom data is available Did not follow the intent-to-treat principle
Number of patients	Randomised = 593 Analysed = 511

<table>
<tr><td></td><td>6-month regimens = 344[1]
9-month regimen = 177
Completed treatment = 444
6-month regimens = 287[2]
9-month regimen = 157
Data available at 36 months = 373
6-month regimens = 246[3]
9-month regimen = 127</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Culture-positive pulmonary tuberculosis
Aged 18 to 60 years
Exclusion
>2 weeks antituberculosis therapy at any time
Pregnancy
Clinical evidence of impaired renal or hepatic function, gout or impaired vision
Baseline characteristics
<table>
<tr><th></th><th>6-month group</th><th>9-month group</th></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>male</td><td>59.1%</td><td>67.8%</td></tr>
<tr><td>female</td><td>40.1%</td><td>32.2%</td></tr>
<tr><td>Age (mean, years)</td><td>37</td><td>38</td></tr>
</table>
</td></tr>
</table>

		Radiographic extent of disease		
		slight	31.4%	27.7%
		limited	33.1%	37.3%
		moderate	14.8%	16.4%
		extensive and gross	16.6%	16.3%
		not classified	1.2%	2.3%
		Radiographic extent of cavitation		
		nil	49.1%	50.3%
		slight	27.9%	23.1%
		moderate	16.9%	21.4%
		extensive	2.3%	2.8%
		not classified	0.9%	2.3%
		Bacteriological status		
		smear-positive, culture-positive	56.1%	57.6%
		smear-negative, culture-positive	41.0%	42.4%
Intervention	*6-month regimens* $2SHRZ_7/4HR_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months			

	$2EHRZ_7/4HR_7$ isoniazid, rifampicin, ethambutol and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg streptomycin: 750 mg intramuscularly, 6 days/week pyrazinamide: 1500 mg/day if the patient weighed less than 50 kg, 2000 mg/day if the patient weighed between 50 and 74 kg, or 2500 mg/day if the patient weighed 75 kg or more ethambutol: 25 mg/kg of body weight/day Chemotherapy was administered on an outpatient or inpatient basis according to the usual practice of the physician
Comparison	*9-month regimen* $2EHR_7/7HR_7$ isoniazid, rifampicin and ethambutol daily for 2 months isoniazid and rifampicin daily for a further 7 months Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg ethambutol: 25 mg/kg of body weight/day Chemotherapy was administered on an outpatient or inpatient basis according to the usual practice of the physician
Location	UK

Bibliographic reference	British Thoracic Society (1984) A controlled trial of 6 months' chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. British Journal of Diseases of the Chest 78: 330-6
Length of follow up	Minimum of 3 years after treatment completion
Outcomes measures and effect size	**Relapse** Defined primarily in bacteriological terms as the occurrence of 2 or more positive cultures in any period of 4 months after treatment completion in specimens taken at least 2 weeks apart, though radiographic relapses were also considered The following were not considered to be indicative relapse: isolated positive culture – a culture that was preceded and followed by several successive negative cultures smear positive, but culture negative Number of participants to experience bacteriological or radiographic recurrence 6-month regimens = 6 of 287 9-month regimen = 2 of 157 OR[4] (95% CI) = 1.65 (0.33 to 8.30) i.e. not statistically significant
Bibliographic reference	British Thoracic Society (1982) A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: results during the 24 months after the end of chemotherapy. American Review of Respiratory Disease 126: 460-2
Length of follow up	24 months after treatment completion
Outcomes measures and effect size	**Adverse events - hepatotoxicity** Number of participants to experience hepatotoxicity 6-month regimens = 14 of 287

	9-month regimen = 7 of 157 OR[4] (95% CI) = 1.10 (0.43 to 2.78) i.e. not statistically significant
	Adverse events - rash Number of participants to experience rash 6-month regimens = 13 of 287 9-month regimen = 1 of 157 OR[4] (95% CI) = 7.40 (0.96 to 57.12) i.e. not statistically significant
	Adverse events - arthralgia Number of participants to experience arthralgia 6-month regimens = 2 of 287 9-month regimen = 0 of 157 OR[4] (95% CI) = 2.76 (0.13 to 57.82) i.e. not statistically significant
Bibliographic reference	British Thoracic Society (1981) A controlled trial of six months chemotherapy in pulmonary tuberculosis. First report: results during chemotherapy. British Journal of Diseases of the Chest 75: 141-53
Length of follow up	Full treatment period
Outcomes measures and effect size	**Response to treatment – culture-negative at 6 months** Number of participants to be culture-negative at 6 months 6-month regimens = 287 of 287

	9-month regimen = 157 of 157 OR[4] (95% CI) = 1.83 (0.04 to 92.44) i.e. not statistically significant
	Adverse events – requiring modification or withdrawal of chemotherapy Number of participants to experience adverse reactions to 1 or more drugs leading to modification or withdrawal of chemotherapy 6-month regimens = 19 of 344 9-month regimen = 7 of 177 OR[4] (95% CI) = 1.42 (0.59 to 3.44) i.e. not statistically significant
	Adherence – treatment default Number of participants to default before treatment completion 6-month regimens = 11 of 344 9-month regimen = 4 of 177 OR[4] (95% CI) = 1.43 (0.45 to 4.55) i.e. not statistically significant
	Adherence – isoniazid metabolites in urine Patients' urine was examined monthly for isoniazid metabolites; the results for the first 5 months for the 6-month groups and first 8 months for the 9-month group were analysed because at the time of collection of the last monthly specimen some patients had already stopped their drugs Number of urine samples that were positive for isoniazid metabolites 6-month regimens = 1334 of 1379

	9-month regimen = 1128 of 1166 OR[4] (95% CI) = 1.00 (0.64 to 1.55) i.e. not statistically significant Authors' interpretation: the majority of patients took their drugs as prescribed
Source of funding	British Medical Research Council
Comments	Intervention does not exactly match the intervention of interest: varies by more than duration (different combinations in each arm) does not use the 4 standard recommended drugs: 1 of the 6-month arms uses streptomycin instead of ethambutol, 9-month arm is missing pyrazinamide

[1] 2SHRZ/4HR = 170; 2EHRZ/4HR = 164

[2] 2SHRZ/4HR = 146; 2EHRZ/4HR = 141

[3] 2SHRZ/4HR = 119; 2EHRZ/4HR = 127

[4] Data for the 6-month groups (2SHRZ/4HR and 2EHRZ/4HR) have been combined into a pooled odds ratio and 95% confidence intervals by the reviewer

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

1.3.3 Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1979/84

Study type	RCT
Study quality	Population does not exactly match the population of interest: children also included (for more details, see 'patient characteristics' below) some cases were drug resistant at baseline (4.1%) Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol

	Randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for treatment completion and availability of outcome data, though rate of attrition was high in both groups Did not follow the intent-to-treat principle
Number of patients	Admitted = 610[1] 2-month group = 303 3-month group = 307 Data available for (patients with one or more of their initial cultures positive) = 139[2] 2-month group = 71 3-month group = 68 Data available for (patients with all cultures initially negative) = 322[3] 2-month group = 161 3-month group = 161 Data available for (all patients) = 603[1,3] 2-month group = 299 3-month group = 304
Patient characteristics	*Inclusion* Symptomatic pulmonary tuberculosis Radiographically active

	Sputum-smear-negative on at least 5 pretreatment samples in the course of 1 week Aged 15-75 years *Exclusion* Patients whose lesions were considered to be fibrotic and inactive Previous anti-tuberculosis treatment
Intervention	*2-month regimen* $2SHRZ_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months Dosing: isoniazid: 300 mg daily rifampicin: 450 mg daily streptomycin: 750 mg daily pyrazinamide: 1500 mg daily, or 2000 mg daily for patients weighing 50 kg or more All treatment was directly supervised by outpatient clinic or hospital staff
Comparison	*3-month regimen* $3SHRZ_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 3 months Dosing: isoniazid: 300 mg daily rifampicin: 450 mg daily streptomycin: 750 mg daily

	pyrazinamide: 1500 mg daily, or 2000 mg daily for patients weighing 50 kg or more All treatment was directly supervised by outpatient clinic or hospital staff
Location	Hong Kong / UK
Bibliographic reference	Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council (1984) A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. American Review of Respiratory Diseases 130: 23-8
Length of follow up	60 months after treatment initiation
Outcomes measures and effect size	**Response to treatment – negative culture at the end of chemotherapy** Number of smear negative patients to have a negative culture at the end of chemotherapy[3] 2-month group = 303 of 303 3-month group = 307 of 307 OR[4] (95% CI) = 0.98 (0.02 to 49.90) i.e. not statistically significant Number of smear negative patients with 1 or more initial positive culture[2] to have a negative culture at the end of chemotherapy 2-month group = 71 of 71 3-month group = 68 of 68 OR[4] (95% CI) = 1.04 (0.02 to 53.35) i.e. not statistically significant Number of smear negative patients with all cultures initially negative[3] to have a negative culture at the end of chemotherapy 2-month group = 161 of 161 3-month group = 161 of 161

	OR[4] (95% CI) = 1.00 (0.02 to 50.71) i.e. not statistically significant
	Relapse Defined as culture yield of 10 or more colonies in 2 different methods in any 3-month period during monthly follow-up or in any 6-month period during 3-monthly follow-up, or 3 or more positive cultures of any growth at different months during any 6-month period; patients with a single positive culture followed immediately by retreatment or default were also classified as bacteriologic relapses Radiographic or clinical deterioration, confirmed by an independent assessor, whether or not this was later confirmed by 1 or more cultures, was also accepted as evidence of relapse Number of smear negative patients to experience relapse[3] 2-month group = 45 of 303 3-month group = 21 of 307 **OR[4] (95% CI) = 2.38 (1.38 to 4.10)** **i.e. statistically significant** Number of smear negative patients to experience bacteriologically confirmed relapse[3] 2-month group = 30 of 303 3-month group = 13 of 307 **OR[4] (95% CI) = 2.49 (1.27 to 4.86)** **i.e. statistically significant** Number of smear negative patients with 1 or more initial positive culture[2] to experience relapse 2-month group = 23 of 71 3-month group = 9 of 68 **OR[4] (95% CI) = 3.14 (1.33 to 7.42)**

	i.e. statistically significant Number of smear negative patients with 1 or more initial positive culture[2] to experience bacteriologically confirmed relapse 2-month group = 16 of 71 3-month group = 7 of 68 OR[4] (95% CI) = 2.54 (0.97 to 6.62) i.e. not statistically significant Number of smear negative patients with all cultures initially negative[3] to experience relapse 2-month group = 17 of 161 3-month group = 11 of 161 OR[4] (95% CI) = 1.61 (0.73 to 3.55) i.e. not statistically significant Number of smear negative patients with all cultures initially negative[3] to experience bacteriologically confirmed relapse 2-month group = 10 of 161 3-month group = 5 of 161 OR[4] (95% CI) = 2.07 (0.69 to 6.19) i.e. not statistically significant
Bibliographic reference	Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council (1979) Sputum-smear-negative pulmonary tuberculosis. Controlled trial of 3-month and 2-month regimens of chemotherapy: first report. Lancet i: 1361-3
Length of follow up	Full treatment period
Outcomes	**Adverse events – any**

measures and effect size	Number of smear negative patients[3] to experience any adverse reaction 2-month group = 76 of 303 3-month group = 98 of 307 OR[4] (95% CI) = 0.71 (0.50 to 1.02) i.e. not statistically significant note: most adverse reactions were reported by the authors to be "trivial or mild cutaneous, vestibular or gastrointestinal episodes"
	Adverse events – requiring withdrawal of one or more drug Number of smear negative patients[3] to experience any adverse reaction requiring the withdrawal of one or more drug 2-month group = 6 of 303 3-month group = 9 of 307 OR[4] (95% CI) = 0.67 (0.24 to 1.90) i.e. not statistically significant
Source of funding	No details given
Comments	Population does not exactly match the population of interest: children also included some cases were drug resistant at baseline (4.1%) Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol

[1] Data not extracted for the 'selective chemotherapy' or 12 month ($3SPH_7/9SH_2$) groups as they both used regimens containing PAS, a drug not licensed for use in the UK

[2] Extracted only data for those with drug susceptible tuberculosis

[3] This population may include both drug susceptible and drug resistant cases

[4] Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; P or PAS, sodium p-aminosalicylate; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide

1.3.4 Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989

Bibliographic reference	Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council (1989) A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. American Review of Respiratory Diseases 139: 871-6
Study type	RCT
Study quality	Population does not exactly match the population of interest: may be some children included (inclusion criteria = ages 15 to 75 years) may be some drug resistant cases amongst the culture negative patients some possibly 'inactive' tuberculosis at baseline Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol Randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Unclear of groups were comparable for treatment completion and availability of outcome data Did not follow the intent-to-treat principle
Number of patients	Admitted = 2020 Analysed = 1692[1] 3-month regimens = 759[2] 4-month regimens = 743[2]

	6-month regimen = 190 Patients with one or more of their initial cultures positive that were drug susceptible = 502 4-month regimens = 325[2] 6-month regimen = 177 Patients with all cultures initially negative = 1118[3] 3-month regimens = 759[2] 4-month regimen = 359
Patient characteristics	*Inclusion* Presented at chest clinic with respiratory symptoms Radiographically active Sputum-smear-negative on at least 5 pretreatment samples in the course of 1 week Aged 15-75 years At the time of entry, all had had at least 4 negative sputum smear examinations and one or more radiographic assessments, and 4 pretreatment culture results *Exclusion* Patients whose lesions were considered to be fibrotic and inactive Previous anti-tuberculosis treatment
Intervention 1	*3-month regimens* $3SHRZ_7$ only patients with all cultures initially negative isoniazid, rifampicin, streptomycin and pyrazinamide daily for 3 months

	$3SHRZ_3$ only patients with all cultures initially negative isoniazid, rifampicin, streptomycin and pyrazinamide thrice-weekly for 3 months Dosing: isoniazid: 300 mg rifampicin: 450 mg, or 600 mg for patients weighing 50 kg or more streptomycin: 750 mg pyrazinamide: 1500 mg, or 2000 mg for patients weighing 50 kg or more All treatment was directly supervised by outpatient clinic or hospital staff
Intervention 2	*4-month regimens* $4SHRZ_7$ patients with all cultures initially negative *or* patients with one or more of their initial cultures positive isoniazid, rifampicin, streptomycin and pyrazinamide daily for 4 months $4SHRZ_3$ only patients with one or more of their initial cultures positive isoniazid, rifampicin, streptomycin and pyrazinamide thrice-weekly for 4 months Dosing: isoniazid: 300 mg rifampicin: 450 mg, or 600 mg for patients weighing 50 kg or more streptomycin: 750 mg pyrazinamide: 1500 mg, or 2000 mg for patients weighing 50 kg or more

	All treatment was directly supervised by outpatient clinic or hospital staff
Comparison	*6-month regimen* 6SHRZ$_3$ only patients with one or more of their initial cultures positive isoniazid, rifampicin, streptomycin and pyrazinamide thrice-weekly for 6 months Dosing: isoniazid: 300 mg rifampicin: 450 mg, or 600 mg for patients weighing 50 kg or more streptomycin: 750 mg pyrazinamide: 1500 mg, or 2000 mg for patients weighing 50 kg or more All treatment was directly supervised by outpatient clinic or hospital staff
Location	Hong Kong / UK
Length of follow up	5 years after treatment initiation
Outcomes measures and effect size	**Response to treatment – negative culture at the end of chemotherapy** Number of participants to have a negative culture at the end of chemotherapy[1] 3-month regimens = 759 of 759[2] 4-month regimens = 743 of 743[2] 6-month regimen = 190 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 2.02 (0.04 to 101.95) i.e. not statistically significant

	Number of participants with 1 or more initial positive culture[2] to have a negative culture at the end of chemotherapy 4-month group = 325 of 325 6-month group = 177 of 177 OR[5] (95% CI) = 1.83 (0.04 to 92.82) i.e. not statistically significant Number of participants with all cultures initially negative[3] to have a negative culture at the end of chemotherapy 3-month group = 759 of 759 4-month group = 359 of 359 OR[5] (95% CI) = 2.11 (0.04 to 106.69) i.e. not statistically significant
	Relapse Number of participants to experience relapse[3] 3-month regimens = 48 of 759[2] 4-month regimens = 24 of 743[2] 6-month regimen = 10 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 0.91 (0.46 to 1.79) i.e. not statistically significant Number of participants to experience bacteriologically confirmed relapse[3] 3-month regimens = 20 of 759[2] 4-month regimens = 12 of 743[2]

	6-month regimen = 4 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 1.01 (0.35 to 2.89) i.e. not statistically significant Number of participants with 1 or more initial positive culture[2] to experience relapse 4-month group = 7 of 325 6-month group = 8 of 177 OR[5] (95% CI) = 0.47 (0.17 to 1.30) i.e. not statistically significant Number of participants with 1 or more initial positive culture[2] to experience bacteriologically confirmed relapse 4-month group = 5 of 325 6-month group = 3 of 177 OR[5] (95% CI) = 0.90 (0.21 to 3.84) i.e. not statistically significant Number of participants with all cultures initially negative[3] to experience relapse 3-month group = 48 of 759 4-month group = 12 of 359 **OR[5] (95% CI) = 1.95 (1.02 to 3.72)** **i.e. statistically significant** Number of participants with all cultures initially negative[3] to experience bacteriologically confirmed relapse 3-month group = 20 of 759

	4-month group = 4 of 359 OR[5] (95% CI) = 2.40 (0.81 to 7.08) i.e. not statistically significant
	Adverse events – any Number of participants[3] to experience any adverse reaction 3-month regimens = 212 of 759[2] 4-month regimens = 250 of 743[2] 6-month regimen = 81 of 190 <6 months[4] vs 6 months: **OR[5] (95% CI) = 0.60 (0.44 to 0.81)** **i.e. statistically significant**
	Adverse events – requiring withdrawal of one or more drug Number of participants[3] to experience any adverse reaction requiring the withdrawal of one or more drug 3-month regimens = 37 of 759[2] 4-month regimens = 34 of 743[2] 6-month regimen = 6 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 1.52 (0.65 to 3.55) i.e. not statistically significant
	Adverse events – requiring temporary interruption of treatment Number of participants[3] to experience any adverse reaction requiring temporary interruption of treatment

	3-month regimens = 74 of 759[2] 4-month regimens = 79 of 743[2] 6-month regimen = 25 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 0.75 (0.48 to 1.18) i.e. not statistically significant
	Adverse events – cutaneous reactions Number of participants[3] to experience a cutaneous reaction requiring temporary interruption of treatment or withdrawal of one or more drug 3-month regimens = 53 of 759[2] 4-month regimens = 57 of 743[2] 6-month regimen = 16 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 0.86 (0.50 to 1.49) i.e. not statistically significant
	Adverse events – gastrointestinal reactions Number of participants[3] to experience a gastrointestinal reaction requiring temporary interruption of treatment or withdrawal of one or more drug 3-month regimens = 45 of 759[2] 4-month regimens = 42 of 743[2] 6-month regimen = 20 of 190 <6 months[4] vs 6 months:

	OR[5] (95% CI) = 0.52 (0.31 to 0.87) **i.e. statistically significant**
	Adverse events – vestibular reactions Number of participants[3] to experience a vestibular reaction requiring temporary interruption of treatment or withdrawal of one or more drug 3-month regimens = 35 of 759[2] 4-month regimens = 34 of 743[2] 6-month regimen = 7 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 1.26 (0.57 to 2.78) i.e. not statistically significant
	Adverse events – hepatic reactions Number of participants[3] to experience a hepatic reaction requiring temporary interruption of treatment or withdrawal of one or more drug 3-month regimens = 12 of 759[2] 4-month regimens = 6 of 743[2] 6-month regimen = 0 of 190 <6 months[4] vs 6 months: OR[5] (95% CI) = 4.75 (0.29 to 79.11) i.e. not statistically significant
Source of funding	No details given
Comments	Population does not exactly match the population of interest:

	may be some children included (inclusion criteria = ages 15 to 75 years) may be some drug resistant cases amongst the culture negative patients some possibly 'inactive' tuberculosis at baseline Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol

[1] Includes some drug resistant tuberculosis

[2] Data for regimens of the same duration were pooled by the author

[3] Population may include both drug susceptible and drug resistant cases

[4] Reviewer pooled the 3- and 4- month arms to produce a comparison of 6 months to less than 6 months of treatment

[5] Odds ratio and 95% confidence intervals calculated by reviewer

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

1.3.5 Mehotra, 1982

Bibliographic reference	Mehotra ML (1982) Agra study of short-course chemotherapy in pulmonary tuberculosis patients. Indian Journal of Tuberculosis 29(1): 29-39
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: interventions contain streptomycin but lack ethambutol Method of randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were statistically comparable for treatment completion and availability of outcome data, however there was a higher number who did not complete treatment and for whom data was not available amongst the 3-month group

	(36%) than the 4.5-month group (24%)
Number of patients	Randomised = 180[1] 3-month regimen = 91 4.5-month regimen = 89 Completed treatment = 126 3-month regimen = 58 4.5-month regimen = 68
Patient characteristics	*Inclusion* Pulmonary tuberculosis – microscopy positive for acid-fast bacilli at the time of admission, and later confirmed by positive culture of the same specimen Aged 12 years or more Resident of Agra city Availability for 2 years of follow-up after the cessation of treatment *Exclusion* Previous treatment for pulmonary tuberculosis, or having received more than 15 days of antituberculosis therapy Concomitant disease that might complicate management of the disease Pregnancy *Baseline characteristics* Patients were comparable in respect of age, sex, extent of disease, and bacillary content of the sputum
Intervention	*3-month regimen* $3RSZH_6$ isoniazid, rifampicin, streptomycin and pyrazinamide 6 days/week for 3 months

	Dosing: isoniazid: 5–8 mg/kg of body weight/day rifampin: 10 mg/kg of body weight/day streptomycin: 750 mg/day pyrazinamide: 25–35 mg/kg of body weight/day Modification of doses - in special circumstances, drug dosages were modified so that fractions of tablets did not have to be given; for example, in patients of low weight (<35 kg): isoniazid: 200 mg/day rifampin: 300 mg/day pyrazinamide: 10 g/day streptomycin: 500mg/day until the patient achieved a weight of 36 kg All treatment was directly supervised and ambulatory After treatment completion and during follow-up, patients received placebo tablets of calcium lactate
Comparison	*4.5-month regimen* $3RSZH_6/1.5RH_6$ isoniazid, rifampicin, streptomycin and pyrazinamide 6 days/week for 3 months isoniazid and rifampicin 6 days/week for 1.5 months Dosing: isoniazid: 5–8 mg/kg of body weight/day rifampin: 10 mg/kg of body weight/day

	streptomycin: 750 mg/day pyrazinamide: 25–35 mg/kg of body weight/day Modification of doses - in special circumstances, drug dosages were modified so that fractions of tablets did not have to be given; for example, in patients of low weight (<35 kg): isoniazid: 200 mg/day rifampin: 300 mg/day pyrazinamide: 10 g/day streptomycin: 500mg/day until the patient achieved a weight of 36 kg All treatment was directly supervised and ambulatory After treatment completion and during follow-up, patients received placebo tablets of calcium lactate
Location	India
Length of follow up	1 year after treatment completion
Outcomes measures and effect size	**Response to treatment – culture conversion** Number of patients to be culture-negative after 3 months of chemotherapy 3-month regimen = 58 of 58 4.5-month regimen = 68 of 68 OR[2] (95% CI) = 0.85 (0.02 to 43.72) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.54 (0.28 to 1.04)

	i.e. not statistically significant
	Changes in signs and symptoms – radiographic status Number of patients to experience deterioration in radiographic appearance 6 months after treatment initiation 3-month regimen = 0 of 55 4.5-month regimen = 0 of 64 OR[2] (95% CI) = 1.16 (0.02 to 59.54) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.98 (0.02 to 49.83) i.e. not statistically significant Number of patients to experience no change in radiographic appearance 6 months after treatment initiation 3-month regimen = 0 of 55 4.5-month regimen = 1 of 64 OR[2] (95% CI) = 0.38 (0.02 to 9.55) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.32 (0.01 to 8.02) i.e. not statistically significant Number of patients to experience moderate regression in radiographic appearance 6 months after treatment initiation 3-month regimen = 31 of 55 4.5-month regimen = 39 of 64

	OR[2] (95% CI) = 0.83 (0.40 to 1.72) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.66 (0.36 to 1.21) i.e. not statistically significant Number of patients to experience marked regression in radiographic appearance 6 months after treatment initiation 3-month regimen = 24 of 55 4.5-month regimen = 24 of 64 OR[2] (95% CI) = 1.29 (0.62 to 2.69) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.97 (0.50 to 1.88) i.e. not statistically significant Number of patients to experience marked regression in radiographic appearance 12 months after treatment initiation 3-month regimen = 19 of 35 4.5-month regimen = 15 of 27 OR[2] (95% CI) = 0.95 (0.35 to 2.61) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 1.30 (0.61 to 2.76) i.e. not statistically significant

	Number of patients to experience marked regression in radiographic appearance 18 months after treatment initiation 3-month regimen = 20 of 35 4.5-month regimen = 16 of 27 OR[2] (95% CI) = 0.92 (0.33 to 2.54) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 1.29 (0.62 to 2.68) i.e. not statistically significant
	Relapse Defined as culture reversal observed for 4 consecutive months with radiographic lesions showing deterioration after the successful completion of prescribed chemotherapy (administration of more than 90% of prescribed chemotherapy, along with negative cultures and radiographic lesions showing no deterioration at the time of cessation of prescribed chemotherapy) Number of patients to experience relapse 3-month regimen = 1 of 40 4.5-month regimen = 1 of 34 OR[2] (95% CI) = 0.85 (0.05 to 14.06) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 0.98 (0.06 to 15.88) i.e. not statistically significant
	Adverse events – requiring treatment interruption

	Criteria used to identify drug toxicity were extreme intolerance, challenge, and clinical observation of toxic reactions Number of patients to experience adverse events requiring treatment interruption 3-month regimen = 5 of 71 4.5-month regimen = 2 of 68 OR[2] (95% CI) = 2.50 (0.47 to 13.35) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 2.53 (0.48 to 13.39) i.e. not statistically significant
	Adherence – treatment default Defined as patients who took less than 90% of the allocated chemotherapy; according to this definition, interruption of treatment for more than 10 days of a 4.5 month regimen and more than 7 days of a 3 month regimen was treated as a default Number of patients to default 3-month regimen = 8 of 71 4.5-month regimen = 7 of 68 OR[2] (95% CI) = 1.11 (0.38 to 3.24) i.e. not statistically significant *Intent-to-treat analysis*[3] OR[2] (95% CI) = 1.13 (0.39 to 3.26) i.e. not statistically significant
Source of funding	Pfizer Limited, India, supplied the placebo tablets

Comments	Intervention does not exactly match the intervention of interest: interventions contain streptomycin but lack ethambutol

[1] Regimens that did not contain rifampicin throughout (3RSZH/1.5SHZ) or that contained ethionamide (3RSZHE^{ide} $_{and}$ 3RSZHE^{ide}/1.5RH), which is not licensed for use in the UK, were not extracted by the reviewer

[2] Odds ratio and 95% confidence intervals calculated by reviewer

[3] Intent-to-treat analysis performed by reviewer using the number of patients randomised to each regimen: 91 in the 3-month group, 89 in the 4.5-month group

Abbreviations: CI, confidence interval; E^{ide}, ethionamide; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide

1.3.6 Nayar et al, 1988

Bibliographic reference	Nayar S, Narang P, Tvagi NK et al (1988) Field trial of short term intermittent chemotherapy of patients with pulmonary tuberculosis in Wardha district. Indian Journal of Tuberculosis 35: 1760
Study type	RCT (field study)
Study quality	Age of participants is not clear Interventions do not use the 4 standard recommended drugs: the regimens are missing ethambutol Doses used are inconsistent with those listed in the British National Formulary – isoniazid and pyrazinamide doses are higher than recommended, although the doses are only given twice per week Randomisation, allocation concealment and blinding were unclear Unclear if groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for treatment completion and availability of outcome data Did not follow the intent-to-treat principle Relapse was the only outcome that could be extracted because the authors reported all other outcomes such that the

	6-month data consisted of those on the 6-month regimens plus the data for those randomised to the 8-month regimens after 6 months of treatment
Number of patients	Eligible for intake = 381[1] Available for assessment = 206 6-month regimen = 98 8-month regimen = 108
Patient characteristics	*Inclusion* Symptomatic pulmonary tuberculosis - identified during door-to-door survey *Diagnostic criteria* Individuals were asked to provide samples of sputum, one spot and other overnight collection; whenever spot sample was not available, two overnight samples were collected Samples were subjected to direct microscopy by Ziehl Neelson's method and cultured on Lowenstein Jensen medium For analysis, symptomatics positive by culture only were considered as bacillary-positive cases Those culture-negative at one examination but positive subsequently were categorised as positive
Intervention	*6-month regimen* $2HRZ_2/4HR_2$ for participants in rural areas isoniazid, rifampicin and pyrazinamide twice-weekly for 2 months isoniazid and rifampicin twice-weekly for a further 4 months Dosing: isoniazid: 600 mg/day rifampicin: 600 mg/day

	pyrazinamide: 3000 mg/day Patients were supplied with their quota of drugs every month at their door step and how to take the doses was fully explained
Comparison	*8-month regimen* $2HRZ_2/6HR_2$ for participants in rural areas isoniazid, rifampicin and pyrazinamide twice-weekly for 2 months isoniazid and rifampicin twice-weekly for a further 6 months Dosing: isoniazid: 600 mg/day rifampicin: 600 mg/day pyrazinamide: 3000 mg/day Patients were supplied with their quota of drugs every month at their door step and how to take the doses was fully explained
Length of follow up	12 months after treatment completion
Location	India
Outcomes measures and effect size	**Relapse** Defined as patients becoming culture positive one month after stopping the treatment Number of participants to experience recurrence 6-month regimens = 1 of 97 8-month regimen = 3 of 96 OR^2 (95% CI) = 0.32 (0.03 to 3.16)

	i.e. not statistically significant
Source of funding	Indian Council of Medical Research
Comments	Age of participants is not clear Interventions do not use the 4 standard recommended drugs: the regimens are missing ethambutol

[1] Reviewer has extracted data only for the arms that contain rifampicin throughout; the 2 arms (1 6-month and 1 8-month) that do not contain rifampicin throughout are included in the supplementary evidence below

[2] Odds ratio and 95% confidence intervals have been calculated by the reviewer

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

1.3.7 Perriens et al, 1995

Bibliographic reference	Perriens JH, St Louis ME, Mukadi YB et al (1995) Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. New England Journal of Medicine 332(12): 779-84
Study type	RCT
Study quality	Intervention used is in line with the standard recommended regimen, but patients are not receiving ART; therefore the co-treatment regimen doesn't match UK practice Method of randomisation and allocation concealment unclear Randomisation occurs after 6 months of treatment (i.e. randomisation determines which patients continue with isoniazid and rifampicin, and which commence a 6-month placebo phase) Only participants were blinded Groups were statistically comparable at the baseline, although the median CD4+ count was higher in the 12-month group (413 vs 338 cells/mm^3) Groups received the same care apart from the interventions studied Groups were comparable for treatment completion and availability of outcome data

<table>
<tr><td></td><td>Time at which follow-up initiated not methodologically sound for the measurement of relapse: measurement initiated after 6 months of treatment; therefore measurement of relapse in 12-month group appears to be initiated before treatment completion</td></tr>
<tr><td>Number of patients</td><td>Randomised = 247
6-month regimen = 123
12-month regimen = 124
Relapse data available = 240
6-month regimen = 121
12-month regimen = 119</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
HIV-seropositive patients
First episode of smear- and culture-positive pulmonary tuberculosis
Baseline characteristics
<table>
<tr><th></th><th>6-month regimen</th><th>12-month regimen</th></tr>
<tr><td>Male sex – no. (%)</td><td>52 (43.0)</td><td>45 (37.8)</td></tr>
<tr><td>Mean (± SD) age – years</td><td>31.7±7.2</td><td>29.8±6.5</td></tr>
<tr><td>Median CD4+ count at the start of treatment – cells/mm^3</td><td>413</td><td>338</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>6-month regimen
2HRZE$_7$/4HR$_7$/6placebo
isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months</td></tr>
</table>

	isoniazid and rifampicin twice-weekly for a further 4 months placebo for the final 6 months Dosing: initial phase: combination tablets (120 mg rifampicin, 50 mg isoniazid and 300 mg pyrazinamide per tablet): 1 tablet/10 kg of body weight/day ethambutol: 3 400 mg tablets/day, or 2 if the body weight was less than 50 kg continuation phase: rifampicin: 600 mg/day, or 450 mg/day if the body weight was less than 50 kg isoniazid: 15 mg/kg of body weight/day Observed directly daily, except on Sundays, in the initial phase; during the continuation phase, therapy was only observed once out of the two weekly doses No patients received ART at any time during the study
Comparison	*12-month regimen* $2HRZE_7/10HR_7$ isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months isoniazid and rifampicin twice-weekly for a further 10 months Dosing: initial phase: combination tablets (120 mg rifampicin, 50 mg isoniazid and 300 mg pyrazinamide per tablet): 1 tablet/10 kg of body weight/day ethambutol: 3 400 mg tablets/day, or 2 if the body weight was less than 50 kg

	continuation phase: rifampicin: 600 mg/day, or 450 mg/day if the body weight was less than 50 kg isoniazid: 15 mg/kg of body weight/day Observed directly daily, except on Sundays, in the initial phase; during the continuation phase, therapy was only observed once out of the two weekly doses No patients received ART at any time during the study
Length of follow up	24 months after treatment initiation
Location	Zaire
Outcomes measures and effect size	**Mortality** Number of patients to die from tuberculosis 6-month regimen = 1 of 123 12-month regimen = 0 of 124 OR[1] (95% CI) = 3.05 (0.12 to 75.58) i.e. not statistically significant
	Relapse Number of patients to experience relapse 6-month regimen = 1 of 123 12-month regimen = 9 of 124 **OR[1] (95% CI) = 0.10 (0.01 to 0.84)** **i.e. statistically significant**
Source of funding	Supported by Projet SIDA, with contributions from the Centers for Disease Control and Prevention, the National Institute of Allergy and Infectious Diseases, the Armed Forces Institute of Pathology (Washington DC), and the Agency

	for Development and Cooperation (Brussels), as well as additional contributions from the Marion Merrell Dow Research Institute and the Belgolaise Bank (Brussels)
Comments	Intervention used is in line with the standard recommended regimen, but patients are not receiving ART; therefore the co-treatment regimen doesn't match UK practice
[1] Odds ratio and 95% confidence intervals have been calculated by the reviewer Abbreviations: ART, antiretroviral treatment; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide	

1.3.8 Research Committee of the Tuberculosis Association of India, 1984

Bibliographic reference	Research Committee of the Tuberculosis Association of India (1984) Short-course chemotherapy of pulmonary tuberculosis – second Tuberculosis Association of India trial. Indian Journal of Tuberculosis 31(9): 81-8
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: some regimens contain streptomycin, and all regimens lack ethambutol doses used are inconsistent with those listed in the British National Formulary – isoniazid dose is higher than recommended Method of randomisation, allocation concealment and blinding were unclear Unclear if groups were comparable at the baseline Groups received the same care apart from the interventions studied Unclear of groups were comparable for treatment completion and availability of outcome data Did not follow the intent-to-treat principle
Number of patients	Total cases 'inducted' = 175[1] Smear-negative patients for whom data is available at treatment completion = 126 3-month regimens = 56[2]

	6-month regimens = 70[3] Smear-negative patients for whom data is available after 104 weeks of follow-up = 102 3-month regimens = 52[4] 6-month regimens = 50[5]
Patient characteristics	*Inclusion* Pulmonary tuberculosis sputum must have been positive for acid-fast bacilli at least twice by direct smear to gain entry to study after 8 weeks of treatment, those who were sputum-negative by direct smear were randomized to one of the 4 regimens Aged 15 to 45 years Resident in New Delhi, with a reasonable chance of continuing to stay in the city during the follow-up period No previous antituberculosis treatment, or less than 10 days Willing for injection or any other treatment which is prescribed for them *Exclusion* Extent of disease more than 3 lung zones Patients having pleural effusion obscuring more than a third of the lung field Initial drug resistance Patients suffering from any tuberculous or non-tuberculous complications (e.g. diabetes, extrapulmonary tuberculosis etc) likely to interfere with the management of the disease Moribund patients Pregnancy at the start of the study Patients whose weight is less than 35 kg

Intervention	*3-month regimens* 2HRZ/1HR/3pla isoniazid, rifampicin and pyrazinamide daily for 8 weeks isoniazid and rifampicin daily for 4 weeks followed by placebo for 14 weeks 2HRZS/1HR/3pla isoniazid, rifampicin, streptomycin and pyrazinamide daily for 8 weeks isoniazid and rifampicin daily for 4 weeks followed by placebo for 14 weeks Dosing: isoniazid: 400 mg/day rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg streptomycin: 750 mg/day pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg All patients were hospitalised during treatment Treatment was fully supervised
Comparison	*6-month regimens* 2HRZ/4HR isoniazid, rifampicin and pyrazinamide daily for 8 weeks isoniazid and rifampicin daily for 18 weeks 2HRZS/4HR isoniazid, rifampicin, streptomycin and pyrazinamide daily for 8 weeks isoniazid and rifampicin daily for 18 weeks

	Dosing: isoniazid: 400 mg/day rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg streptomycin: 750 mg/day pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg All patients were hospitalised during treatment Treatment was fully supervised
Location	India
Length of follow up	104 weeks after treatment initiation
Outcomes measures and effect size	**Response to treatment – sputum conversion at the end of chemotherapy** Number of smear-negative patients to undergo sputum conversion by the end of chemotherapy 3-month regimens = 56 of 56[6] 6-month regimens = 70 of 70[6] OR[7] (95% CI) = 0.80 (0.02 to 41.03) i.e. not statistically significant
	Response to treatment – radiological change at the end of chemotherapy Number of smear-negative patients to show 'marked' radiological improvement by the end of chemotherapy 3-month regimens = 39 of 56[6] 6-month regimens = 57 of 70[6] OR[7] (95% CI) = 0.52 (0.23 to 1.20) i.e. not statistically significant

	Number of smear-negative patients to show 'slight' radiological improvement by the end of chemotherapy 3-month regimens = 9 of 56[6] 6-month regimens = 9 of 70[6] OR[7] (95% CI) = 1.30 (0.48 to 3.53) i.e. not statistically significant Number of smear-negative patients to show no radiological change by the end of chemotherapy 3-month regimens = 2 of 56[6] 6-month regimens = 4 of 70[6] OR[7] (95% CI) = 0.61 (0.11 to 3.46) i.e. not statistically significant Number of smear-negative patients to show worsening in their radiological status by the end of chemotherapy 3-month regimens = 6 of 56[6] 6-month regimens = 0 of 70[6] OR[7] (95% CI) = 18.15 (0.9995 to 329.54) i.e. not statistically significant
	Relapse Number of smear-negative patients to experience bacteriological relapse during follow-up 3-month regimens = 12 of 56[6] 6-month regimens = 1 of 70[6] **OR[7] (95% CI) = 18.82 (2.36 to 149.85)** **i.e. statistically significant**

Source of funding	Lepetit Laboratories, Italy, and Ranbaxy Laboratories, Delhi, supplied the rifampicin Brocco Industries, Italy, supplied the pyrazinamide
Comments	Intervention does not exactly match the intervention of interest: some regimens contain streptomycin, and all regimens lack ethambutol

[1] Includes both smear-positive and smear-negative patients; however, since smear-positive only received the 6-month regimens data for this population was excluded from the analysis

[2] 2HRZ/1HR/3pla = 29; 2HRZS/1HR/3pla = 27

[3] 2HRZ/4HR = 37; 2HRZS/4HR = 33

[4] 2HRZ/1HR/3pla = 22; 2HRZS/1HR/3pla = 30

[5] 2HRZ/4HR = 25; 2HRZS/4HR = 25

[6] Data for regimens of the same duration were pooled by the reviewer

[7] Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; pla, placebo; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide

1.3.9 Singapore Tuberculosis Service / British Medical Research Council, 1979/86

Study type	RCT
Study quality	Population does not exactly match the population of interest: some children may also have been included some cases were drug resistant; data for these were not extracted by the reviewer Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol An appropriate method of randomisation was used, and allocation concealment was performed: use of sealed, numbered envelopes provided by the coordinating centre in London (patients and investigators were in Singapore)

	Blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Unclear if groups were comparable for treatment completion Did not follow the intent-to-treat principle 'Favourable response to treatment' is a substitute for an outcome of interest (cure / treatment success), and was not clearly defined within the paper(s)
Number of patients	Randomised = 400[1] Analysed (drug susceptible only) for response to treatment = 330 4-month regimens = 161[2] 6-month regimens = 169[3] Analysed (drug susceptible only) for relapse during long-term follow-up = 269 4-month regimens = 131[4] 6-month regimens = 138[5]
Patient characteristics	*Inclusion* Aged 15 years or more Smear- and culture-positive pulmonary tuberculosis Patients of Chinese, Malay or Indian ethnic origin *Exclusion* Previous antituberculosis chemotherapy
Intervention	*4-month regimens*[7]

	$2SHRZ_7/2HR_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months $2SHRZ_7/2HRZ_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid, rifampicin and pyrazinamide daily for a further 2 months Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg on admission streptomycin: 750 mg intramuscularly pyrazinamide: 2000 mg/day, or 1500 mg/day if the patient weighed less than 50 kg on admission All patients received every dose of chemotherapy under the direct supervision of hospital or outpatient clinic staff
Comparison	*6-month regimens*[7] $2SHRZ_7/4HR_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months $2SHRZ_7/4HRZ_7$ isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid, rifampicin and pyrazinamide daily for a further 2 months Dosing: isoniazid: 300 mg/day

	rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg on admission streptomycin: 750 mg intramuscularly pyrazinamide: 2000 mg/day, or 1500 mg/day if the patient weighed less than 50 kg on admission All patients received every dose of chemotherapy under the direct supervision of hospital or outpatient clinic staff
Location	Singapore
Bibliographic reference	Singapore Tuberculosis Service / British Medical Research Council (1979) Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. American Review of Respiratory Disease 119: 579-85
Length of follow up	Full treatment period
Outcomes measures and effect size	**Response to treatment – favourable response** Number of participants whose response to chemotherapy was defined as 'favourable' at the end of treatment 4-month regimens = 161 of 161 6-month regimens = 169 of 169 OR[6] (95% CI) = 0.95 (0.02 to 48.31) i.e. not statistically significant
	Adverse events note: the authors state that "the great majority [of adverse reactions] occurred during the first 2 months [of treatment], when all patients were receiving the same 4 drugs" For this reason, the authors did not report the occurrence of adverse events separately for each duration of treatment, and the reviewer did not extract the data provided; it can also be concluded that any differences that arose in the rates of events between the groups was not due to the different durations of treatment
Bibliographic reference	Singapore Tuberculosis Service / British Medical Research Council (1986) Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. American Review of Respiratory Disease 133: 779-83

Length of follow up	5 to 8 years after treatment initiation
Outcomes measures and effect size	**Relapse** Defined as a culture growing 10 or more colonies in 2 different months during any 3-month period during follow-up Number of participants to experience relapse during follow-up 4-month regimens = 20 of 131 6-month regimens = 3 of 138 **OR[6] (95% CI) = 8.11 (2.35 to 28.00)** **i.e. statistically significant**
Source of funding	Ministry of Health, Singapore, provided a research grant and the nursing, laboratory, radiologic and auxillary staff; Ciba-Geigy and Gruppo Lepetit provided all rifampicin as a gift; Singapore Airlines provided air freight at a concessional rate
Comments	Population does not exactly match the population of interest: some children may also have been included some cases were drug resistant; data for these were not extracted by the reviewer Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol

[1] Includes both drug susceptible and drug resistant cases

[2] 2SHRZ/2HR = 81; 2SHRZ/2HRZ = 80

[3] 2SHRZ/4HR = 84; 2SHRZ/4HRZ = 85

[4] 2SHRZ/2HR = 70; 2SHRZ/2HRZ = 61

[5] 2SHRZ/4HR = 67; 2SHRZ/4HRZ = 71

[6] Odds ratio and 95% confidence intervals calculated by the reviewer

[7] Data for regimens of the same length were pooled by the reviewer

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

1.3.10 Swaminathan et al, 2010

Bibliographic reference	Swaminathan S, Narendran G, Venkatesan P et al (2010) Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomised controlled trial. American Journal of Respiratory and Critical Care Medicine 181: 743-51
Study type	RCT
Study quality	Population did not exactly match the population of interest: may be some children in the included population (inclusion criteria = 15 years or more) some extrapulmonary tuberculosis, although limited to pleural or lymph node tuberculosis some drug resistant tuberculosis Intervention used is in line with the standard recommended regimen, but patients are not receiving ART; therefore the co-treatment regimen doesn't match UK practice Doses of antituberculosis drugs used are inconsistent with those listed in the British National Formulary – isoniazid and ethambutol doses are higher than recommended Appropriate method of randomisation used: computer-generated random allocation sequence Allocation concealment principle observed: random allocation sequence was prepared by an independent statistician and were concealed in sealed, opaque envelopes and opened at a site away from the patient care facility Unblinded Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were not followed up for an equal length of time: ‘follow-up’ was timed from treatment initiation; therefore, since treatment durations were of different duration, follow-up for outcomes that were measured after treatment completion was not equal

	Groups were comparable for treatment completion and availability of outcome data Favourable response to treatment was considered a substitute outcome for cure/treatment success
Number of patients	Randomised = 334 7 exclusions due to identification of multi-drug resistant tuberculosis (n = 4), identification of *M. xenopi* (n = 1), initiation of ART (n = 2) 'Modified ITT analysis' = 327 6-month regimen = 167 9-month regimen = 160 Drug sensitive = 197 6-month regimen = 100 9-month regimen = 97 Culture positive pulmonary tuberculosis = 227 6-month regimen = 117 9-month regimen = 110 Culture negative pulmonary tuberculosis = 72 6-month regimen = 34 9-month regimen = 38
Patient characteristics	*Inclusion* HIV-infected patients who are ART-naive Symptoms and signs suggestive of tuberculosis Aged 15 years and above

Laboratory criteria

haemoglobin >7 g/l

granulocyte count >1.1 x 10^9/l

platelet count > 100 x 10^9/l

serum alanine aminotransferase concentration <2.5 times the upper limit of normal

serum creatinine concentration <1.1 mg/dl

random blood sugar <140 mg/dl

Diagnostic criteria

Tuberculin skin test

Pulmonary tuberculosis: positive sputum smear or a radiographic lesion persisting for more than 14 days after antibiotics

chest x-rays were read by a panel of 3 doctors and were based on a consensus reading

Extrapulmonary tuberculosis: diagnosed on the basis of cyto-/histopathological (for lymph node) or biochemical (for pleural effusion) parameters, with or without a positive acid-fast bacilli smear

Exclusion

Moribund condition

Pregnancy

Baseline characteristics

	6-month regimen	**9-month regimen**
Total	167	160
Median (IQR) age – years	33 (29–38)	33 (29–39)
Median (IQR) weight – kg	44 (39–50)	44 (39–50)

		Median (IQR) CD4+ count – cells/mm^3	152 (80–304)	167 (88–280)	
		CD4+ count <200 cells/mm^3 – %	63	64	
		Median viral load – copies/ml	94,300	168,000	
		Males - %	79	75	
		Mantoux ≥5 mm – %	48	53	
		Mantoux >10 mm – %	41	46	
		Pulmonary tuberculosis			
		culture positive – n	117	110	
		culture negative – n	34	38	
		Extrapulmonary tuberculosis			
		culture positive – n	4	2	
		culture negative – n	12	10	
		Drug susceptibility			
		susceptible to all first-line drugs – %	88	88	
		resistant to isoniazid alone – %	4	5	
		resistant to isoniazid and ethambutol or streptomycin – %	7	7	
		Radiographic features in sputum culture-positive pulmonary tuberculosis			
		normal – n (%)	16 (14)	13 (12)	
		parenchymal opacities – n (%)	69 (59)	70 (64)	
		pleural effusion – n (%)	17 (15)	13 (12)	

	hilar adenopathy – n (%)	29 (25)	15 (14)
	miliary tuberculosis – n (%)	7 (6)	7 (6)
	cavities – n (%)	19 (16)	20 (18)
	others – n (%)	10 (9)	7 (6)
Intervention	*6-month regimen* 2HRZE/4HR isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months isoniazid and rifampicin thrice-weekly for a further 4 months Dosing: isoniazid: 600 mg/day rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 60 kg pyrazinamide: 1500 mg/day ethambutol: 1200 mg/day Co-trimoxazole prophylaxis was given to all patients with CD4+ counts <250 cells/mm^3 Patients did not receive ART during antituberculosis chemotherapy The taking of all doses in the intensive phase was directly observed by the study staff During the continuation phase patients attended the clinic once per week, when they took the drugs under supervision; two doses were then handed over for self-administration and patients were counselled and motivated to take them regularly		
Comparison	*9-month regimen* 2HRZE/7HR		

	isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months isoniazid and rifampicin thrice-weekly for a further 7 months Dosing: isoniazid: 600 mg/day rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 60 kg pyrazinamide: 1500 mg/day ethambutol: 1200 mg/day Co-trimoxazole prophylaxis was given to all patients with CD4+ counts <250 cells/mm^3 Patients did not receive ART during antituberculosis chemotherapy The taking of all doses in the intensive phase was directly observed by the study staff During the continuation phase patients attended the clinic once per week, when they took the drugs under supervision; two doses were then handed over for self-administration and patients were counselled and motivated to take them regularly
Length of follow up	36 months after treatment initiation
Location	India
Outcomes measures and effect size	**Mortality** *'Modified ITT analysis'*[1] Number of deaths (all cause) 6-month regimen = 33 of 167 9-month regimen = 37 of 160 OR[2] (95% CI) = 0.82 (0.48 to 1.38) i.e. not statistically significant

	Drug sensitive cases only Number of deaths (all cause) 6-month regimen = 3 of 100 9-month regimen = 10 of 97 OR[2] (95% CI) = 0.27 (0.07 to 1.01) i.e. not statistically significant
	Cure ('favourable response') For culture-positive pulmonary tuberculosis, this was defined as those in whom all of the 6 available sputum cultures were negative during the last 2 months of treatment For culture-negative pulmonary tuberculosis and extrapulmonary tuberculosis, this was defined by the resolution of signs and symptoms, regression of lymph nodes and/or radiographic clearance *'Modified ITT analysis'* Number of patients to achieve a 'favourable response' at the end of treatment 6-month regimen = 138 of 167 9-month regimen = 122 of 160 RR (95% CI) = 1.08 (0.97 to 1.21) p = 0.15 OR[2] (95% CI) = 1.48 (0.86 to 2.55) i.e. not statistically significant *Drug sensitive cases only* Number of patients to achieve a 'favourable response' at the end of treatment 6-month regimen = 85 of 100

	9-month regimen = 75 of 97 OR[2] (95% CI) = 1.66 (0.80 to 3.44) i.e. not statistically significant *Pulmonary tuberculosis only - culture positive at baseline*[1] Number of patients to achieve a 'favourable response' at the end of treatment 6-month regimen = 96 of 117 9-month regimen = 81 of 110 OR[2] (95% CI) = 1.64 (0.87 to 3.09) i.e. not statistically significant *Pulmonary tuberculosis only - culture negative at baseline*[1] Number of patients to achieve a 'favourable response' at the end of treatment 6-month regimen = 28 of 34 9-month regimen = 31 of 38 OR[2] (95% CI) = 1.05 (0.32 to 3.51) i.e. not statistically significant
	Treatment failure Bacteriological failure was defined as at least 2 positive cultures during the last 2 months of treatment (at least 1 with a grade of more than 1+) *'Modified ITT analysis'*[1] Number of patients to experience bacteriological failure of chemotherapy 6-month regimen = 8 of 167

	9-month regimen = 11 of 160 OR[2] (95% CI) = 0.68 (0.27 to 1.74) i.e. not statistically significant *Drug sensitive cases only* Number of patients to experience bacteriological failure of chemotherapy 6-month regimen = 3 of 100 9-month regimen = 7 of 97 OR[2] (95% CI) = 0.40 (0.10 to 1.58) i.e. not statistically significant *Pulmonary tuberculosis only - culture positive at baseline*[1] Number of patients to experience bacteriological failure of chemotherapy 6-month regimen = 8 of 117 9-month regimen = 11 of 110 OR[2] (95% CI) = 0.66 (0.26 to 1.71) i.e. not statistically significant *Pulmonary tuberculosis only - culture negative at baseline*[1] Number of patients to experience bacteriological failure of chemotherapy 6-month regimen = 0 of 34 9-month regimen = 0 of 38 OR[2] (95% CI) = 1.12 (0.02 to 57.77) i.e. not statistically significant

	Relapse Bacteriological recurrence was defined by at least 2 positive cultures (at least 1 with a grade of more than 1+) Recurrence was only recorded for those who successfully completed treatment (i.e. achieved a favourable status) Recurrences were classified as: exogenous reinfection, if 2 or more differences in bands/spots/peaks were observed by any of the genotypic methods used (IS6110 analysis, MIRU-VNTR typing, or spoligotyping) paradoxical reaction, if there was an increase in the size of a lymph node or extent of radiographic involvement without evidence of drug resistance or associated infection *'Modified ITT analysis'* Number of patients to experience bacteriological recurrence 6-month regimen = 21 of 167 9-month regimen = 8 of 160 **OR[2] (95% CI) = 2.73 (1.17 to 6.36)** **i.e. statistically significant** Number of patients who successfully completed treatment to experience bacteriological recurrence 6-month regimen = 21 of 138 9-month regimen = 8 of 122 RR (95% CI) = 2.07 (1.33 to 3.23) p = 0.03 **OR[2] (95% CI) = 2.56 (1.09 to 6.01)** **i.e. statistically significant**
	Adverse events – drug toxicity

	'Modified ITT analysis'[1] Number of patients to experience drug toxicity 6-month regimen = 1 of 167 9-month regimen = 1 of 160 OR[2] (95% CI) = 0.96 (0.06 to 15.45) i.e. not statistically significant *Drug sensitive cases only* Number of patients to experience drug toxicity 6-month regimen = 1 of 100 9-month regimen = 0 of 97 OR[2] (95% CI) = 2.93 (0.12 to 73.05) i.e. not statistically significant *Pulmonary tuberculosis only - culture positive at baseline*[1] Number of patients to experience drug toxicity 6-month regimen = 1 of 117 9-month regimen = 0 of 110 OR[2] (95% CI) = 2.85 (0.11 to 70.60) i.e. not statistically significant *Pulmonary tuberculosis only - culture negative at baseline*[1] Number of patients to experience drug toxicity 6-month regimen = 0 of 34

	9-month regimen = 1 of 38 OR[2] (95% CI) = 0.36 (0.01 to 9.20) i.e. not statistically significant
	Adherence – treatment default *'Modified ITT analysis'*[1] Number of patients to default of their treatment for >1 month 6-month regimen = 11 of 167 9-month regimen = 16 of 160 OR[2] (95% CI) = 0.63 (0.29 to 1.41) i.e. not statistically significant *Drug sensitive cases only* Number of patients to default of their treatment for >1 month 6-month regimen = 5 of 100 9-month regimen = 4 of 97 OR[2] (95% CI) = 1.22 (0.32 to 4.70) i.e. not statistically significant
Source of funding	None of the authors had a financial relationship with a commercial entity that has an interest in the subject of this paper
Comments	Population did not exactly match the population of interest: may be some children in the included population (inclusion criteria = 15 years or more) some extrapulmonary tuberculosis, although limited to pleural or lymph node tuberculosis

	some drug resistant tuberculosis Intervention used is in line with the standard recommended regimen, but patients are not receiving ART; therefore the co-treatment regimen doesn't match UK practice
[1] Data extracted by reviewer from a 'trial profile' flow diagram; diagram was generally difficult to interpret [2] Odds ratio and 95% confidence intervals have been calculated by the reviewer Abbreviations: ART, antiretroviral treatment; CI, confidence interval; E, ethambutol; H, isoniazid; IQR, interquartile range; ITT, intent-to-treat; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; RR, risk ratio; Z, pyrazinamide	

1.3.11 Teo et al, 2002

Bibliographic reference	Teo SK, Tan KK & Khoo TK (2002) Four-month chemotherapy in the treatment of smear-negative pulmonary tuberculosis: results at 30 and 60 months. Annals, Academy of Medicine Singapore 31: 175-81
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: regimens lack ethambutol varied by more than duration – the continuation phase of the 6-month regimen was intermittent (3 times weekly), whereas the 4-month regimen was daily throughout Method of randomisation, allocation concealment and blinding were unclear, although the clinicians reading radiographs or assessing relapse had no knowledge of which regimen a patient was assigned to Unclear if groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for treatment completion and availability of outcome data Did not follow the intent-to-treat principle
Number of patients	Randomised = 113 4-month regimen = 59

	6-month regimen = 54 Data available after 60 months of follow-up = 79 4-month regimen = 41 6-month regimen = 38
Patient characteristics	*Inclusion* Patients who had respiratory symptoms and chest X-ray abnormality compatible with a diagnosis of pulmonary tuberculosis, but with negative sputum smear examination for acid-fast bacilli on 4 consecutive occasions Positive culture[1] *Exclusion* Recent or past history of treatment pulmonary tuberculosis History of mental disorder, alcohol or drug abuse Pregnancy
Intervention	*4-month regimen* $2HRZ_7/2HR_7$ isoniazid, rifampicin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for 2 months Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg Treatment was given under direct supervision

Comparison	*6-month regimen* $2HRZ_7/4HR_3$ isoniazid, rifampicin and pyrazinamide daily for 2 months isoniazid and rifampicin 3-times weekly for 4 months Dosing: initial phase isoniazid: 300 mg/day rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg continuation phase isoniazid: 15 mg/kg of body weight/day rifampicin: 600 mg/day Treatment was given under direct supervision
Location	Singapore
Length of follow up	60 months after treatment initiation
Outcomes measures and effect size	**Treatment failure** Defined as failure of sputum culture conversion towards the end of therapy Number of smear-negative culture-positive patients to experience treatment failure 4-month regimen = 0 of 59 6-month regimen = 1 of 54 OR[2] (95% CI) = 0.30 (0.01 to 7.52)

	i.e. not statistically significant
	Changes in signs and symptoms – radiographic status Number of smear-negative culture-positive patients to show no change in radiological status by the end of chemotherapy 4-month regimen = 0 of 59 6-month regimen = 0 of 54 OR[7] (95% CI) = 0.92 (0.02 to 4.97) i.e. not statistically significant Number of smear-negative culture-positive patients to show less than 50% radiological clearing by the end of chemotherapy 4-month regimen = 0 of 59 6-month regimen = 0 of 54 OR[7] (95% CI) = 0.92 (0.02 to 4.97) i.e. not statistically significant Number of smear-negative culture-positive patients to show more than 50% radiological clearing by the end of chemotherapy 4-month regimen = 52 of 59 6-month regimen = 52 of 54 OR[7] (95% CI) = 0.29 (0.06 to 1.44) i.e. not statistically significant Number of smear-negative culture-positive patients to show complete radiological clearing by the end of chemotherapy 4-month regimen = 5 of 59

	6-month regimen = 1 of 54 OR[7] (95% CI) = 4.91 (0.55 to 43.42) i.e. not statistically significant
	Relapse Defined as a clinical and radiological deterioration following therapy with or without bacteriological confirmation Bacteriological relapse was defined as the presence of a positive sputum culture with 5 or more colonies in at least 2 of 3 specimens during a 3-month period Number of smear-negative culture-positive patients to experience relapse 4-month regimen = 0 of 59 6-month regimen = 0 of 54 OR[2] (95% CI) = 0.92 (0.02 to 4.97) i.e. not statistically significant
Source of funding	Supported by a grant from the Ministry of Health, Singapore
Comments	Intervention does not exactly match the intervention of interest: regimens lack ethambutol varied by more than duration – the continuation phase of the 6-month regimen was intermittent (3 times weekly), whereas the 4-month regimen was daily throughout

[1] Reviewer did not extract data for smear-negative culture-negative as these patients were randomised to 1 of 2 4-month regimens (varied by dosing frequency rather than duration)

[2] Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide

1.3.12 Ziaullah et al, 2004

Bibliographic reference	Ziaullah, Basit A & Javaid A (2004) Comparison of the efficacy of 06 months vs 09 months therapy in smear positive pulmonary TB. Pakistan Journal of Chest Medicine 10(2): 5-9
Study type	RCT
Study quality	Population does not exactly match the population of interest: children also included (for more details, see 'patient characteristics' below) Randomisation, allocation concealment and blinding were unclear Unclear if groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for treatment completion and availability of outcome data, though rate of attrition was high in both groups Sputum conversion, a measure of response to treatment, is a substitute for an outcome of interest (cure, treatment success and treatment failure) Did not follow the intent-to-treat principle
Number of patients	Randomised = 200 6-month group = 93 9-month group = 107 Data available for 'cure' = 95 6-month group = 44 9-month group = 51 Data available for 'treatment failure' = 113 6-month group = 44 9-month group = 69

<table>
<tr><td></td><td>Data available for ‘response to treatment - sputum conversion’ = 133
6-month group = 64
9-month group = 69
Data available for ‘relapse’ = 39
6-month group = 19
9-month group = 24</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Pulmonary tuberculosis
Diagnostic criteria
Chest x-ray
Sputum microscopy
Exclusion
Previous anti-tuberculosis treatment
Baseline characteristics
<table>
<tr><th>Age (years)</th><th>Male</th><th>Female</th><th>Total</th></tr>
<tr><td>5-14</td><td>34</td><td>32</td><td>66</td></tr>
<tr><td>15-29</td><td>38</td><td>28</td><td>66</td></tr>
<tr><td>30-44</td><td>13</td><td>9</td><td>22</td></tr>
<tr><td>45-59</td><td>11</td><td>11</td><td>22</td></tr>
<tr><td>60+</td><td>14</td><td>10</td><td>24</td></tr>
</table></td></tr>
</table>

Intervention	*6-month regimen* $2HRZE_7/4HR_7$ isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months in fixed-dose combinations isoniazid and rifampicin daily in fixed-dose combinations for a further 4 months
Comparison	*9-month regimen* $2HRZE_7/7HR_7$ isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months in fixed-dose combinations isoniazid and rifampicin daily in fixed-dose combinations for a further 6 months
Length of follow up	18 months after treatment completion
Location	Pakistan
Outcomes measures and effect size	**Cure** Defined as those who were sputum-smear-negative in the last month of treatment and on at least one previous occasion 6-month group = 25 of 93 9-month group = 19 of 107 OR[1] (95% CI) = 1.73 (0.88 to 3.40) i.e. not statistically significant
	Treatment failure Defined as those who are sputum-smear-positive at 5 months or later during treatment 6-month group = 0 of 93 9-month group = 1 of 107

	OR[1] (95% CI) = 0.38 (0.02 to 9.43) i.e. not statistically significant
	Response to treatment – sputum conversion Defined as those who convert from sputum-smear-positive to sputum-smear-negative at the end of 2 months of treatment 6-month group = 63 of 93 9-month group = 67 of 107 OR[1] (95% CI) = 1.25 (0.70 to 2.25) i.e. not statistically significant
	Relapse Defined as those who, once treated for pulmonary tuberculosis and declared cured or completed treatment[2], are once again diagnosed with bacteriologically positive (smear or culture) tuberculosis 6-month group = 5 of 19[3] 9-month group = 0 of 24[3] OR[1] (95% CI) = 18.59 (0.96 to 361.22) i.e. not statistically significant
Source of funding	No details given
Comments	Population does not exactly match the population of interest: children also included

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

[2] Treatment completion was defined as those who completed treatment but did not meet the criteria to be classified as a cure or a treatment failure

[3] Those eligible for monitoring for relapse were those who were cured or who completed treatment

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

1.4 RQ M: In children and young people with drug susceptible, active respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

1.4.1 Kansoy et al, 1998

Bibliographic reference	Kansoy S, Kurtas N, Aksit S et al (1996) Superiority of Intermittent-Short Course Chemotherapy in Childhood Pulmonary Tuberculosis. Turkish Journal of Medical Sciences 26(1): 41-43
Study type	RCT
Study quality	The interventions did not differ in the two groups by treatment duration alone: initial 3-drug phase was shorter in the 9-month regimen (2 weeks) than in the 12-month regimen (1 month) 3 month extension of the 12-month regimen contains only rifampicin – i.e. not simply an extension of an equivalent regimen to the 9-month regimen 9-month regimen received treatment daily during the initial 2-week phase, and twice-weekly during the 8.5-month continuation phase; the 12-month regimen consisted of daily dosing throughout Interventions do not use the 4 standard recommended drugs: the regimens are missing pyrazinamide and ethambutol, and they contain streptomycin Prescribed doses of isoniazid and streptomycin are above that recommended by the British National Formulary A number of outcomes could not be extracted as they were not reported at or after treatment completion:

	therapy period for early clinical response – not relevant to the effectiveness of treatment duration number of participants to show clinical improvement – recorded after 6 months of treatment number of participants to completely resolve – recorded after 6 months of treatment weight gain – recorded after 6 months of treatment note: the data for these can be seen in the evidence tables for review question I Randomisation, allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were followed up for an equal length of time Treatment completion was not comparable and outcome data was not similarly available: 9-month group: 0 of 18 excluded due to non-adherence 12-month group: 3 of 18 excluded due to non-adherence, and outcome data was not provided for these Did not follow the intent-to-treat principle 'Recurrence' is a substitute for an outcome of interest (relapse); its definition generally does not distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection
Number of patients	Randomised = 36 9-month group = 18 12-month group = 18 Outcome data available for = 33 9-month group = 18 12-month group = 15

Patient characteristics	*Inclusion* Ages 5 months to 13 years Pulmonary TB *Diagnostic criteria* Clinical: afternoon fever excessive sweating cough anorexia weight loss Epidemiologic direct contact with a tuberculous adult (bacillary positive or negative) Radiologic parenchymal or mediastinal lymph nodes in chest roentgenograms Immunologic tuberculin test positivity (PPD) Histobacteriologic acid-fast bacilli in the sputum, or gastric washings or in any histologic specimen *Exclusion* Poor “family compliance” *Baseline*

<table>
<tr><td></td><td>
<table>
<tr><th></th><th>9-month
(n = 18)</th><th>12-month
(n = 15)</th></tr>
<tr><td>Male/female</td><td>12/6</td><td>10/5</td></tr>
<tr><td>Age (mean years ± SD)</td><td>7.6±3.9</td><td>7.7±4.0</td></tr>
<tr><td>Diagnostic criteria
clinical
epidemiologic
immunologic
radiologic
histobacteriologic</td><td>
18
14
15
18
2</td><td>
15
12
12
15
2</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>9-month regimen
0.5SRH$_7$/8.5RH$_2$
daily streptomycin, isoniazid and rifampicin for two weeks
twice weekly isoniazid and rifampicin for 8.5 months
Dosing:
streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g
isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg
rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg
All patients were treated on an outpatient basis</td></tr>
<tr><td>Comparison</td><td>12-month regimen</td></tr>
</table>

	$1SRH_7/8RH_7/3R_7$ daily streptomycin, isoniazid and rifampicin 1 month daily isoniazid and rifampicin for 8 months daily rifampicin for 3 months Dosing: streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg All patients were treated on an outpatient basis
Length of follow up	12 months after treatment completion
Location	Izmir, Turkey
Outcomes measures and effect size	**Recurrence** Number to experience recurrence (based on clinical or radiologic examination) in 12 months after treatment completion: 9-month group = 0 of 18 12-month group = 0 of 18 OR^2 (95% CI) = 1.00 (0.02 to 53.12) i.e. not statistically significant
	Adverse events – hepatotoxicity Defined as elevated serum aspartate aminotransferase and alanine aminotransferase (note: thresholds not given) Number to experience hepatotoxicity:

	9-month group = 0 of 18 12-month group = 1 of 18 OR[2] (95% CI) = 0.32 (0.01 to 8.27) i.e. not statistically significant
	Adherence Number excluded due to "poor compliance" (note: definition not provided): 9-month group = 0 of 18 12-month group = 3 of 18 p[1] > 0.05 OR[2] (95% CI) = 0.12 (0.01 to 2.50) i.e. not statistically significant
Source of funding	Details not given
Comments	Because the interventions vary by dosing frequency in addition to treatment duration, this study is also considered for possible inclusion in review question I The interventions did not differ in the two groups by treatment duration alone: initial 3-drug phase was shorter in the 9-month regimen (2 weeks) than in the 12-month regimen (1 month) 3 month extension of the 12-month regimen contains only rifampicin – i.e. not simply an extension of an equivalent regimen to the 9-month regimen 9-month regimen received treatment daily during the initial 2-week phase, and twice-weekly during the 8.5-month continuation phase; the 12-month regimen consisted of daily dosing throughout Interventions do not use the 4 standard recommended drugs: the regimens are missing pyrazinamide and ethambutol, and they contain streptomycin A number of outcomes could not be extracted as they were not reported at or after treatment completion:

	therapy period for early clinical response – not relevant to the effectiveness of treatment duration number of participants to show clinical improvement – recorded after 6 months of treatment number of participants to completely resolve – recorded after 6 months of treatment weight gain – recorded after 6 months of treatment note: the data for these can be seen in the evidence tables for review question I

[1] Calculated by authors using the chi-square test or student's t-test; $p < 0.05$ was taken as significant

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

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis

1.5 RQ N & Q: In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

RQ Q has been integrated in this question.

PULMONARY TUBERCULOSIS

1.5.1 Bilaçeroglu et al, 1999

Bibliographic reference	Bilaçeroglu S, Perim K, Büyüksirin M et al (1999) Prednisolone: a beneficial and safe adjunct to antituberculosis treatment? A randomised controlled trial. International Journal of Tuberculosis and Lung Disease 3(1): 47-54
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* only laboratory staff and those reading chest scans were blinded *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?* follow-up period was appropriate (1 to 3 years), although it is unclear if it was the same in each group *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 – change in bacillary count is a surrogate for cure/treatment success/treatment failure *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 178 prednisolone group = 91 antituberculosis chemotherapy alone group = 87 Outcome data available for = 178 prednisolone group = 91 antituberculosis chemotherapy alone group = 87
Patient characteristics	*Inclusion* Advanced pulmonary tuberculosis causing persistent high-grade fever (≥38°C), weight loss (≥2 kg/week) and/or low serum albumin levels (<3 g/dL) HIV-negative *Diagnostic criteria* Confirmed by acid-fast bacilli positivity on smear or culture, and/or granulomatous inflammation with caseous necrosis in the pulmonary biopsy specimen Other febrile causes were excluded by serial blood culture, sputum and urine culture, total body gallium-67

scintigraphy for occult abscesses, screening for occult malignancy, witholding antituberculosis treatment for 3 days to monitor temperature response, and a trial of intravenous broad-spectrum antibiotics for the same 3 days

Exclusion

Accompanying uncontrollable hypertension, recalcitrant diabetes, active or recent peptic ulcer or gastrointestinal bleeding, resistant hypokalemia or florid sepsis

Baseline

	Prednisolone group (n = 91)	**Antituberculosis chemotherapy alone group** (n = 87)
Age (mean±SD), years	36±2.8	34±3.1
Sex, male:female	70:21	64:23
Weight (mean±SD), kg	50.3±1.9	51.1±1.4
Serum albumin level (mean±SD), g/dl	2.57±0.29	2.62±0.17
Fever (mean±SD), °C	38.7±0.4	38.4±0.2
Patients with cavities:patients with miliary lesions	74:17	67:20
Radiographic extent of the disease		
fraction of both lung fields (mean±SD)	7/8±1/8	13/16±1/16
number of patients with bilateral involvement	91	87
Bacillary count on smear (mean±SD)	2±1	2±1

Intervention *Antituberculosis chemotherapy plus prednisolone*

	Prednisolone (40 days) initially administered 20 mg b.i.d IV/IM for 10 days, after which it was given orally and reduced by 10 mg every 10 days Antituberculosis chemotherapy: drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given doses not stated
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given doses not stated
Length of follow up	1 to 3 years
Location	Izmir, Turkey
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 0 of 91 antituberculosis chemotherapy alone group = 0 of 87 OR[1] (95% CI) = 0.96 (0.02 to 48.73) i.e. not statistically significant
	Response to treatment – bacillary count Number of to experience a drop in bacillary count 50 days after prednisolone was initiated[3]

	prednisolone group = 91 of 91 antituberculosis chemotherapy alone group = 81 of 87 OR[1] (95% CI) = 14.60 (0.81 to 263.12) i.e. not statistically significant Number of to experience a marked drop in bacillary count 50 days after prednisolone was initiated[3] prednisolone group = 78 of 91 antituberculosis chemotherapy alone group = 54 of 87 **OR[1] (95% CI) = 3.67 (1.77 to 7.61)** **i.e. statistically significant** Time (mean, days) to drop in bacillary count **p = 0.04** **i.e. statistically significant**
	Changes in signs and symptoms – fever Change (mean, °C) in temperature within 72 hours prednisolone group (n = 91) = -1.2 antituberculosis chemotherapy alone group (n = 87) = 0.2 MD[2] = 1.4
	Changes in signs and symptoms – weight change Weight change (mean, kg) during treatment prednisolone group (n = 91) = 7.2 antituberculosis chemotherapy alone group (n = 87) = 4.2

	MD[2] = 3.0 **p = 0.002** **i.e. statistically significant**
	Changes in signs and symptoms – radiographic improvement Radiographic improvement was defined as the combined average percentage of the reductions in the sizes of the initial lesions (infiltrates, cavities and/or pleural effusion): marked (>90%) moderate (50–89%) slight (10–49%) no improvement (<10%) Number of to experience radiographic improvement (marked, moderate or slight) 50 days after prednisolone initiation[3] prednisolone group = 91 of 91 antituberculosis chemotherapy alone group = 83 of 87 OR[1] (95% CI) = 9.86 (0.52 to 185.96) i.e. not statistically significant Number of to experience marked radiographic improvement 50 days after prednisolone initiation[3] prednisolone group = 15 of 91 antituberculosis chemotherapy alone group = 8 of 87 OR[1] (95% CI) = 1.95 (0.78 to 4.86) i.e. not statistically significant
	Relapse

	Number of patients to experience radiographic, bacteriologic or clinical relapse during follow-up prednisolone group = 0 of 91 antituberculosis chemotherapy alone group = 0 of 87 OR[1] (95% CI) = 0.96 (0.02 to 48.73) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference and 95% confidence interval calculated by reviewer

[3] Read off graph by reviewer

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

1.5.2 Mayanja-Kizza et al, 2005

Bibliographic reference	Mayanja-Kizza H, Jones-Lopez E, Okwera A et al (2005) Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. Journal of Infectious Diseases 191(6): 856-65
Study type	RCT
Study quality	*Appropriate method of randomisation used?* eligible patients were randomly assigned in blocks of 6 to receive either prednisolone or placebo; the randomisation schedule was developed before the trial by use of computer-generated random numbers with corresponding treatment assignments *Allocation concealment used?* assignments were placed in sealed envelopes and drawn sequentially by a study nurse who was not involved with patient care

	Blinding used? double-blind *Groups comparable at baseline?* fever and night sweats were present in significantly more patients who went on to receive prednisolone than amongst those that went on to receive placebo *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?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – event-free survival is a substitute for mortality and adverse events; sputum conversion is a substitute for treatment success; recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?* yes

Number of patients	Randomised = 187 prednisolone group = 93 placebo group = 94 Treatment completion = 181 prednisolone group = 90 placebo group = 91 Outcome data available after 2 years of follow-up = 136 prednisolone group = 69 placebo group = 67
Patient characteristics	*Inclusion* Initial episodes of acid fast smear–positive pulmonary tuberculosis HIV-infected patients >18 years of age *Exclusion* Previous treatment for tuberculosis Advanced HIV infection (World Health Organization stage IV) Karnofsky performance score <80 Peripheral blood CD4+ T cell count <200 cells/μL Kaposi sarcoma Active herpes zoster Glucose level >160 mg/dL or diabetes mellitus by history

Serum aminotransferase level >65 IU/L

Potassium level >5.5 mmol/L

Positive β-urinary human chorionic gonadotrophin test

Previous use of immunomodulators

Presence or history of hypertension

Psychiatric disease

Peptic ulcer disease

Pancreatitis

Baseline

	Prednisolone group (n = 93)	**Placebo group** (n = 94)
Sex		
males, n (%)	55 (59)	58 (62)
BCG scar present, n (%)	40 (44)	42 (46)
PPD induration		
≥5 mm, n (%)	83 (89)	79 (84)
mean±SD, mm	16±5.4	16±5.4
Karnofsky performance status		
90, n (%)	28 (30)	21 (22)
80, n (%)	60 (65)	68 (72)

		70, n (%)	5 (5)	5 (5)	
		Age (mean±SD), years	31±7.1	31±7.2	
		Body mass index (mean±SD), kg/m^2	19±2.8	19±2.6	
		Haemoglobin level (mean±SD), g/dl	11±1.8	11±1.8	
		White blood cell count (mean±SD), cells/mm^3	8±2.8	7.8±2.8	
		Lymphocyte count (mean±SD), cells/mm^3	1.9±0.8	2.0±0.9	
		Aspartate aminotransferase level (mean±SD), IU/l	26±12	24±12	
		Glucose level (mean±SD), mg/dl	85±24	88±24	
		Potassium level (mean±SD), mmol/dl	4.7±0.4	4.8±0.5	
		Symptoms			
		cough, n (%)	93 (100)	94 (100)	
		chest pain, n (%)	53 (57)	55 (59)	
		hemoptysis, n (%)	5 (5)	11 (12)	
		dyspnea, n (%)	36 (40)	31 (33)	
		fever, n (%)	62 (67)	46 (49)	
		weight loss, n (%)	78 (84)	76 (81)	
		purulent sputum, n (%)	76 (82)	81 (86)	
		night sweats, n (%)	60 (65)	50 (53)	
		Physical examination			
		respiratory			

		consolidation, n (%)	90 (97)	93 (99)	
		wheezing or rhonchi, n (%)	2 (2)	1 (1)	
		pleural effusion, n (%)	0 (0)	1 (1)	
		lymph node enlargement, n (%)	6 (6)	4 (4)	
		sputum smear			
		scanty, n (%)	7 (8)	7 (7)	
		grade 1, n (%)	22 (24)	17 (18)	
		grade 2, n (%)	13 (14)	26 (28)	
		grade 3, n (%)	49 (54)	44 (47)	
		cavitatory	80 (86)	74 (79)	
		chest radiograph finding			
		normal, n (%)	2 (1)	0 (0)	
		minimal, n (%)	3 (3)	4 (4)	
		moderately advanced, n (%)	23 (25)	25 (27)	
		far advanced, n (%)	66 (71)	65 (69)	
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (8 weeks) given at a dose of 2.75 mg/kg daily for 4 weeks and tapered over the course of the next 4 weeks to complete an 8-week course Antituberculosis chemotherapy: HRZE – duration and dosing unclear				

	Medications were self-administered
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (8 weeks) given at a dose of 2.75 mg/kg daily for 4 weeks and tapered over the course of the next 4 weeks to complete an 8-week course Antituberculosis chemotherapy: HRZE – duration and dosing unclear Medications were self-administered
Length of follow up	36 months
Location	Uganda
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 17 of 93 placebo group = 14 of 94 OR[1] (95% CI) = 1.28 (0.59 to 2.77) i.e. not statistically significant
	Event-free survival Number of patients to survive to 36 months without significant adverse event prednisolone group = 36 of 93 placebo group = 40 of 94 OR[1] (95% CI) = 0.85 (0.48 to 1.53) i.e. not statistically significant

	Treatment failure Defined as the failure to clear acid-fast bacilli from the sputum after 5 consecutive months of antituberculous therapy to which the organism was susceptible Number of patients to experience treatment failure prednisolone group = 1 of 93 placebo group = 1 of 94 OR[1] (95% CI) = 1.01 (0.06 to 16.41) i.e. not statistically significant
	Response to treatment – sputum conversion Number of patients to have a sputum culture negative for *M. tuberculosis* after 1 month of treatment prednisolone group = 58 of 93 placebo group = 35 of 94 **OR[1] (95% CI) = 2.79 (1.54 to 5.05)** **i.e. statistically significant** Number of patients to have a sputum culture negative for *M. tuberculosis* after 2 months of treatment prednisolone group = 80 of 93 placebo group = 80 of 94 OR[1] (95% CI) = 1.08 (0.48 to 2.44) i.e. not statistically significant
	Recurrence Defined as the recurrence of active TB after the establishment of cure

	Number of patients to experience recurrence within 2 years of initiating treatment prednisolone group = 8 of 93 placebo group = 11 of 94 OR[1] (95% CI) = 0.71 (0.27 to 1.85) i.e. not statistically significant
	Adverse events Number of patients to experience any adverse event prednisolone group = 87 of 93 placebo group = 82 of 94 OR[1] (95% CI) = 2.55 (0.86 to 7.54) i.e. not statistically significant Number of patients to experience a severe or life-threatening adverse event prednisolone group = 22 of 93 placebo group = 18 of 94 OR[1] (95% CI) = 1.31 (0.65 to 2.64) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: BCG, Bacille Calmette-Guerin; CI, confidence intervals; H, isoniazid; OR, odds ratio; PPD, purified protein derivative; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.5.3 Park et al, 1997

Bibliographic reference	Park IW, Choi BW & Hue SH (1997) Prospective study of corticosteroid as an adjunct in the treatment of endobronchial tuberculosis in adults. Respirology 2: 275-81
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, although details provided are limited *Groups followed up for an equal and appropriate length of time?* not for the full treatment period: only 2 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

<table>
<tr><td></td><td>Intervention used is the same as the intervention of interest?
yes, although some patients received streptomycin instead of ethambutol
Have substitute outcomes been used instead of the patient-important outcomes of interest?
no
Analysis followed the intent-to-treat principle?
unclear</td></tr>
<tr><td>Number of patients</td><td>Randomised = 34
prednisolone group= 17
antituberculosis chemotherapy alone group = 17</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Endobronchial tuberculosis
Diagnostic criteria
Endobronchial lesions suggestive of endobronchial tuberculosis – such as cheese-like material, stenosis, granular, ulceration, or inflammatory changes – observed bronchoscopy with either caseating necrosis on tissue biopsy or positive stains/culture of acid-fast bacilli on the sputum, bronchial washing or brushing
Exclusion
Systemic disease or infection
History of previous tuberculosis
Patients who have stopped antituberculosis medications or corticosteroids due to severe side effects
Pregnancy
Baseline
<table>
<tr><th></th><th>Prednisolone group</th><th>Antituberculosis</th></tr>
</table>
</td></tr>
</table>

			(n = 17)	**chemotherapy alone group** (n = 17)	
		Sex, male:female	3:14	4:13	
		Age			
		15–19, n (%)	3 (33.5)	2 (11.8)	
		20–29, n (%)	8 (47.2)	7 (41.0)	
		30–39, n (%)	1 (5.8)	2 (11.8)	
		40–49, n (%)	4 (23.7)	2 (11.8)	
		50–59, n (%)	1 (5.8)	2 (11.8)	
		>60, n (%)	0 (0)	2 (11.8)	
		Age (mean), years	31.0	34.8	
		Sputum-positive, %	70.6	58.8	
		Pulmonary function			
		FEV1 (mean±SD), % predicted	77.3±16.7	87.0±13.9	
		FVC (mean±SD), % predicted	77.1±21.3	84.6±17.7	
		Posteroanterior chest-x-ray			
		total atelectasis, n	2	0	
		segmental atelectasis, n	3	5	
		Bronchoscopic findings			
		actively caseating, n	12	7	
		stenosis without fibrosis, n	9	9	

	stenosis with fibrosis, n	5	2
	non-specific bronchitic, n	5	6
	glandular, n	2	4
	granular, n	2	2
	ulcerative, n	0	0

Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (4 to 8 weeks) administered at a dosage of 0.5 mg, approximately 1.0 mg/kg of body weight/day, for 4 to 8 weeks, and then tapered gradually Antituberculosis chemotherapy: HRZS, HRZE or HRZSE dosing and duration not specified
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRZS, HRZE or HRZSE dosing and duration not specified
Length of follow up	2 months after treatment initiation
Location	Seoul, Korea
Outcomes measures and effect size	**Change in signs and symptoms – endobronchial lesions** Including actively caseating lesions, stenosis with and without fibrosis, glandular-type lesions and granular-type lesions Number of endobronchial lesions identified using bronchoscopy before treatment to have improved after 2 months of treatment prednisolone group= 24 of 35

	antituberculosis chemotherapy alone group = 22 of 30 OR[1] (95% CI) = 0.79 (0.27 to 2.33) i.e. not statistically significant
	Change in signs and symptoms – pulmonary lesions Including atelectasis, patchy infiltration, fibrostreaky density, hilar mass shadow, nodular lesions and cavitatory lesions Number of lesions identified using chest-x-ray before treatment to have improved after 2 months of treatment prednisolone group= 22 of 29 antituberculosis chemotherapy alone group = 23 of 28 OR[1] (95% CI) = 0.68 (0.19 to 2.48) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

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

1.5.4 Tuberculosis Research Centre (Madras), 1983

Bibliographic reference	Tuberculosis Research Centre (Madras) (1983) Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. Tuberculosis Research Centre. Tubercle 64: 73-91
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?* 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?* yes, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – sputum conversion is a substitute for cure/treatment failure *Analysis followed the intent-to-treat principle?*

	unclear
Number of patients	Randomised = 530 prednisolone group = 261 antituberculosis chemotherapy alone group = 269 Outcome data available at 24 months = 530 prednisolone group = 261 antituberculosis chemotherapy alone group = 269
Patient characteristics	*Inclusion* Newly diagnosed pulmonary tuberculosis Aged ≥12 years *Diagnostic criteria* At least 2 positive sputum cultures *Baseline* Unclear
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (8 weeks) 20 mg 3 times/day (except Sundays) for the first week, 3 doses of 10 mg, 5 mg, and 5 mg daily for the next 5 weeks, 5 mg twice-daily in the 7^{th} week and 5 mg daily in the eighth week Antituberculosis chemotherapy: $2SHRZ_7/3SHZ_2$, $2SHRZ_7/5SHZ_2$ or $2SHZ_7/5SHZ$ isoniazid at 400 mg/day during initial phase, followed by 15 mg/kg of body weight/day thereafter, rifampicin at 12 mg/kg of body weight/day, pyrazinamide at 40 mg/kg of body weight/day, and streptomycin at 750 mg/kg of body weight/day

	Treated as outpatients, though were given their drugs under close supervision by a clinic nurse
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: $2SHRZ_7/3SHZ_2$, $2SHRZ_7/5SHZ_2$ or $2SHZ_7/5SHZ$ isoniazid at 400 mg/day during initial phase, followed by 15 mg/kg of body weight/day thereafter, rifampicin at 12 mg/kg of body weight/day, pyrazinamide at 40 mg/kg of body weight/day, and streptomycin at 750 mg/kg of body weight/day Treated as outpatients, though were given their drugs under close supervision by a clinic nurse
Location	Madras, India
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – sputum conversion** Number of patients with all cultures negative after 1 month of treatment prednisolone group = 81 of 261 antituberculosis chemotherapy alone = 80 of 269 OR[1] (95% CI) = 1.06 (0.73 to 1.54) i.e. not statistically significant Number of patients with all cultures negative after 2 months of treatment prednisolone group = 167 of 261 antituberculosis chemotherapy alone = 167 of 269 OR[1] (95% CI) = 1.09 (0.76 to 1.54) i.e. not statistically significant Number of patients with all cultures negative after 3 months of treatment prednisolone group = 187 of 261

	antituberculosis chemotherapy alone = 183 of 269 OR[1] (95% CI) = 1.19 (0.82 to 1.72) i.e. not statistically significant
	Changes in signs and symptoms – radiographic improvement Number of patients to achieve moderate or greater radiographic improvement after 2 months of treatment prednisolone group = 130 of 261 antituberculosis chemotherapy alone = 107 of 269 **OR[1] (95% CI) = 1.50 (1.06 to 2.12)** **i.e. statistically significant** Number of patients in whom cavitation was present on admission but disappeared by the end of treatment prednisolone group = 103 of 245 antituberculosis chemotherapy alone = 88 of 250 OR[1] (95% CI) = 1.34 (0.93 to 1.92) i.e. not statistically significant Number of patients in whom the cavitation that was present on admission had lessened by the end of treatment prednisolone group = 97 of 245 antituberculosis chemotherapy alone = 111 of 250 OR[1] (95% CI) = 0.82 (0.57 to 1.17) i.e. not statistically significant
	Relapse Defined as 2 or more cultures positive for *M. tuberculosis* out of 6 examined in any 3 consecutive monthly

	examinations up to 24 months after treatment initiation, or in any 4 consecutive monthly examinations beyond 24 months Number to experience bacteriological relapse requiring treatment prednisolone group = 5 of 261 antituberculosis chemotherapy alone = 6 of 269 OR[1] (95% CI) = 0.86 (0.26 to 2.84) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

PLEURAL TUBERCULOSIS

1.5.5 Elliott et al, 2004

Bibliographic reference	Elliott AM, Luzze H, Quigley MA et al (2004) A randomised, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. Journal of Infectious Diseases 190: 869-78
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – computer-generated randomisation sequence *Allocation concealment used?* yes – sequence was generated by a statistician who was not involved in the care of the patients; prednisolone and matching placebo tablets were packaged in identical plastic bags labelled with randomisation code numbers by 2 people who were not involved in the study *Blinding used?* yes – sequence was generated by a statistician who was not involved in the care of the patients; prednisolone and matching placebo tablets were packaged in identical plastic bags labelled with randomisation code numbers by 2 people who were not involved in the study; medical staff gave participants the next number in the sequence in the order in which they were enrolled; all participants and medical, laboratory, and statistical staff remained blinded to the treatment allocation until all data collection had been completed *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?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 297 prednisolone group = 99 antituberculosis chemotherapy alone group = 98 Outcome data available at 24 weeks for anorexia, weight and cough = 151 prednisolone group = 80 antituberculosis chemotherapy alone group = 71 Outcome data available at 24 weeks for residual effusion = 148 prednisolone group = 76

<table>
<tr><td></td><td>antituberculosis chemotherapy alone group = 72</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion

Presented with clinical features suggesting pleural tuberculosis, with a pleural effusion occupying at least one-third of 1 hemithorax (as determined by a radiograph)

≥18 years old

HIV-1-associated

Residents of Kampala

Diagnostic criteria

Pleural tuberculosis was considered to be confirmed if a patient had a positive culture for Mycobacterium tuberculosisfrom pleural biopsy tissue, pleural fluid, or sputum or if histopathologic analysis of pleural tissue was consistent with tuberculous pleurisy

Exclusion

Previous treatment or prophylaxis for tuberculosis

Recent treatment with glucocorticoids

Pregnant or breast-feeding

Baseline
<table>
<tr><th></th><th>Prednisolone group
(n = 98)</th><th>Placebo group
(n = 99)</th></tr>
<tr><td>Sex
males, n
females, n</td><td>
54
45</td><td>
60
38</td></tr>
<tr><td>Age (mean±SD), years</td><td>34±9</td><td>34±8</td></tr>
</table>
</td></tr>
</table>

		Weight (mean±SD), kg	54±9	53±8	
		Blood pressure			
		systolic (mean±SD), mm Hg	102±13	101±10	
		diastolic (mean±SD), mm Hg	73±11	72±11	
		Symptoms			
		fever, n	66	60	
		cough, n	91	84	
		dyspnea, n	83	86	
		chest pain, n	84	82	
		anorexia, n	72	77	
		weight loss, n	86	83	
		Signs			
		fever ≥37.5°C, n	55	53	
		Karnofsky score ≥80%, n	59	49	
		oral thrus, n	9	5	
		herpes zoster scars, n	13	12	
		lymphadenopathy, n	12	11	
		Laboratory findings			
		CD4+ count (median (interquartile range)), cells/μl	118 (57–211)	93 (58–219)	
		confirmed tuberculosis, n	89	91	

<table>
<tr><td></td><td colspan="3"><table>
<tr><td>isoniazid resistance, n</td><td>5</td><td>5</td></tr>
<tr><td>pyrazinamide resistance, n</td><td>1</td><td>0</td></tr>
<tr><td>Radiography findings</td><td></td><td></td></tr>
<tr><td>1 zone affected, n</td><td>14</td><td>18</td></tr>
<tr><td>2 zones affected, n</td><td>49</td><td>46</td></tr>
<tr><td>≥3 zones affected, n</td><td>33</td><td>33</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Antituberculosis chemotherapy plus prednisolone

Prednisolone (8 weeks)

supplied as 5-mg tablets and was given concomitantly with tuberculous therapy at a dosage of 50 mg daily for 2 weeks, followed by 40 mg daily for 2 weeks, followed by 25 mg daily for 2 weeks, followed by 15 mg daily for 2 weeks; prednisolone treatment was then stopped

Antituberculosis chemotherapy: 2HRZE/4HR

doses were adjusted according to each patient’s weight, using the American Thoracic Society’s standard criteria

Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week</td></tr>
<tr><td>Comparison</td><td colspan="3">Antituberculosis chemotherapy plus placebo

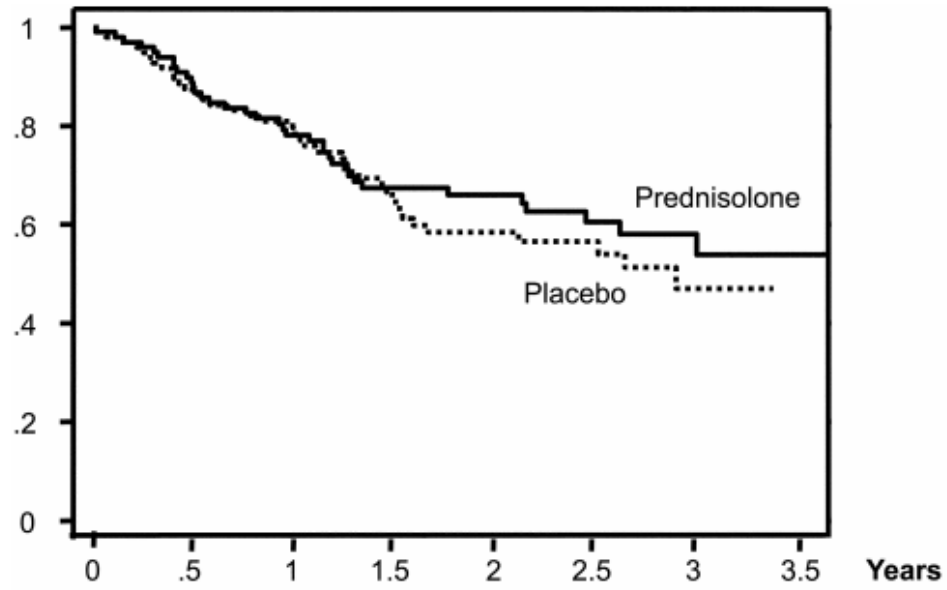
Placebo (8 weeks)

supplied as 5-mg tablets and was given concomitantly with tuberculous therapy at a dosage of 50 mg daily for 2 weeks, followed by 40 mg daily for 2 weeks, followed by 25 mg daily for 2 weeks, followed by 15 mg daily for 2 weeks; placebo treatment was then stopped

Antituberculosis chemotherapy: 2HRZE/4HR

doses were adjusted according to each patient’s weight, using the American Thoracic Society’s standard criteria</td></tr>
</table>

	Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week
Length of follow up	42 months
Location	Kampala, Uganda
Outcomes measures and effect size	**Mortality** Mortality rate (deaths/100 person years) prednisolone group (n = 99) = 21 antituberculosis chemotherapy alone group (n = 98) = 25 RR (95% CI) = 0.84 (0.53 to 1.32) i.e. not statistically significant Kaplan-Meier survival curve



Changes in signs and symptoms – anorexia

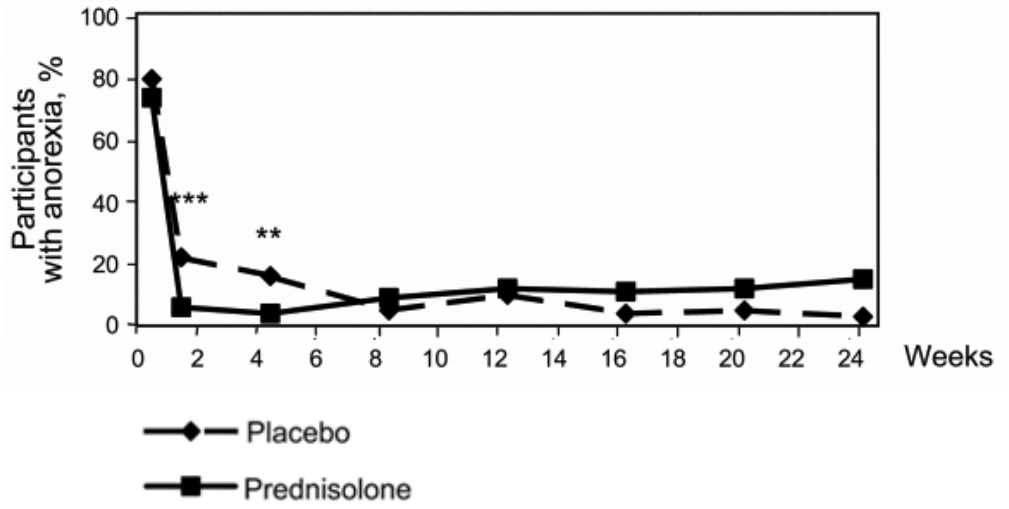
Number of patients to be anorexic after 24 weeks of treatment[2]

prednisolone group = 12 of 99

antituberculosis chemotherapy alone group = 3 of 98

OR[1] (95% CI) = 4.37 (1.19 to 16.00)

i.e. statistically significant



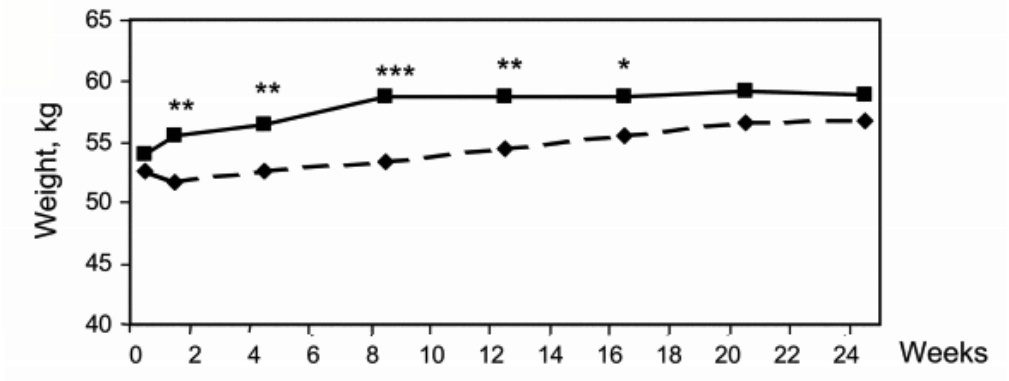
Changes in signs and symptoms – weight

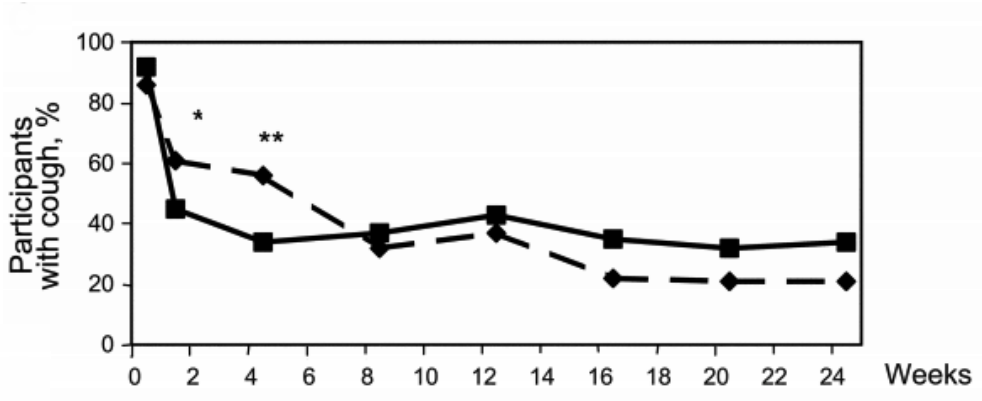
Weight (mean, kg) after 24 weeks of treatment[2]

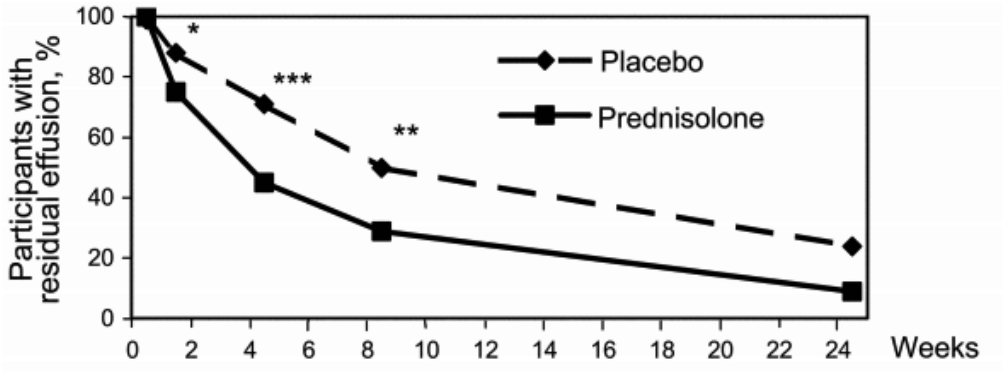
prednisolone group = 59

antituberculosis chemotherapy alone group = 56

MD[3] = 3 kg



	Placebo Prednisolone
	Changes in signs and symptoms – cough Number of patients with a cough after 24 weeks of treatment[2] prednisolone group = 26 of 99 antituberculosis chemotherapy alone group = 14 of 98 **OR[1] (95% CI) = 2.14 (1.04 to 4.40)** **i.e. statistically significant**  Placebo Prednisolone
	Changes in signs and symptoms – pleural effusion Number of patients with pleural effusion after 24 weeks of treatment[2] prednisolone group = 7 of 99

	antituberculosis chemotherapy alone group = 17 of 98 **OR[1] (95% CI) = 0.36 (0.14 to 0.92)** **i.e. statistically significant** 
	Recurrence Recurrence rate (cases/100 person years) prednisolone group = 4.5 antituberculosis chemotherapy alone group = 1.8 RR (95% CI) = 2.3 (0.6 to 9.0) i.e. not statistically significant
	Adverse events requiring treatment discontinuation Number of patients to experience an adverse event that required discontinuation of placebo/prednisolone prednisolone group = 9 of 99 antituberculosis chemotherapy alone group = 2 of 98 **OR[1] (95% CI) = 4.80 (1.01 to 22.82)**

	i.e. statistically significant
	Adverse events – incidence of HIV-related disease Number of patients to experience Kaposi sarcoma prednisolone group = 6 of 99 antituberculosis chemotherapy alone group = 0 of 98 OR[1] (95% CI) = 13.70 (0.76 to 246.52) i.e. not statistically significant Number of patients to experience cryptococcal meningitis prednisolone group = 3 of 99 antituberculosis chemotherapy alone group = 5 of 98 OR[1] (95% CI) = 0.58 (0.14 to 2.50) i.e. not statistically significant Number of patients to experience oesophageal candidiasis prednisolone group = 35 of 99 antituberculosis chemotherapy alone group = 23 of 98 OR[1] (95% CI) = 1.78 (0.96 to 3.32) i.e. not statistically significant Number of patients to experience herpes zoster prednisolone group = 22 of 99 antituberculosis chemotherapy alone group = 19 of 98 OR[1] (95% CI) = 1.19 (0.60 to 2.37)

	i.e. not statistically significant Number of patients to experience oral or genital herpes simplex prednisolone group = 22 of 99 antituberculosis chemotherapy alone group = 20 of 98 OR[1] (95% CI) = 1.11 (0.56 to 2.21) i.e. not statistically significant Number of patients to experience oral thrush prednisolone group = 31 of 99 antituberculosis chemotherapy alone group = 31 of 98 OR[1] (95% CI) = 1.43 (0.79 to 2.56) i.e. not statistically significant Number of patients to experience gastroenteritis prednisolone group = 34 of 99 antituberculosis chemotherapy alone group = 28 of 98 OR[1] (95% CI) = 1.31 (0.72 to 2.39) i.e. not statistically significant
Source of funding	Details not provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Read off graph by reviewer

[3] Mean difference calculated by reviewer

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

1.5.6 Galarza et al, 1995

Bibliographic reference	Galarza I, Cañete C, Granados A et al (1995) Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. Thorax 50: 1305-7
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes, although the details provided were 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?*

<table>
<tr><td></td><td>yes
Population studied is the same as the population of interest?
yes
Intervention used is the same as the intervention of interest?
yes, although patients received only 2 drugs, lacking ethambutol and pyrazinamide
Have substitute outcomes been used instead of the patient-important outcomes of interest?
no
Analysis followed the intent-to-treat principle?
yes</td></tr>
<tr><td>Number of patients</td><td>Randomised = 117
prednisolone group = 57
placebo group = 60</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Pleural effusion of tuberculous aetiology
Exclusion
HIV infection
Baseline
Definite microbiological or pathological diagnosis was obtained in 63% of patients
<table>
<tr><th></th><th>Prednisolone group
(n = 57)</th><th>Placebo group
(n = 60)</th></tr>
<tr><td>Age (mean (range)), years</td><td>26 (11–53)</td><td>28 (14–53)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Sex, male:female</td><td>33:27</td><td>30:31</td></tr>
<tr><td>Side
right, n (%)
left, n (%)</td><td>
34
23</td><td>
36
24</td></tr>
<tr><td>Fever (mean (range)), days</td><td>3.32 (0–50)</td><td>4.15 (0–60)</td></tr>
<tr><td>Thickening (mean (range)), mm</td><td>1.77 (0–40)</td><td>2.23 (0–15)</td></tr>
<tr><td>FVC (mean (range)), % predicted</td><td>95 (65–130)</td><td>95 (63–140)</td></tr>
<tr><td>Follow-up (mean (range)), months</td><td>46 (12–94)</td><td>46 (12–96)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone

Prednisolone (30 days)

administered in a single oral dose of 1 mg/kg of body weight/day during the first 15 days, and then gradually tapered off as follows: to 0 5 mg/kg of body weight/day from day 16-20 of treatment, then to 0-25 mg/ kg of body weight/day from day 21-26, and finally to 0 10 mg/kg of body weight/day for the remaining days of the month

Antituberculosis chemotherapy: 6HR

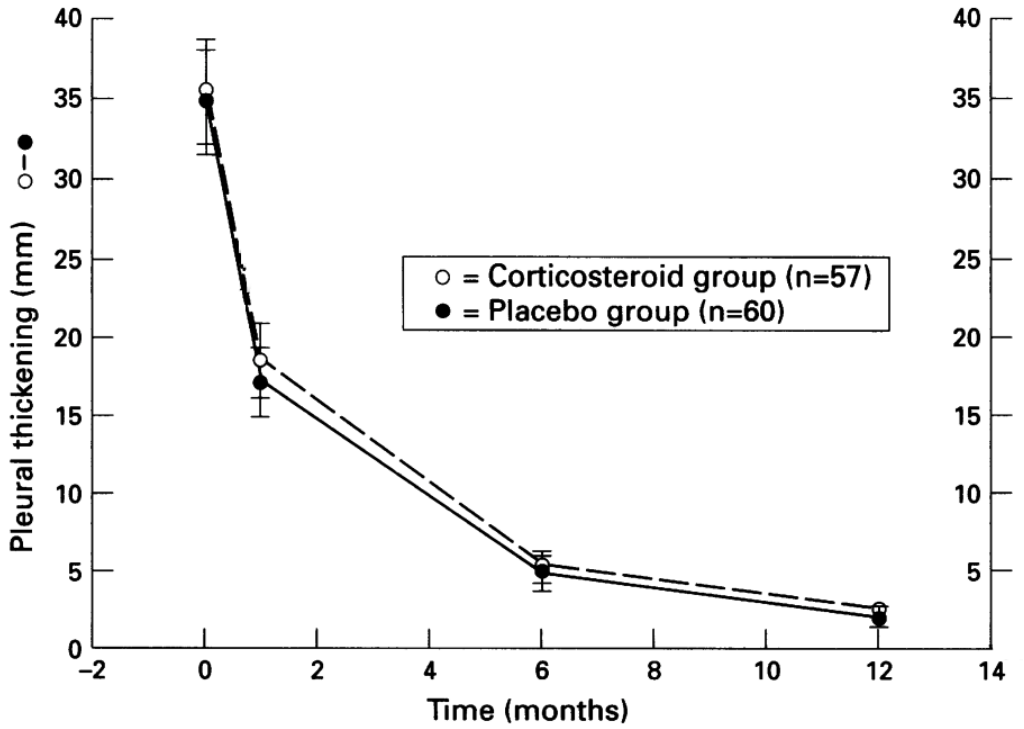
isoniazid, 5 mg/kg/day or a total daily dose of 300 mg, and rifampicin, 10 mg/kg of body weight/day or a total daily dose of 600 mg/day, once a day for six months as a combination tablet</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy plus placebo

Placebo (30 days)

administered in a single oral dose of 1 mg/kg of body weight/day during the first 15 days, and then gradually tapered off as follows: to 0 5 mg/kg of body weight/day from day 16-20 of treatment, then to 0-25 mg/ kg of body weight/day from day 21-26, and finally to 0 10 mg/kg of body weight/day for the remaining days of the month

Antituberculosis chemotherapy: 6HR</td></tr>
</table>

	isoniazid, 5 mg/kg/day or a total daily dose of 300 mg, and rifampicin, 10 mg/kg of body weight/day or a total daily dose of 600 mg/day, once a day for six months as a combination tablet
Length of follow up	46 months
Location	Barcelona, Spain
Outcomes measures and effect size	**Changes in signs and symptoms – pleural thickening** Number of patients to show pleural thickening at 12 months, as assessed using a chest x-ray prednisolone group = 1 of 57 placebo group = 5 of 60 OR[2] (95% CI) = 0.20 (0.02 to 1.74) i.e. not statistically significant Pleural thickening (mean (range), days) at 46 months, as assessed using a chest x-ray prednisolone group (n = 57) = 1.77 (0–40) placebo group (n = 60) = 2.23 (0–15) MD[3] = -0.46



Changes in signs and symptoms – pleural hemithorax reabsorption

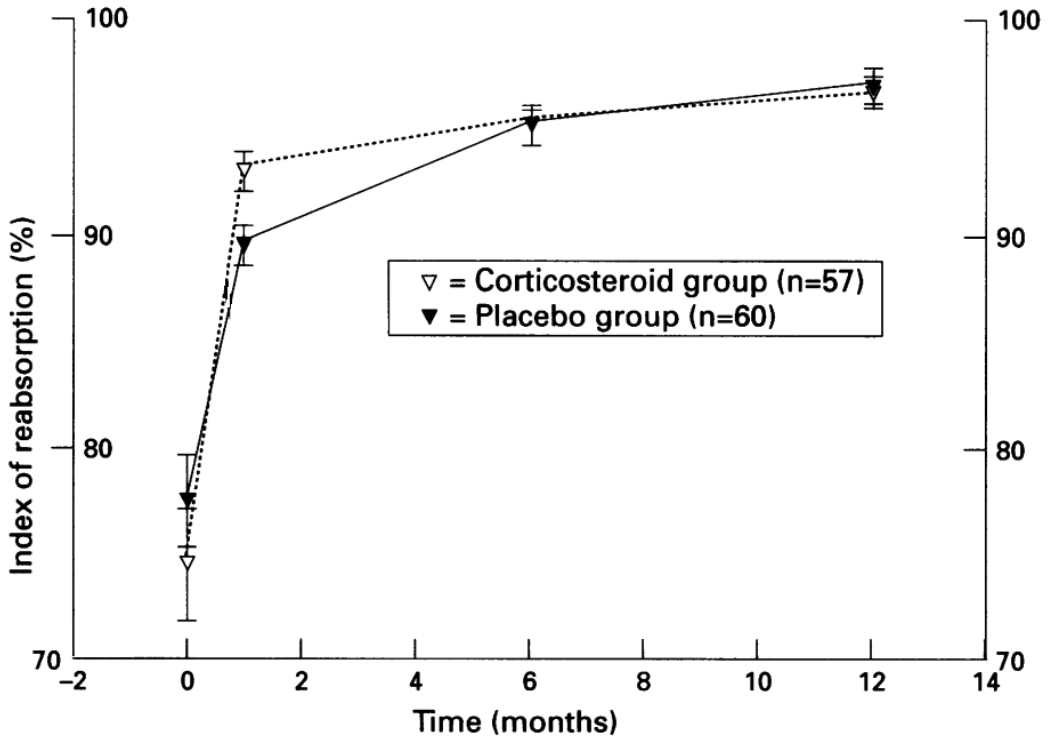
Index of reabsorption (mean±SE (range), %) at 12 months[1]

prednisolone group (n = 57) = 93±8 (70–119)

placebo group (n = 60) = 89±8 (76–113)

MD[3] (95% CI) = 4 (-18 to 26)

i.e. not statistically significant

	
	Changes in signs and symptoms – fever Duration of fever (mean (range), days) at 46 months prednisolone group (n = 57) = 3.32 (0–50) placebo group (n = 60) = 4.15 (0–60) MD[3] = -0.83
Source of funding	Fondo de Investigaciones de la Seguridad Social
Comments	

[1] Standard error read of the graph by reviewer

[2] Odds ratio and 95% confidence intervals, where possible, calculated by reviewer

[3] Mean difference and 95% confidence intervals, where possible, calculated by reviewer

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

1.5.7 Lee et al, 1988

Bibliographic reference	Lee C-H, Wang W-J, Lan R-S et al (1988) Corticosteroids in the treatment of tuberculosis pleurisy. A double-blind, placebo-controlled, randomised study. Chest 94(6): 1256-9
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, 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 *Intervention used is the same as the intervention of interest?* yes, although patients did not receive pyrazinamide *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 45 Outcome data available for = 40 prednisolone group = 21 placebo group = 19
Patient characteristics	*Inclusion* Onset of pleural effusion without previous treatment; other aetiologies of pleural effusion, such as congestive heart failure, pneumonia and malignancy, were excluded through diagnostic testing Aged <45 years *Diagnostic criteria* Diagnosis of tuberculous pleurisy was confirmed on the basis of pleural biopsy

<table>
<tr><td></td><td>
Exclusion
Other diseases or pulmonary diseases
Conditions that contraindicated the use of corticosteroids, such as diabetes, peptic ulcer or hypertension
Baseline
<table>
<tr><th></th><th>Prednisolone group
(n = 21)</th><th>Placebo group
(n = 19)</th></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>male, n</td><td>12</td><td>12</td></tr>
<tr><td>female, n</td><td>9</td><td>7</td></tr>
<tr><td>Age (mean (range)), years</td><td>28.4 (18–44)</td><td>28.9 (18–45)</td></tr>
<tr><td>Time from onset of symptoms to diagnosis (mean), days</td><td>20.6</td><td>15.4</td></tr>
<tr><td>Initial amount of pleural effusions[1]</td><td></td><td></td></tr>
<tr><td>small, n</td><td>9</td><td>5</td></tr>
<tr><td>moderate, n</td><td>9</td><td>9</td></tr>
<tr><td>large, n</td><td>3</td><td>5</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus prednisolone
Prednisolone
administered in an oral dose of 0.75 mg/kg of body weight/day initially
the dosage was tapered once the chest radiograph showed improvement
the dosage was diminished by two-thirds if any of the following conditions existed: 1) the effusion was right-sided and
</td></tr>
</table>

	the fluid level was only one intercostal space higher than that of the left hemidiaphragm, 2) the effusion was left-sided and the fluid level was at the same height as the right hemidiaphragm, or 3) complete disappearance of pleural effusion; the dosage of prednisolone was then diminished by 5 mg/week until discontinued Antituberculosis chemotherapy: 3HRE/6-9HR isoniazid at 300 mg/day, rifampicin at 450 mg/day, ethambutol at 20 mg/kg of body weight/day for the initial 3 months, followed by isoniazid and rifampicin at the same doses for the subsequent 6 to 9 months
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo administered in an oral dose of 0.75 mg/kg of body weight/day initially the dosage was tapered once the chest radiograph showed improvement the dosage was diminished by two-thirds if any of the following conditions existed: 1) the effusion was right-sided and the fluid level was only one intercostal space higher than that of the left hemidiaphragm, 2) the effusion was left-sided and the fluid level was at the same height as the right hemidiaphragm, or 3) complete disappearance of pleural effusion; the dosage of prednisolone was then diminished by 5 mg/week until discontinued Antituberculosis chemotherapy: 3HRE/6-9HR isoniazid at 300 mg/day, rifampicin at 450 mg/day, ethambutol at 20 mg/kg of body weight/day for the initial 3 months, followed by isoniazid and rifampicin at the same doses for the subsequent 6 to 9 months
Length of follow up	Exact period unclear, though at least 1 year
Location	Taipei, Taiwan
Outcomes measures and effect size	**Change in signs and symptoms – disappearance of clinical signs and symptoms** Time (mean±SD[2] (range), days) to disappearance of clinical signs and symptoms (including fever, chest pain and dyspnea) prednisolone group (n = 21) = 2.4±1.6 (1–7) placebo group (n = 19) = 9.2±16.5 (1–75) $p<0.05$

	MD[3] (95% CI) = -6.8 (-14.3 to 0.7) i.e. not statistically significant
	Change in signs and symptoms – pleural effusion Time (mean[4] (range), days) to clearance of pleural effusion (as defined by roentgenologic evidence of clearing of the lung field, with visualisation of the diaphragm and costophrenic angle) prednisolone group (n = 21) = 54.5 (6–365) placebo group (n = 19) = 123.2 (7–395) **p<0.01** **MD[3] = -68.7**
	Change in signs and symptoms – pleural adhesions Number of patients to experience pleural adhesions prednisolone group = 1 of 21 placebo group = 3 of 19 p = 0.27 OR[5] (95% CI) = 0.27 (0.03 to 2.82) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Small = less than one-third of one hemithorax; moderate = between one-third and two-thirds of one hemithorax; large = morTime (e than two-thirds of one hemithorax

[2] Standard deviation calculated from the individual patient data read off the graph by reviewer

[3] Mean difference and 95% confidence intervals, where possible, calculated by reviewer

[4] Standard deviation could not be calculated by reviewer as individual patient data could not be read off the graph

[5] Odds ratio and 95% confidence intervals calculated by reviewer

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

1.5.8 Wyser et al, 1996

Bibliographic reference	Wyser C, Walzl G, Smedema JP et al (1996) Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomised study. Chest 110(2): 333-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* although not statistically significant (p = 0.06), more patients receiving placebo (44.4%) had pleuritis *and* pulmonary tuberculosis than amongst those receiving prednisolone (21.2) *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?* follow-up not for the full treatment period *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, although patients did not receive ethambutol *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – 'morbidity' is a patient-reported, surrogate outcome made of a composite of well-being, appetite, night sweats, pleuritic chest pain, tiredness, dyspnea and cough *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 74 Outcome data available for = 70 prednisolone group = 34 placebo group = 36
Patient characteristics	*Inclusion* Exudative pleural effusions Biopsy specimen-proven tuberculous pleurisy *Diagnostic criteria* Diagnosis confirmed by the presence of caseating granulomas with or without acid-fast bacilli on histologic study and/or a positive *M. tuberculosis* culture

Exclusion

Other causes of pleural exudates, such as pneumonia or malignancy

Contraindications to corticosteroid use, such as diabetes mellitus, uncontrolled hypertension, peptic ulcer disease and empyema

HIV-seropositive

Neoplastic disease

Baseline

	Prednisolone group (n = 34)	**Placebo group** (n = 36)
Sex male, %	 61.8	 61.2
Age (mean±SD), years	32.9±13.0	32.8±12.5
Duration of illness prior to hospital admission (mean±SD), weeks	2.9±2.7	3.7±2.2
Pleuritis only, %	78.8	55.6
Pleuritis and pulmonary tuberculosis	21.2	44.4
Initial amount of pleural effusions on chest x-ray small, % moderate, % large, %	 2.9 14.7 82.4	 0 13.9 86.1
Positive M. tuberculosis culture pleural fluid, %	 8.8	 13.9

	pleural biopsy specimen, %	78.8	77.8
	bronchial lavage, %	14.7	8.6
	Histology		
	caseating granuloma, %	93.7	91.7
	non-caseating granuloma, %	6.1	8.3
	Ziehl-Neelsen positive, %	51.5	47.2
	Appearance on thoracoscopy[1]		
	type 1	9.0	5.7
	type 2	66.6	62.8
	type 3	30.4	31.5
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone administered in an oral dose of 0.75 mg/kg of body weight/day initially after 2 to 4 weeks, depending on the therapeutic response as assessed by a progressive reduction of symptoms and radiologic improvement, the dosage was tapered over a 2-week period by 5 mg/dl in all patients Antituberculosis chemotherapy: 6HRZ isoniazid at 8 mg/kg of body weight/day, rifampicin at 10 mg/kg of body weight/day and pyrazinamide at 25 mg/kg of body weight/day for 6 months All patients received 25 mg/kg of body weight/day of pyridoxine		
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo		

	administered in an oral dose of 0.75 mg/kg of body weight/day initially after 2 to 4 weeks, depending on the therapeutic response as assessed by a progressive reduction of symptoms and radiologic improvement, the dosage was tapered over a 2-week period by 5 mg/dl in all patients Antituberculosis chemotherapy: 6HRZ isoniazid at 8 mg/kg of body weight/day, rifampicin at 10 mg/kg of body weight/day and pyrazinamide at 25 mg/kg of body weight/day for 6 months All patients received 25 mg/kg of body weight/day of pyridoxine
Length of follow up	24 weeks
Location	Cape Town, South Africa
Outcomes measures and effect size	**Changes in signs and symptoms – 'morbidity'** A combined index score for morbidity, measured using a visual analogue scale, incorporating well-being, appetite, night sweats, pleuritic chest pain, tiredness, dyspnea and cough Morbidity score (median (range)) at 24 weeks prednisolone group (n = 34) = 0 (0–0) placebo group (n = 36) = 0 (0–0) Median difference[2] = 0 i.e. not statistically significant
	Changes in signs and symptoms – pleural thickening Number of people to with residual pleural thickening, as assessed using a chest x-ray prednisolone group = 17 of 34 placebo group = 18 of 36 OR[3] (95% CI) = 1.00 (0.39 to 2.55)

	i.e. not statistically significant Number of people to with residual pleural thickening, as assessed using a CT scan prednisolone group = 17 of 34 placebo group = 21 of 36 OR[3] (95% CI) = 0.71 (0.28 to 1.84) i.e. not statistically significant Pleural thickening (mean±SD, mm) at 24 weeks, as assessed using a chest x-ray prednisolone group (n = 34) = 2.1±2.7 placebo group (n = 36) = 2.5±3.7 MD[4] (95% CI) = -0.4 (-1.9 to 1.1) i.e. not statistically significant Change in pleural thickening (MD (95% CI), mm) from baseline to 24 weeks, as assessed using a chest x-ray[5] prednisolone group (n = 34) = -7.3 (-9.0 to -5.6) placebo group (n = 36) = -7.9 (-10.1 to -5.7) Difference in change in means[6] = -0.6 Pleural thickening (mean±SD, mm) at 24 weeks, as assessed using a CT scan prednisolone group (n = 34) = 3.0±3.7 placebo group (n = 36) = 4.3±5.1 MD[4] (95% CI) = -1.3 (-3.4 to 0.8)
	Adverse events Number of people to experience an adverse event

	prednisolone group = 4 of 34 placebo group = 3 of 36 OR[3] (95% CI) = 1.47 (0.30 to 7.10) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Type 1 = non-specific inflammation of the parietal pleura with no or only a few fibrinous adhesions; type 2 = 'classic' tuberculous pleurisy with an inflamed reddish pleura and multiple greyish-white nodules; type 3 = fibrous inflammation with a thickened parietal pleura and multiple fibrous adhesions and/or loculations

[2] Median difference calculated by reviewer

[3] Odds ratio and 95% confidence interval calculated by reviewer

[4] Mean difference and 95% confidence interval calculated by reviewer

[5] Changes in mean and 95% confidence interval calculated by reviewer

[5] Difference in the changes in mean calculated by reviewer

Abbreviations: CI, confidence intervals; CT, computerised tomography; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

1.5.9 Singh & Yesikar, 1965

Bibliographic reference	Singh D & Yesikar SS (1965) Role of intrapleural corticosteroids in tuberculous pleural effusion. A clinicotherapeutic trial of 50 cases. Journal of the Indian Medical Association 45(6): 306-9
Study type	Non-randomised controlled trial
Study quality	*Appropriate method of randomisation used?* no

	Allocation concealment used? no *Blinding used?* 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 *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, although patients did not receive rifampicin, pyrazinamide and ethambutol but received streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?*

	yes
Number of patients	Randomised = 50 dexamethasone group = 30 antituberculosis chemotherapy alone group = 20
Patient characteristics	*Inclusion* Pleural effusion with tuberculous aetiology Typical onset and course of disease Positive Mantoux test
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone 4 mg of dexamethasone injected intrapleurally and the pleural fluid aspirated every 15 days until the puncture was dry Antituberculosis chemotherapy: SH isoniazid at 300 mg/day and streptomycin at 1 g/day All patients received vitamins and haematinics All patients were hospitalised and were at rest
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: SH isoniazid at 300 mg/day and streptomycin at 1 g/day Half of the patients also underwent aspirations every 15 days until the puncture was dry All patients received vitamins and haematinics All patients were hospitalised and were at rest

Length of follow up	Unclear
Location	Bhopal, India
Outcomes measures and effect size	**Changes in signs and symptoms – effusion** Time (mean, days) taken for complete absorption of pleural effusion dexamethasone group (n = 30) = 23.5 antituberculosis chemotherapy alone group (n = 20) = 71.2 MD[1] = -47.7 Time (mean, days) taken for complete absorption of pleural effusion among those with a large effusion dexamethasone group (n = 9) = 30.0 antituberculosis chemotherapy alone group (n = 4) = 93.8 MD[1] = -63.8 Time (mean, days) taken for complete absorption of pleural effusion among those with a medium effusion dexamethasone group (n = 16) = 22.5 antituberculosis chemotherapy alone group (n = 12) = 72.5 MD[1] = -50.0 Time (mean, days) taken for complete absorption of pleural effusion among those with a small effusion dexamethasone group (n = 5) = 15.0 antituberculosis chemotherapy alone group (n = 4) = 45.0 MD[1] = -30.0
	Changes in signs and symptoms – cough Time (mean, days) to relief of cough

	dexamethasone group (n = 30) = 20.1 antituberculosis chemotherapy alone group (n = 20) = 32.2 MD[1] = -12.1
	Changes in signs and symptoms – shortness of breath Time (mean, days) to relief of shortness of breath dexamethasone group (n = 30) = 3.1 antituberculosis chemotherapy alone group (n = 20) = 15.7 MD[1] = -12.6
	Changes in signs and symptoms – chest pain Time (mean, days) to relief of chest pain dexamethasone group (n = 30) = 6.9 antituberculosis chemotherapy alone group (n = 20) = 20.7 MD[1] = -13.8
	Changes in signs and symptoms – temperature Time (mean, days) to normalisation of temperature dexamethasone group (n = 30) = 9.0 antituberculosis chemotherapy alone group (n = 20) = 28.8 MD[1] = -19.8
	Changes in signs and symptoms – weight Final weight (mean, kg) dexamethasone group (n = 30) = 43.4

	antituberculosis chemotherapy alone group (n = 20) = 41.8 MD[1] = 1.6 Change in mean weight (kg) from baseline to the end of follow-up dexamethasone group (n = 30) = 2.0 antituberculosis chemotherapy alone group (n = 20) = 1.5 MD[1] = 0.5
	Recurrence Number of patients to experience recurrence dexamethasone group = 0 of 30 antituberculosis chemotherapy alone group = 4 of 20 OR[2] (95% CI) = 0.06 (0.00 to 1.19) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Mean difference and 95% confidence interval calculated by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer

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

TUBERCULOSIS WITH SEVERE BRONCHIAL OBSTRUCTION

1.5.10 Toppet et al, 1990

Bibliographic reference	Toppet M, Malfroot A, Derde MP et al (1990) Corticosteroids in primary tuberculosis with bronchial obstruction. Archives of Disease in Childhood 65: 1222-6
Study type	RCT
Study quality	*Appropriate method of randomisation used?* numbered envelopes *Allocation concealment used?* unclear *Blinding used?* 'open' trial, although examination of bronchoscopy and radiographs blinded *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* unclear – those receiving steroids were recommended a sodium-restricted diet, potassium glucoconate supplements and gastric protection by aluminium phosphate, but it is unclear if those on antituberculosis chemotherapy alone received these *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 or just the 4 standard recommended drugs: lack pyrazinamide *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – need for multiple bronchoscopies is a surrogate for changes in signs and symptoms *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 29 prednisolone group = 15 antituberculosis chemotherapy alone group = 14 Outcome data available for outcomes based on bronchoscopy = 29 prednisolone group = 15 antituberculosis chemotherapy alone group = 14 Outcome data available for outcomes based on radiography = 23 prednisolone group = 13 antituberculosis chemotherapy alone group = 10
Patient characteristics	*Inclusion* Children

Symptomatic tuberculosis with severe bronchial obstruction suspected by radiology and demonstrated by bronchoscopy

A compression of at least 50% of a bronchus

A bronchoscopy score equal or higher than 2, according to the following scoring system:

localisation: trachea = 4; main bronchus = 3; lobar bronchus = 2; segmental bronchus = 1

importance of the obstruction: total or >75% = 4; 50-75% = 2; <50% = 1; no obstruction = 0

Diagnostic criteria

A combination of the following:

recent tuberculin conversion with an induration of at least 10 mm after 48 or 72 hours

clinical signs such as an unexpected course of pulmonary consolidation, long standing unexplained fever or cough

family history of tuberculosis

chest radiographs

bronchoscopy

Exclusion

Patients who already had bronchial fistulisation were not included in this study as the aim was to verify whether fistulisation could be prevented

Meningitis

Miliary tuberculosis

Patients without clinical and radiological abnormalities and negative bacteriology for *M. tuberculosis*

Baseline[1]

	Prednisolone (n = 15)	**Antituberculosis chemotherapy alone group**

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>(n = 10)</td></tr>
<tr><td>Age (mean±SD (range)), years</td><td>4.3±4.2 (0.3–12)</td><td>5.5±4.2 (0.5–15)</td></tr>
<tr><td>Sex
males, n
females, n</td><td>
11
4</td><td>
8
6</td></tr>
<tr><td>M. tuberculosis culture
positive, n
negative, n</td><td>
9
6</td><td>
9
5</td></tr>
<tr><td>Score on radiology[2] (mean±SD (range))</td><td>4.8±2.2 (3–10)</td><td>3.9±1.4 (2–6)</td></tr>
<tr><td>Score on bronchoscopy[3] (mean±SD (range))</td><td>15.4±6.9 (2–26)</td><td>11.8±5.7 (3–21)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone
Prednisolone (3 to 3.5 months)
started at a daily dose of 2 mg/kg of body weight for 15 days and was progressively decreased to be stopped between 2.5 and 3 months
Antituberculosis chemotherapy: 2HRZE/10HR
10 mg/kg of body weight/day of isoniazid (up to a maximum of 300 mg/day), 15 mg/kg of body weight/day of rifampicin (up to a maximum of 600 mg/day) and 20 mg/kg of body weight/day of ethambutol for 2 months
isoniazid and rifampicin at the same doses for the following 10 months</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: 2HRZE/10HR</td></tr>
</table>

	10 mg/kg of body weight/day of isoniazid (up to a maximum of 300 mg/day), 15 mg/kg of body weight/day of rifampicin (up to a maximum of 600 mg/day) and 20 mg/kg of body weight/day of ethambutol for 2 months isoniazid and rifampicin at the same doses for the following 10 months
Length of follow up	Full treatment period (12 months)
Location	Brussels, Belgium
Outcomes measures and effect size	**Changes in signs and symptoms – radiological status** Number of patients whose radiological score normalised during treatment prednisolone group = 13 of 15 antituberculosis chemotherapy alone group = 9 of 14 OR[4] (95% CI) = 3.61 (0.57 to 22.90) i.e. not statistically significant Number of patients whose radiological score improved in ≤1 month prednisolone group = 7 of 15 antituberculosis chemotherapy alone group = 0 of 14 **OR[4] (95% CI) = 25.59 (1.29 to 506.48)** **i.e. statistically significant** Number of patients whose radiological score deteriorated during treatment prednisolone group = 2 of 15 antituberculosis chemotherapy alone group = 5 of 14 OR[4] (95% CI) = 0.28 (0.04 to 1.76) i.e. not statistically significant

	Changes in signs and symptoms – bronchial status Change (mean±SD) in bronchoscopy score[3] from baseline to 1 month post-treatment prednisolone group (n = 15) = 12.1±6.9 antituberculosis chemotherapy alone group (n = 14) = 5.9±5.0 **MD[5] (95% CI) = 6.2 (1.83 to 10.57)** **i.e. statistically significant**
	Response to treatment – need for multiple bronchoscopies Number of patients to require >2 bronchoscopies prednisolone group = 1 of 15 antituberculosis chemotherapy alone group = 6 of 14 **OR[4] (95% CI) = 0.10 (0.01 to 0.94)** **i.e. statistically significant**
Source of funding	No details provided
Comments	

[1] Authors provided individual patient data; reviewer summarised for comparison of the 2 groups

[2] Radiological score: size of the adenopathy scored 1 to 3; segmental consolidation or hyperinflation scored 1; lobar consolidation or hyperinflation scored 3; pulmonary consolidation or hyperinflation scored 6

[3] Bronchoscopy score:

localisation: trachea = 4; main bronchus = 3; lobar bronchus = 2; segmental bronchus = 1

importance of the obstruction: total or >75% = 4; 50-75% = 2; <50% = 1; no obstruction = 0

[4] Odds ratio and 95% confidence interval calculated by reviewer

[5] Mean difference and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

1.5.11 Chotmongkol et al, 1996

Bibliographic reference	Chotmongkol V, Jitpimolmard S & Thavornpitak Y (1996) Corticosteroid in tuberculous meningitis. Journal of the Medical Association of Thailand 79(2): 83-90
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear – patients were randomised by a block size of 4 using coded treatment (A = placebo; B = prednisolone) *Allocation concealment used?* unclear *Blinding used?* double-blind – participants receiving care and individuals administering care were blind to treatment allocation; unclear if investigators were blind to treatment allocation, or to important confounding or prognostic factors *Groups comparable at baseline?* clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, although not statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness than in the placebo group (10%) additionally, there were more patients with severe (stage 3) disease and fewer patients with less severe (stage 1) disease in the prednisolone group than in the placebo group, although again this was not statistically significant *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 – 12 months after treatment completion

	Groups comparable for treatment completion and availability of outcome data? yes – 100% in both groups *Study used precise definitions and reliable measures of outcome?* yes, although details provided are limited *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: lack ethambutol and contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – need for additional intervention (response to treatment) is a substitute for treatment success/failure *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 59 prednisolone group = 29 placebo group = 30
Patient characteristics	*Inclusion* Tuberculous meningitis Aged more than 15 years Negative serologic test for syphilis and HIV *Diagnostic criteria*

According to characteristic clinical features and CSF findings:

lymphocytic meningitis

low glucose level

elevation of protein content

sterile routine bacterial and fungal culture

negative latex agglutination test for bacterial and cryptococcal antigen

negative cytologic study for malignancy

Severity of disease

Classified according to the system of Gordon and Parsons (1972):

stage 1: patients were conscious and rational with meningism but no focal neurological signs or signs of hydrocephalus

stage 2: patients were confused or had focal neurological signs such as squint, hemiparesis or signs of hydrocephalus

stage 3: the patients' mental state could not be assessed because of stupor or delirium, complete hemiplegia or paraplegia

Baseline

	Prednisolone group (n = 29)	**Placebo group** (n = 30)	**p value**
Age (mean±SD), years	42±18.6	39±18.3	0.51
Sex (males), %	55.2	53.3	0.90
Staging			
1, %	10.3	20.0	

		2, %	69.0	66.7		
		3, %	20.7	13.3		
		Headache, %	93.1	96.7	0.61	
		Fever (temperature > 38.0°C), %	93.1	76.7	0.15	
		Stiff neck, %	96.6	96.7	1.00	
		Mental impairment (confusion, stuporous), %	69.0	63.3	0.85	
		Papilloedema, %	24.1	16.7	0.70	
		Cranial nerve palsies, %	24.1	20.0	0.94	
		Decreased vision, %	10.3	10.0		
		Motor weakness (parapesis, hemiparesis), %	17.2	10.0	0.10	
		Other foci of tuberculous infection, %	58.6	43.3	0.36	
		lung, %	51.7	26.7		
		lymph node, %	0.0	10.0		
		spine, %	0.0	3.3		
		larynx, %	3.4	0.0		
		peritoneum, %	3.4	0.0		
		intestine, %	0.0	3.3		
		Abnormal chest x-ray, %	51.7	26.7	0.08	
		Abnormal CT scan of brain (hydrocephalus, lacunar infarction, tuberculoma, brain oedema), %	83.3	84.6	1.0	
		Hyponatraemia (<125 mEq/L), %	20.7	10.0	0.29	

	CSF abnormalities			
	high opening pressure (>300 mmH2O), %	51.7	56.7	0.90
	white blood cell count (/mm3)			
	mean	403	388	0.80
	range	25–1202	10–2000	
	protein content (mg/dl)			
	mean	247.8	287	0.67
	range	57–9570	76–8500	
	positive AFB stain, %	3.4	0.0	
	positive culture for *M. tuberculosis*, %	13.8	3.3	
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (5 weeks) 60 mg/day taken orally with alum milk in 3 divided doses after meals during the first week the dose was reduced to 45, 30, 20 and 10 mg/day for the second, third, forth and fifth weeks respectively, then discontinued Antituberculosis chemotherapy: 2HRZS/4HR 300 mg isoniazid, 600 mg rifampicin (450 mg for those weighing less than 50 kg), 1500 mg pyrazinamide and 750 mg streptomycin for the first 2 months isoniazid and rifampicin at the same doses for the following 4 months			
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (5 weeks)			

	tablets of identical appearance to the prednisolone 60 mg/day taken orally with alum milk in 3 divided doses after meals during the first week the dose was reduced to 45, 30, 20 and 10 mg/day for the second, third, forth and fifth weeks respectively, then discontinued Antituberculosis chemotherapy: 2HRZS/4HR 300 mg isoniazid, 600 mg rifampicin (450 mg for those weighing less than 50 kg), 1500 mg pyrazinamide and 750 mg streptomycin for the first 2 months isoniazid and rifampicin at the same doses for the following 4 months
Length of follow up	12 months after treatment completion
Location	Khon Kaen, Thailand
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 5 of 29 placebo group = 2 of 30 p = 0.25 OR[1] (95% CI) = 2.92 (0.52 to 16.42) i.e. not statistically significant Stage 1 prednisolone group = 0 of 3 placebo group = 0 of 6 OR[1] (95% CI) = 1.86 (0.03 to 115.45) i.e. not statistically significant

	Stage 2 prednisolone group = 1 of 20 placebo group = 0 of 20 OR[1] (95% CI) = 3.15 (0.12 to 82.17) i.e. not statistically significant Stage 3 prednisolone group = 4 of 6 placebo group = 2 of 4 OR[1] (95% CI) = 2.00 (0.15 to 26.74) i.e. not statistically significant
	Response to treatment – need for additional intervention (ventricular shunting) Number of patients to require ventricular shunting (as indicated by persistent high CSF pressure after 4 weeks of repeated lumbar puncture) prednisolone group = 5 of 29 placebo group = 4 of 30 p = 0.73 OR[1] (95% CI) = 1.35 (0.33 to 5.64) i.e. not statistically significant
	Changes in signs and symptoms – neurological abnormalities during treatment Number of patients to experience neurological abnormalities newly developed during treatment prednisolone group = 2 of 29

	placebo group = 4 of 30 p = 0.67 OR[1] (95% CI) = 0.48 (0.08 to 2.86) i.e. not statistically significant Number of patients to experience urinary retention newly developed during treatment prednisolone group = 1 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 1.04 (0.06 to 17.38) i.e. not statistically significant Number of patients to experience arm weakness newly developed during treatment prednisolone group = 1 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 3.21 (0.13 to 82.07) i.e. not statistically significant Number of patients to experience paraparesis newly developed during treatment prednisolone group = 0 of 29 placebo group = 2 of 30 OR[1] (95% CI) = 0.19 (0.01 to 4.20) i.e. not statistically significant Number of patients to experience hemiparesis newly developed during treatment prednisolone group = 0 of 29

	placebo group = 1 of 30 OR[1] (95% CI) = 0.33 (0.01 to 8.52) i.e. not statistically significant
	Changes in signs and symptoms – neurological abnormalities after treatment Number of patients to experience neurological abnormalities after treatment prednisolone group = 4 of 29 placebo group = 2 of 30 p = 0.42 OR[1] (95% CI) = 2.24 (0.38 to 13.30) i.e. not statistically significant Number of patients to experience decreased vision after treatment prednisolone group = 2 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 2.15 (0.18 to 25.07) i.e. not statistically significant Number of patients to experience spastic paraparesis after treatment prednisolone group = 1 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 1.04 (0.06 to 17.38) i.e. not statistically significant Number of patients to experience hemiparesis after treatment

	prednisolone group = 1 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 3.21 (0.13 to 82.07) i.e. not statistically significant
	Changes in signs and symptoms - headache Time (mean, days) until disappearance of headache prednisolone group (n = 29) = 15.9 placebo group (n = 30) = 13.3 p = 0.61 MD[2] = 2.6
	Changes in signs and symptoms - fever Time (mean (range), days) until normal body temperature prednisolone group (n = 29) = 5.6 (1 – 27) placebo group (n = 30) = 9.3 (2 – 21) p = 0.06 MD[2] = -3.7
	Recurrence Number of patients to experience recurrence of meningitis during follow-up prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83)

	i.e. not statistically significant
	Adverse events - gastrointestinal bleeding Number of patients to experience gastrointestinal bleeding prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83) i.e. not statistically significant
	Adverse events - hyperglycaemia Number of patients to experience hyperglycaemia prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83) i.e. not statistically significant
Source of funding	Tablets of prednisolone and placebo were provided by Siam Pharmaceutical Co. Ltd.
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference calculated by reviewer

Abbreviations: AFB, acid-fast bacilli; CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; H, isoniazid; HIV, human immunodeficiency virus; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis; Z, pyrazinamide

1.5.12 Girgis et al, 1983

Bibliographic reference	Girgis NI, Farid Z, Hanna LS (1983) The use of dexamethasone in preventing ocular complications in tuberculous meningitis. Transactions of the Royal Society of Tropical Medicine and Hygiene 77(5): 658-9
Study type	Non-randomised controlled trial
Study quality	*Appropriate method of randomisation used?* no – allocation was not randomised, rather patients were alternately assigned to receive antituberculosis chemotherapy plus dexamethasone or antituberculosis chemotherapy alone *Allocation concealment used?* no *Blinding used?* unclear *Groups comparable at baseline?* authors state that groups were comparable with respect to age, sex and disease severity on admission to hospital; however, although not statistically significant, more patients in the dexamethasone group (32/70) were comatose on admission than in the antituberculosis chemotherapy alone group (41/66) – that is, the condition of those in the dexamethasone group could be considered to be more severe *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?*

<table>
<tr><td></td><td>yes, although details provided are limited

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: lack rifampicin and pyrazinamide, but contain streptomycin

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

no</td></tr>
<tr><td>Number of patients</td><td>Included = 136

dexamethasone group = 66

antituberculosis chemotherapy alone group = 70</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion

Tuberculous meningitis

Diagnostic criteria

Isolation of tubercle bacilli from the CSF, or a CSF findings consistent with tuberculous meningitis (increased protein, low glucose, and lymphocytotic pleocytosis)

Baseline
<table>
<tr><th></th><th>Dexamethasone group
(n = 66)</th><th>Antituberculosis chemotherapy alone group
(n = 70)</th></tr>
<tr><td>Sex

males, %</td><td>

45.5</td><td>

54.3</td></tr>
</table>
</td></tr>
</table>

	females, %	54.5	45.7
	Age (mean (range)), years	14.6 (0.5 – 52)	13.6 (0.6 – 42)
	CSF positive for tubercle bacilli, %	45.5	48.6
	Duration of symptoms prior to admission (mean (range)), days	27.8 (6 – 120)	25.5 (5 – 105)
	Clinical condition on admission		
	alert, %	3.0	7.1
	drowsy, %	34.8	47.1
	comatose, %	62.1	45.7
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone (3 weeks) 8 to 12 mg/day Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid, 25 mg/kg of body weight/day streptomycin and 25 mg/kg of body weight/day ethambutol for the first 60 days 10 mg/kg of body weight/day isoniazid and 25 mg/kg of body weight/ day ethambutol for the remainder of the 2-year treatment period		
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid, 25 mg/kg of body weight/day streptomycin and 25 mg/kg of body weight/day ethambutol for the first 60 days 10 mg/kg of body weight/day isoniazid and 25 mg/kg of body weight/ day ethambutol for the remainder of the 2-year		

	treatment period
Length of follow up	Unclear
Location	Cairo, Egypt
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 39 of 66 antituberculosis chemotherapy alone group = 42 of 70 OR[1] (95% CI) = 0.96 (0.49 to 1.91) i.e. not statistically significant Alert on admission dexamethasone group = 0 of 2 antituberculosis chemotherapy alone group = 2 of 5 OR[1] (95% CI) = 0.28 (0.01 to 8.76) i.e. not statistically significant Drowsy on admission dexamethasone group = 8 of 23 antituberculosis chemotherapy alone group = 14 of 33 OR[1] (95% CI) = 0.72 (0.24 to 2.18) i.e. not statistically significant Comatose admission dexamethasone group = 31 of 41

	antituberculosis chemotherapy alone group = 26 of 32 OR[1] (95% CI) = 0.72 (0.23 to 2.23) i.e. not statistically significant CSF positive for tubercle bacilli dexamethasone group = 19 of 30 antituberculosis chemotherapy alone group = 21 of 34 OR[1] (95% CI) = 1.07 (0.39 to 2.95) i.e. not statistically significant
	Adverse events – ocular complications Number of patients with ocular complications dexamethasone group = 2 of 66 antituberculosis chemotherapy alone group = 7 of 70 OR[1] (95% CI) = 0.28 (0.06 to 1.41) i.e. not statistically significant Number of patients with CSF positive for tubercle bacilli with ocular complications dexamethasone group = 2 of 30 antituberculosis chemotherapy alone group = 4 of 34 OR[1] (95% CI) = 2.46 (0.42 to 14.52) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; E, ethambutol H, isoniazid; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.5.13 Girgis et al, 1991

Bibliographic reference	Girgis NI, Farid Z, Kilpatrick ME (1991) Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatric Infectious Disease Journal 10(3): 179-83
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – number randomisation chart *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?* limited data available for the incidence of neurologic abnormalities due to a high rate of mortality, though the loss to follow-up was similar in the 2 groups (dexamethasone = 72 of 145; antituberculosis chemotherapy alone = 79 of 135)

	Study used precise definitions and reliable measures of outcome? yes, although details provided are limited *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: lack rifampicin and pyrazinamide, but contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Included = 280 dexamethasone group = 145 antituberculosis chemotherapy alone group = 135
Patient characteristics	*Inclusion* Tuberculous meningitis *Diagnostic criteria* Clinical history Signs and symptoms compatible with tuberculous meningitis: low grade fever severe progressive headache

vomiting

generalised weakness

diplopia

cranial nerve affections

deterioration of mental alertness

duration of illness more than 30 days

comparison of results from the first and second CSF examinations

poor response to antibacterial therapy (250,000 units/kg of body weight/day of penicillin or 160 mg/kg of body weight/day of ampicillin plus 100 mg/kg of body weight/day of chloramphenicol) for 48 hours

Baseline

	Dexamethasone group (n = 145)		**Antituberculosis chemotherapy alone group** (n = 135)	
	CSF culture-positive (n = 75)	**CSF culture-negative** (n = 70)	**CSF culture-positive** (n = 85)	**CSF culture-negative** (n = 50)
Sex				
male, n	38	43	46	31
female, n	37	27	39	19
Age				
(median), years	12	6	6	16
<1 year, n	4	8	5	5

		1–5 years, n	19	27	25	11	
		6–15 years, n	23	11	21	7	
		16–25 years, n	15	7	12	14	
		>25 years, n	14	17	22	13	
		Duration of symptoms prior to hospitalisation					
		<14 days, n	13	20	21	20	
		15–28 days, n	49	24	46	14	
		29–43 days, n	5	18	6	7	
		>43 days, n	8	8	12	9	
		State of consciousness on admission					
		alert, n	4	2	4	1	
		drowsy, n	27	15	35	10	
		comatose, n	44	53	46	39	
		Cranial nerve afflictions, n	41	59	37	46	
		Pupillary abnormalities, n	65	63	70	48	
		Fundus changes, n	2	5	2	4	
		Hemiparesis, n	1	2	2	3	
		Hydrocephalus, n	1	2	0	1	
Intervention	*Antituberculosis chemotherapy plus dexamethasone*						

	Dexamethasone (3 weeks) 12 mg/day in adults, and 8 mg/day in children weighing less than 25 kg Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg), 25 mg/kg of body weight/day streptomycin (to a maximum of 1000 mg) and 25 mg/kg of body weight/day ethambutol (to a maximum of 1200 mg) for the first 6 weeks 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg) and 15 mg/kg of body weight/day ethambutol for the remainder of the 2-year treatment period In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg), 25 mg/kg of body weight/day streptomycin (to a maximum of 1000 mg) and 25 mg/kg of body weight/day ethambutol (to a maximum of 1200 mg) for the first 6 weeks 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg) and 15 mg/kg of body weight/day ethambutol for the remainder of the 2-year treatment period In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed
Length of follow up	Full treatment period
Location	Cairo, Egypt
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 72 of 145 antituberculosis chemotherapy alone group = 79 of 135 OR[1] (95% CI) = 0.70 (0.44 to 1.12) i.e. not statistically significant

	CSF positive for tubercle bacilli dexamethasone group = 32 of 75 antituberculosis chemotherapy alone group = 50 of 85 **OR[1] (95% CI) = 0.52 (0.28 to 0.98)** **i.e. statistically significant** CSF negative for tubercle bacilli dexamethasone group = 40 of 70 antituberculosis chemotherapy alone group = 29 of 50 OR[1] (95% CI) = 0.97 (0.46 to 2.01) i.e. not statistically significant Alert on admission dexamethasone group = 0 of 6 antituberculosis chemotherapy alone group = 2 of 5 OR[1] (95% CI) = 0.11 (0.00 to 2.93) i.e. not statistically significant Drowsy on admission dexamethasone group = 10 of 42 antituberculosis chemotherapy alone group = 18 of 45 OR[1] (95% CI) = 0.47 (0.19 to 1.18) i.e. not statistically significant Comatose admission

	dexamethasone group = 62 of 97 antituberculosis chemotherapy alone group = 59 of 85 OR[1] (95% CI) = 0.78 (0.42 to 1.45) i.e. not statistically significant
	Changes in signs and symptoms – neurologic abnormalities (developed during treatment) Number of patients to develop neurologic abnormalities (fundus, hemiparesis or hydrocephalus) during treatment dexamethasone group = 8 of 145 antituberculosis chemotherapy alone group = 15 of 135 OR[1] (95% CI) = 0.47 (0.19 to 1.14) i.e. not statistically significant CSF positive for tubercle bacilli dexamethasone group = 4 of 75 antituberculosis chemotherapy alone group = 10 of 85 OR[1] (95% CI) = 0.42 (0.13 to 1.41) i.e. not statistically significant CSF negative for tubercle bacilli dexamethasone group = 4 of 70 antituberculosis chemotherapy alone group = 5 of 50 OR[1] (95% CI) = 0.67 (0.17 to 2.60) i.e. not statistically significant
	Changes in signs and symptoms – neurologic abnormalities (permanent residual sequelae)

	Number of patients to with permanent residual neurologic abnormalities (fundus, hemiparesis or hydrocephalus) dexamethasone group = 14 of 145 antituberculosis chemotherapy alone group = 27 of 135 **OR[1] (95% CI) = 0.43 (0.21 to 0.86)** **i.e. statistically significant** CSF positive for tubercle bacilli dexamethasone group = 6 of 75 antituberculosis chemotherapy alone group = 13 of 85 OR[1] (95% CI) = 0.48 (0.17 to 1.34) i.e. not statistically significant CSF negative for tubercle bacilli dexamethasone group = 8 of 70 antituberculosis chemotherapy alone group = 14 of 50 **OR[1] (95% CI) = 0.33 (0.13 to 0.87)** **i.e. statistically significant**
	Changes in signs and symptoms – fever Time (mean±SD, days) to become afebrile (defined as a temperature of <37.5°C) (patients who were CSF positive for tubercle bacilli on admission) dexamethasone group (n = 75) = 20±13 antituberculosis chemotherapy alone group (n = 85) = 23±12 MD[2] (95% CI) = -3 (-6.9 to 0.9)

	i.e. not statistically significant
	Changes in signs and symptoms – responsiveness Time (mean±SD, days) to become fully alert (defined as adult patients able to respond and answer complicated questions correctly, and infants knowing their mothers, responding to voice or noise and able to feed properly) (patients who were CSF positive for tubercle bacilli on admission) dexamethasone group (n = 75) = 35±33 antituberculosis chemotherapy alone group (n = 85) = 31±23 MD[2] (95% CI) = 4 (-4.9 to 12.9) i.e. not statistically significant
Source of funding	Supported by the United States Navy Department, the Department of Defence, the United States Government and the Egyptian Ministry of Health
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; E, ethambutol H, isoniazid; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis

1.5.14 Malhotra et al, 2009

Bibliographic reference	Malhotra HS, Garg RK, Singh MK et al (2009) Corticosteroids (dexamethasone *versus* intravenous methyl prednisolone) in patients with tuberculous meningitis. Annals of Tropical Medicine & Parasitology 103(7): 625-34
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – computer-generated randomisation sheet *Allocation concealment used?*

	unclear *Blinding used?* no *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?* yes, although some patients received streptomycin instead of ethambutol during the initial phase of treatment *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes

Number of patients	Randomised = 97 dexamethasone group = 32 methylprednisolone group = 33 antituberculosis chemotherapy alone group = 32 Outcome data available for = 91 dexamethasone group = 31 methylprednisolone group = 30 antituberculosis chemotherapy alone group = 30
Patient characteristics	*Inclusion* Tuberculous meningitis Aged >14 years *Diagnostic criteria* Based on the results of clinical and radiological examination, the evaluation of cell types and numbers, and protein and glucose concentrations in the CSF The essential clinical indicator was the presence of a meningitic syndrome, as defined by the presence of headache vomiting and fever In the CSF samples, a predominantly lymphocytotic pleocytosis and an elevated protein concentration were taken as further evidence tuberculous meningitis 'Definite' meningitis = acid-fast bacilli detected in the CSF; contrast-enhanced CT often demonstrated the presence of exudates, hydrocephalus, tuberculoma and infarction, singly or in combination 'Probable' meningitis = suspected active pulmonary TB, as indicated by a chest x-ray; acid-fast bacilli in any specimen other than CSF; and/or clinical evidence of other extrapulmonary tuberculosis 'Possible' meningitis = at least 4 of the following:

history of tuberculosis

predominance of lymphocytes in the CSF

illness lasting >5 days

a ratio of CSF glucose concentration:plasma glucose concentration of <0.5

altered consciousness

yellow CSF

focal neurological signs

Drug susceptibility was not tested

Severity of disease

Classified according to the system of the British Medical Research Council:

stage 1: no definite neurological symptoms; scoring 15 on the Glasgow coma scale

stage 2: signs of meningeal irritation with slight or no clouding of sensorium and minor neurological deficit or no deficit; scoring 11–14 on the Glasgow coma scale

stage 3: severe clouding of sensorium, convulsions, focal neurological deficit and involuntary movements; scoring ≤10 on the Glasgow coma scale

Exclusion

HIV infection

Contraindication of corticosteroids

Previous use of antituberculosis chemotherapy and/or corticosteroids

Evidence of a brain abscess or tumour – e.g. an intracranial space-occupying lesion visible by CT

Baseline

	Dexamethasone	**Methylprednisolone**	**Antituberculosis**

				chemotherapy alone
	Sex			
	male, n	15	14	14
	female, n	16	16	16
	Age (mean (range)), years	31.97 (15–66)	30.00 (15–67)	32.87 (15–70)
	Duration of illness (mean (range)), days	56.13 (7–240)	35.17 (6–180)	60.77 (7–200)
	Glasgow coma scale score (median (range))	15 (8–15)	14.5 (5–15)	15 (8–15)
	Severity of disease			
	stage 1, n	7	7	7
	stage 2, n	18	17	18
	stage 3, n	6	6	5
	History of tuberculosis, n	4	6	7
	Fever, n	27	29	27
	Headache, n	27	27	25
	Vomiting, n	22	17	17
	Seizures, n	7	11	7
	Visual symptoms, n	15	14	16
	Altered sensorium, n	12	15	12
	Cranial nerve palsies, n	12	11	9
	Focal deficits, n	5	4	4

<table>
<tr><td></td><td>
<table>
<tr><td>Visual impairment, n</td><td>11</td><td>9</td><td>8</td></tr>
<tr><td>Miliary shadow on chest x-ray, n</td><td>2</td><td>5</td><td>3</td></tr>
<tr><td>Parenchymal shadow on chest x-ray, n</td><td>1</td><td>0</td><td>3</td></tr>
<tr><td>Pleural effusion on chest x-ray, n</td><td>0</td><td>2</td><td>1</td></tr>
<tr><td>Basal exudates on CT scan of brain, n</td><td>13</td><td>11</td><td>10</td></tr>
<tr><td>Hydrocephalus on CT scan of brain, n</td><td>10</td><td>3</td><td>7</td></tr>
<tr><td>Infarction on CT scan of brain, n</td><td>5</td><td>4</td><td>3</td></tr>
<tr><td>Culture-positive for M. tuberculosis, n</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>PCR-positive for M. tuberculosis, n</td><td>5</td><td>8</td><td>3</td></tr>
</table>
</td></tr>
<tr><td>Intervention 1</td><td>Antituberculosis chemotherapy plus dexamethasone

Dexamethasone (4 weeks)

0.4, 0.3, 0.2 and 0.1 mg/kg of bodyweight/day during weeks 1, 2, 3 and 4, respectively

Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR

10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months

10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months

Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required</td></tr>
<tr><td>Intervention 2</td><td>Antituberculosis chemotherapy plus methylprednisolone

Methylprednisolone (5 days)</td></tr>
</table>

	daily doses of 1 g for patients weighing >50 kg, or 20 mg/kg for lighter patients, for 5 days Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR 10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months 10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR 10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months 10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required
Length of follow up	10 months after treatment initiation
Location	Lucknow, India
Outcomes measures and effect size	**Mortality** Number of deaths after 6 months of treatment dexamethasone group = 8 of 32 methylprednisolone group = 9 of 33 antituberculosis chemotherapy alone group = 13 of 32

	Any corticosteroid vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.52 (0.21 to 1.27) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.56 (0.15 to 2.02) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.48 (0.14 to 1.68) i.e. not statistically significant Stage 1 dexamethasone group = 0 of 7 methylprednisolone group = 0 of 7 antituberculosis chemotherapy alone group = 1 of 7 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.15 (0.01 to 4.18) i.e. not statistically significant Stage 2 dexamethasone group = 5 of 18 methylprednisolone group = 6 of 17 antituberculosis chemotherapy alone group = 8 of 18 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1]

	OR (95% CI) = 0.57 (0.18 to 1.85) i.e. not statistically significant Stage 3 dexamethasone group = 3 of 6 methylprednisolone group = 3 of 6 antituberculosis chemotherapy alone group = 4 of 5 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.25 (0.02 to 2.94) i.e. not statistically significant
	Changes in signs and symptoms – disability Assessed using a modified Rankin scale: score of 0 = no symptoms at all score of 1 = no significant disability despite the presence of symptoms, with the subject able to carry out all their usual duties and activities score of 2 = slight disability, with the subject unable to carry out all their previous activities, but able to look after their own affairs without assistance score of 3 = moderate disability, with the subject requiring help but able to walk without assistance score of 4 = moderately severe disability, with the subject unable to walk without assistance and unable to attend to own bodily needs without assistance score of 5 = severe disability, with the subject bedridden, incontinent and requiring constant nursing care and attention Final scores: 0 = good outcome

	1–2 = intermediate disability 3–5 = severe disability Number of patients to experience severe disability after 6 months of treatment dexamethasone group = 5 of 32 methylprednisolone group = 6 of 33 antituberculosis chemotherapy alone group = 5 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.10 (0.35 to 3.49) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 1.30 (0.22 to 7.55) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.96 (0.21 to 4.47) i.e. not statistically significant Severe disability among patients defined as stage 1 at baseline dexamethasone group = 1 of 7 methylprednisolone group = 1 of 7 antituberculosis chemotherapy alone group = 1 of 7 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.00 (0.07 to 13.37)

	i.e. not statistically significant Severe disability among patients defined as stage 2 at baseline dexamethasone group = 3 of 18 methylprednisolone group = 3 of 17 antituberculosis chemotherapy alone group = 3 of 18 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.03 (0.23 to 4.73) i.e. not statistically significant Severe disability among patients defined as stage 3 at baseline dexamethasone group = 1 of 6 methylprednisolone group = 2 of 6 antituberculosis chemotherapy alone group = 1 of 5 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.22 (0.10 to 17.10) i.e. not statistically significant Number of patients to experience intermediate disability after 6 months of treatment dexamethasone group = 3 of 32 methylprednisolone group = 0 of 33 antituberculosis chemotherapy alone group = 4 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.34 (0.07 to 1.62)

	i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.72 (0.11 to 4.84) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.09 (0.00 to 1.92) i.e. not statistically significant Number of patients with a good outcome after 6 months of treatment dexamethasone group = 15 of 32 methylprednisolone group = 15 of 33 antituberculosis chemotherapy alone group = 8 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] **OR (95% CI) = 2.57 (1.01 to 6.56)** **i.e. statistically significant** *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 2.65 (0.70 to 9.99) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 2.50 (0.67 to 9.39) i.e. not statistically significant
	Adverse events - hepatic

	Number of patients to experience clinical or subclinical hepatitis dexamethasone group = 5 of 32 methylprednisolone group = 7 of 33 antituberculosis chemotherapy alone group = 8 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.68 (0.25 to 1.88) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.56 (0.13 to 2.44) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.81 (0.20 to 3.30) i.e. not statistically significant Number of patients to experience clinical hepatitis dexamethasone group = 1 of 32 methylprednisolone group = 2 of 33 antituberculosis chemotherapy alone group = 2 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.73 (0.12 to 4.58) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2]

	OR (95% CI) = 0.48 (0.03 to 8.28) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.97 (0.08 to 11.54) i.e. not statistically significant
	Adverse events – gastrointestinal bleeding Number of patients to experience gastrointestinal bleeding dexamethasone group = 4 of 32 methylprednisolone group = 2 of 33 antituberculosis chemotherapy alone group = 1 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 3.15 (0.36 to 27.37) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 5.21 (0.26 to 103.00) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.97 (0.08 to 11.54) i.e. not statistically significant
	Adverse events – paradoxical tuberculoma Number of patients to experience paradoxical tuberculoma

	dexamethasone group = 2 of 32 methylprednisolone group = 1 of 33 antituberculosis chemotherapy alone group = 5 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.26 (0.06 to 1.17) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.47 (0.06 to 3.66) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.14 (0.01 to 1.42) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Pooled odds ratio, combining the data for the dexamethasone and methylprednisolone arms into a single 'corticosteroid' arm, and 95% confidence interval calculated by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer; data for the control group (received antituberculosis chemotherapy alone) was divided in half to allow 2 pairwise comparisons of dexamethasone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone and methylprednisolone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone

[3] Pooled mean difference, combining the data for the dexamethasone and methylprednisolone arms into a single 'corticosteroid' arm, calculated by reviewer

[4] Mean difference calculated by reviewer; data for the control group (received antituberculosis chemotherapy alone) was divided in half to allow 2 pairwise comparisons of dexamethasone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone and

methylprednisolone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; E, ethambutol H, isoniazid; MD, mean difference; OR, odds ratio; PCR, polymerase chain reaction; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis; Z, pyrazinamide

1.5.15 O'Toole et al, 1969

Bibliographic reference	O'Toole RD, Thornton GF, Mukherjee MK et al (1969) Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. Annals of Internal Medicine 70(1): 39-48
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – block randomisation using coded medication *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* yes, although details provided are limited *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?* 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: lack rifampicin, pyrazinamide and ethambutol, but contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* unclear
Number of patients	Outcome data available for = 23 dexamethasone group = 11 placebo group = 12
Patient characteristics	*Inclusion* Tuberculous meningitis (only those patients presenting with short histories or acute signs and symptoms mimicking pyrogenic meningitis were admitted to the hospital since hospital policy is to refer tuberculous meningitis to other institutions) Moderately advanced or severe disease *Severity of disease* Classified according to the system of the British Medical Research Council: stage 1: mild cases; without altered consciousness or focal neurologic signs

<table>
<tr><td></td><td>
stage 2: moderately advanced cases; altered consciousness; not comatose; moderate neurologic deficits, such as single cranial nerve palsies, parapesis and hemiparesis

stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia

Baseline
<table>
<tr><th></th><th>Dexamethasone group
(n = 11)</th><th>Placebo group
(n = 12</th></tr>
<tr><td>Age, years
<2, n
2 to 45, n
>45, n</td><td>
2
8
1</td><td>
3
9
0</td></tr>
<tr><td>Severity of disease
stage 1, n
stage 2, n
stage 3, n</td><td>
1
6
4</td><td>
0
8
4</td></tr>
<tr><td>Culture-positive CSF, n</td><td>8</td><td>6</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus dexamethasone

Dexamethasone (4 weeks)

adults received 2.25 mg parenterally every 6 hours during the first week; the dose was reduced to 1.50 mg every 6 hours for he second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week

paediatric dosage was derived from a standard table based on surface area
</td></tr>
</table>

	Antituberculosis chemotherapy: isoniazid (10 mg/kg of body weight/day, or 20 mg/kg of body weight/day in children less than 2 years of age) and streptomycin (20 mg/kg of body weight/day, up to a maximum of 1 g); total duration of antituberculosis chemotherapy unclear All patients received high doses of vitamin B_6
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (4 weeks) adults received 2.25 mg parenterally every 6 hours during the first week; the dose was reduced to 1.50 mg every 6 hours for he second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week paediatric dosage was derived from a standard table based on surface area Antituberculosis chemotherapy: isoniazid (10 mg/kg of body weight/day, or 20 mg/kg of body weight/day in children less than 2 years of age) and streptomycin (20 mg/kg of body weight/day, up to a maximum of 1 g); total duration of antituberculosis chemotherapy unclear All patients received high doses of vitamin B_6
Length of follow up	Unclear
Location	Calcutta, India
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 6 of 11 placebo group = 9 of 12 OR[1] (95% CI) = 0.40 (0.07 to 2.34) i.e. not statistically significant Number of deaths amongst those <2 years of age dexamethasone group = 2 of 2

	placebo group = 3 of 3 OR[1] (95% CI) = 0.71 (0.01 to 49.71) i.e. not statistically significant Number of deaths amongst those classed as stage 2 on admission dexamethasone group = 3 of 6 placebo group = 5 of 8 OR[1] (95% CI) = 0.60 (0.07 to 5.14) i.e. not statistically significant Number of deaths amongst those classed as stage 3 on admission dexamethasone group = 3 of 4 placebo group = 4 of 4 OR[1] (95% CI) = 0.26 (0.01 to 8.52) i.e. not statistically significant (Mean) survival time (days) dexamethasone group = 14 placebo group = 14 MD[2] = 0
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial

1.5.16 Kumarvelu et al, 1994

Bibliographic reference	Kumarvelu S, Prasad K, Khosla A et al (1994) Randomised controlled trial of dexamethasone in tuberculous meningitis. Tubercle and Lung Disease 75(3): 203-7
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – random numbers table *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?* follow-up was equal in both groups although was only for 3 months after treatment initiation (i.e. not for the full treatment period) *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?*

	‘full/partial recovery’ and ‘unchanged’ status not defined *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis chemotherapeutic regimens lacked ethambutol *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – used composites of outcomes of interest: ‘poor’ and ‘good’ outcome were composites of mortality and changes in signs and symptoms *Analysis followed the intent-to-treat principle?* some data was only available for patients with either ‘severe’ or ‘mild-to-moderate’ disease on admission who survived; since the authors do not provide the number of patients with either ‘severe’ or ‘mild-to-moderate’ disease on admission who were randomised to each intervention, this data could not be analysed in accordance with the intent-to-treat principle
Number of patients	Randomised = 47 dexamethasone group = 24 antituberculosis chemotherapy alone group = 23 Outcome data available at 3 months = 41 dexamethasone group = 20 antituberculosis chemotherapy alone group = 21
Patient characteristics	*Inclusion* Probable tuberculous meningitis *Diagnostic criteria* Diagnosis of probable tuberculous meningitis was made if at least 3 of the following criteria were present:

clinical: fever >38°C, headache, neck stiffness with or without seizures or altered sensorium for at least 2 weeks

characteristic CSF findings: leukocytes >20 /mm^3 with lymphocytotic predominance, proteins >1 g/l, sugar <2/3 of corresponding blood sugar, cultures negative for pyrogenic organisms and fungi, and negative cytology for malignant cells

contrast-enhanced CT scan of the head: basal exudates or hydrocephalus with or without infarcts and tuberculoma

clinical, radiological or histological evidence of extracranial tuberculosis

Severity of disease

Analysed on admission using the following scoring system:

Parameter	**Weightage (points)**
Sensorium	
normal	1
delirium	2
drowsy	3
semi-coma	4
coma	5
Associated pulmonary tuberculosis	0.5
Associated extensive tuberculous or non-tuberculous disease	0.5
Age <10 years or >50 years	0.5
CSF protein >3 g/l	0.5
CT scan evidence	
exudates	

grade I	1
grade II	2
grade III	3
hydrocephalus	
mild	1
moderate	2
severe	3
mid-line shift	1
Leukopenia or leukocytosis	0.5
Systolic hypotension	1

‘Severe’ disease = a score of 8 or more

‘Mild-to-moderate’ disease = a score of less than 8

Exclusion

Aged <10 years

Previous antituberculosis chemotherapy for >4 weeks

Previous glucocorticoid use

Baseline

	Dexamethasone group	**Antituberculosis chemotherapy alone**
Clinical features		
hypotension, %	29	13

		meningeal signs, %	92	100	
		altered sensorium, %	92	74	
		seizures, %	46	30	
		papilloedema, %	50	22	
		cerebrovascular event, %	29	35	
		spinal arachnoiditis, %	17	4	
		extrameningeal tuberculosis, %	46	52	
		CSF parameters			
		abnormal cell count, %	83	100	
		lymphocyte predominance, %	63	61	
		raised proteins, %	75	83	
		low glucose levels, %	91	88	
		CT parameters			
		exudates, %	79	91	
		hydrocephalus, %	58	52	
		infarct, %	13	22	
		tuberculoma, %	21	9	
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone (6 weeks) adults: 16 mg divided into 4 doses in the first week, followed by 8 mg/day for 21 days, after which doses were tapered				

	off over the next 14 days children: 0.6 mg/kg of body weight/day for the first 7 days, followed by 0.3 mg/kg of body weight/day for 21 days, after which doses were tapered off over the next 14 days Antituberculosis chemotherapy: isoniazid (300 mg/day in adults, or 10 mg/kg of body weight/day in children), rifampicin (450 mg/day in adults, or 15 mg/kg of body weight/day in children) and pyrazinamide (1500 mg/day in adults, or 30 mg/kg of body weight/day in children); total duration of antituberculosis chemotherapy unknown Pyridoxine supplements were given routinely
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: isoniazid (300 mg/day in adults, or 10 mg/kg of body weight/day in children), rifampicin (450 mg/day in adults, or 15 mg/kg of body weight/day in children) and pyrazinamide (1500 mg/day in adults, or 30 mg/kg of body weight/day in children); total duration of antituberculosis chemotherapy unknown Pyridoxine supplements were given routinely
Length of follow up	3 months after treatment initiation
Location	New Delhi, India
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 9 of 24 antituberculosis chemotherapy alone group = 9 of 23 OR[1] (95% CI) = 0.93 (0.29 to 3.03) i.e. not statistically significant
	Response to treatment – full/partial recovery Definition not provided Number of patients to achieve a full or partial recovery

	dexamethasone group = 15 of 24 antituberculosis chemotherapy alone group = 13 of 23 OR[1] (95% CI) = 1.28 (0.40 to 4.12) i.e. not statistically significant Number of patients who were defined as 'severe' on admission and to survive to achieve a full or partial recovery dexamethasone group = 4 of 4 antituberculosis chemotherapy alone group = 1 of 2 OR[1] (95% CI) = 9.00 (0.22 to 362.50) i.e. not statistically significant Number of patients who were defined as 'mild-to-moderate' on admission and to survive to achieve a full or partial recovery dexamethasone group = 11 of 11 antituberculosis chemotherapy alone group = 12 of 12 OR[1] (95% CI) = 0.92 (0.02 to 50.28) i.e. not statistically significant
	Response to treatment – unchanged status Definition not provided Number of patients whose status was unchanged dexamethasone group = 0 of 24 antituberculosis chemotherapy alone group = 1 of 23 OR[1] (95% CI) = 0.31 (0.01 to 7.91)

	i.e. not statistically significant Number of patients who were defined as 'severe' on admission and to survive whose status was unchanged dexamethasone group = 0 of 4 antituberculosis chemotherapy alone group = 1 of 2 OR[1] (95% CI) = 0.11 (0.00 to 4.48) i.e. not statistically significant Number of patients who were defined as 'mild-to-moderate' on admission and to survive whose status was unchanged dexamethasone group = 0 of 11 antituberculosis chemotherapy alone group = 0 of 12 OR[1] (95% CI) = 1.09 (0.02 to 59.40) i.e. not statistically significant
	Response to treatment – 'poor' outcome Defined as death or survival with major sequelae (persistent vegetative state, blindness, symptomatic hydrocephalus, moderate-to-severe intellectual impairment, severe functional disability (totally dependent), or uncontrolled seizures) Number of patients to experience a poor outcome dexamethasone group = 5 of 24 antituberculosis chemotherapy alone group = 8 of 23 OR[1] (95% CI) = 0.49 (0.13 to 1.82) i.e. not statistically significant
	Response to treatment – 'good' outcome Defined as survival with minor (mild intellectual impairment, mild-to-moderate functional disability (able to enact the activities of daily living with minimal or no assistance)) or no sequelae

	Number of patients to experience a good outcome dexamethasone group = 15 of 24 antituberculosis chemotherapy alone group = 13 of 23 OR[1] (95% CI) = 1.28 (0.40 to 4.12) i.e. not statistically significant
	Changes in signs and symptoms – sensorium Time (mean, days) to recovery of sensorium amongst patients who survived dexamethasone group (n = 15)[2] = 14.6 antituberculosis chemotherapy alone group (n = 14)[2] = 11.3 MD[3] = 3.3 Time (mean, days) to recovery of sensorium amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 19 antituberculosis chemotherapy alone group (n = 2) = 25 MD[3] = -6 Time (mean, days) to recovery of sensorium amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 13 antituberculosis chemotherapy alone group (n = 12) = 9 MD[3] = 4
	Changes in signs and symptoms – fever Time (mean, days) to recovery of fever amongst patients who survived

	dexamethasone group (n = 15)[2] = 13 antituberculosis chemotherapy alone group (n = 14)[2] = 10.3 MD[3] = 2.7 Time (mean, days) to recovery of fever amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 13 antituberculosis chemotherapy alone group (n = 2) = 18 MD[3] = -5 Time (mean, days) to recovery of fever amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 13 antituberculosis chemotherapy alone group (n = 12) = 9 MD[3] = 4
	Changes in signs and symptoms – headache Time (mean, days) to recovery of headache amongst patients who survived dexamethasone group (n = 15)[2] = 18.5 antituberculosis chemotherapy alone group (n = 14)[2] = 11.1 MD[3] = 7.4 Time (mean, days) to recovery of headache amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 20 antituberculosis chemotherapy alone group (n = 2) = 12 MD[3] = 8

	Time (mean, days) to recovery of headache amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 18 antituberculosis chemotherapy alone group (n = 12) = 11 MD[3] = 7
	Changes in signs and symptoms – cognitive status Assessed using a mini-mental score (tests orientation, registration, calculation, recall and language functions; scores range from 0 to 30, with 0 being the worst performance and 30 being 'normal') Time (mean, days) to improvement in mini-mental score amongst patients who survived dexamethasone group (n = 15)[2] = 8.3 antituberculosis chemotherapy alone group (n = 14)[2] = 4.9 MD[3] = 3.4 Time (mean, days) to improvement in mini-mental score amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 9 antituberculosis chemotherapy alone group (n = 2) = 10 MD[3] = -1 Time (mean, days) to improvement in mini-mental score amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 8 antituberculosis chemotherapy alone group (n = 12) = 4 MD[3] = 4
	Changes in signs and symptoms – activity of daily living

	Assessed using the Barthel index (includes bowel and bladder control, grooming, toilet use, feeding, transfer, mobility, dressing, walking upstairs and bathing; a score of 0 indicates a totally dependent patient, whereas a score of 20 means an independent existence) Time (mean, days) to improvement in Barthel score amongst patients who survived dexamethasone group (n = 15)[2] = 7.6 antituberculosis chemotherapy alone group (n = 14)[2] = 2.3 MD[3] = 5.3 Time (mean, days) to improvement in Barthel score amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 12 antituberculosis chemotherapy alone group (n = 2) = 4 MD[3] = 8 Time (mean, days) to improvement in Barthel score amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 6 antituberculosis chemotherapy alone group (n = 12) = 2 MD[3] = 4
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Data for those with severe disease on admission who survived and those with mild-to-moderate disease on admission who survived was combined into a pooled mean difference by reviewer

[3] Mean difference calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.5.17 Schoeman et al, 1997

Bibliographic reference	Schoeman JF, Van Zyl LE, Laubscher JA et al (1997) Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 99(2): 226-31
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* blinded: clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function unclear patients or other health professionals were blinded *Groups comparable at baseline?* yes, although details provided are limited *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?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 141 prednisolone group = 70 antituberculosis chemotherapy alone group = 71 Outcome data available for incidence of mortality and the incidence of tuberculoma = 141 prednisolone group = 70 antituberculosis chemotherapy alone group = 71 Outcome data available for IQ = 119 prednisolone group = 65 antituberculosis chemotherapy alone group = 54 Outcome data available for motor function = 126 prednisolone group = 66

	antituberculosis chemotherapy alone group = 60 Outcome data available for vision = 119 prednisolone group = 63 antituberculosis chemotherapy alone group = 56 Outcome data available for hearing = 116 prednisolone group = 60 antituberculosis chemotherapy alone group = 56
Patient characteristics	*Inclusion* Tuberculous meningitis Children (age threshold not provided) *Diagnostic criteria* Based on history and typical CSF changes, together with 2 or more of the following: strongly positive (>15 mm) Mantoux test chest radiograph findings suggesting tuberculosis i.e. a miliary picture or hilar lymph node adenopathy, often accompanied by a segmental lesion acute hydrocephalus with basal enhancement on CT scanning isolation of *M. tuberculosis* in gastric aspirate and/or CSF *Severity of disease* Classified according to the system of the British Medical Research Council: stage 1: mild cases; without altered consciousness or focal neurologic signs stage 2: moderately advanced cases; altered consciousness; not comatose; moderate neurologic deficits, such as single cranial nerve palsies, parapesis and hemiparesis

<table>
<tr><td></td><td>
stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia

Only patients with stage 2 or 3 were included

Baseline
<table>
<tr><th></th><th>Prednisolone group</th><th>Placebo group</th></tr>
<tr><td>Severity of disease
stage 2, n
stage 3, n</td><td>
37
33</td><td>
36
35</td></tr>
<tr><td>Baseline pressure (mean±SD), mm Hg</td><td>28.5±12.7</td><td>26.0±11.8</td></tr>
<tr><td>Pulse pressure (mean±SD), mm Hg</td><td>6.1±5.5</td><td>5.6±5.8</td></tr>
<tr><td>Ventricular size (mean±SD), ratio of biventricular diameter to biparietal diameter</td><td>0.26±0.08</td><td>0.25±0.08</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus prednisolone

Prednisolone (1 month)

2 to 4 mg/kg of body weight/day - the first 16 patients in the steroid group received prednisolone at 2 mg/kg/day, and the remaining patients received 4 mg/kg/day[2]

Antituberculosis chemotherapy: 6HRZE

20 mg/kg of body weight/day isoniazid, 20 mg/kg of body weight/day rifampicin, 40 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol daily for 6 months

All children with communicating hydrocephalus were treated with daily acetazolamide (100 mg/kg of bodyweight) and furosemide (1 mg/kg of bodyweight) for 1 month

All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery
</td></tr>
</table>

Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 6HRZE 20 mg/kg of body weight/day isoniazid, 20 mg/kg of body weight/day rifampicin, 40 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol daily for 6 months All children with communicating hydrocephalus were treated with daily acetazolamide (100 mg/kg of bodyweight) and furosemide (1 mg/kg of bodyweight) for 1 month All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery
Length of follow up	6 months from treatment initiation (i.e. full treatment period)
Location	South Africa
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 4 of 70 antituberculosis chemotherapy alone group = 13 of 71 **OR[1] (95% CI) = 0.28 (0.09 to 0.90)** **i.e. statistically significant** Number of deaths among those classified as stage 2 on admission prednisolone group = 1 of 37 antituberculosis chemotherapy alone group = 1 of 36 OR[1] (95% CI) = 0.97 (0.06 to 16.16) i.e. not statistically significant Number of deaths among those classified as stage 3 on admission prednisolone group = 3 of 33

	antituberculosis chemotherapy alone group = 12 of 35 **OR[1] (95% CI) = 0.19 (0.05 to 0.76)** **i.e. statistically significant**
	Changes in signs and symptoms - disability Number of patients to be disabled (severely or mildly) at 6 months prednisolone group = 54 of 70 antituberculosis chemotherapy alone group = 49 of 71 OR[1] (95% CI) = 1.52 (0.71 to 3.21) i.e. not statistically significant Number of patients to be severely disabled at 6 months prednisolone group = 14 of 70 antituberculosis chemotherapy alone group = 19 of 71 OR[1] (95% CI) = 0.68 (0.31 to 1.50) i.e. not statistically significant
	Changes in signs and symptoms - tuberculoma Number of patients to develop tuberculomas in the first month of treatment prednisolone group = 2 of 70 antituberculosis chemotherapy alone group = 9 of 71 **OR[1] (95% CI) = 0.20 (0.04 to 0.97)** **i.e. statistically significant**
	Changes in signs and symptoms - IQ

	Number of patients to have an IQ of less than 75 at 6 months prednisolone group = 31 of 70 antituberculosis chemotherapy alone group = 36 of 71 OR[1] (95% CI) = 0.77 (0.40 to 1.50) i.e. not statistically significant
	Changes in signs and symptoms – motor function Number of patients to be experience hemiplegia or quadriplegia at 6 months prednisolone group = 24 of 70 antituberculosis chemotherapy alone group = 24 of 71 OR[1] (95% CI) = 1.02 (0.51 to 2.05) i.e. not statistically significant
	Changes in signs and symptoms - vision Number of patients with visual deterioration (decreased vision or blindness) at 6 months prednisolone group = 9 of 70 antituberculosis chemotherapy alone group = 7 of 71 OR[1] (95% CI) = 1.35 (0.47 to 3.85) i.e. not statistically significant Number of patients to be blind at 6 months prednisolone group = 3 of 70 antituberculosis chemotherapy alone group = 3 of 71 OR[1] (95% CI) = 1.01 (0.20 to 5.21)

	i.e. not statistically significant
	Changes in signs and symptoms - hearing Number of patients with deterioration in their hearing (decreased hearing, though not deaf) at 6 months prednisolone group = 3 of 70 antituberculosis chemotherapy alone group = 6 of 71 OR[1] (95% CI) = 0.49 (0.12 to 2.02) i.e. not statistically significant Number of patients to be deaf at 6 months prednisolone group = 0 of 70 antituberculosis chemotherapy alone group = 0 of 71 OR[1] (95% CI) = 1.01 (0.02 to 51.82) i.e. not statistically significant
Source of funding	South Africa Medical Research Council
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] The doubling of the dose was enacted when the investigators became aware of a study that showed rifampicin to decrease the bioavailability of prednisolone by 66% and increased the plasma clearance of the drug by 45%

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computed tomography; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.5.18 Thwaites et al, 2004/7 / Török et al, 2011

Study type	RCT

Study quality	*Appropriate method of randomisation used?* yes – computer-generated sequence of random numbers was used to allocate treatment in blocks of 30 *Allocation concealment used?* yes *Blinding used?* double-blinded: placebo and dexamethasone were identical in appearance; all participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up *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?* yes

	Have substitute outcomes been used instead of the patient-important outcomes of interest? no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 545 dexamethasone group = 274 placebo group = 271 Lost to follow-up (last observation carried forward) = 62 dexamethasone group = 35 placebo group = 27
Patient characteristics	*Inclusion* Clinical evidence of meningitis Over 14 years of age *Diagnostic criteria* Combination of nuchal rigidity and CSF abnormalities 'Definite' tuberculosis = acid-fast bacilli were seen in the CSF 'Probable tuberculosis = patients with one or more of the following: suspected active pulmonary tuberculosis on chest radiography acid-fast bacilli found in any specimen other than the CSF clinical evidence of other extrapulmonary tuberculosis 'Possible" tuberculosis = patients with at least four of the following:

a history of tuberculosis, predominance of lymphocytes in the CSF

a duration of illness of more than five days

a ratio of CSF glucose to plasma glucose of less than 0.5

altered consciousness

yellow cerebrospinal fluid

focal neurologic signs

Severity of disease

Patients were stratified on entry according to the British Medical Research Council criteria, modified as follows:

stage 1 = a score on the Glasgow coma scale of 15 (possible range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs

stage 2 = a score on the Glasgow coma scale of either 11 to 14, or of 15 with focal neurologic signs

stage 3 = a score on the Glasgow coma score of 10 or less

Exclusion

Corticosteroids contraindicated

>1 dose of any corticosteroid

>30 days of antituberculosis chemotherapy immediately before study entry

Baseline

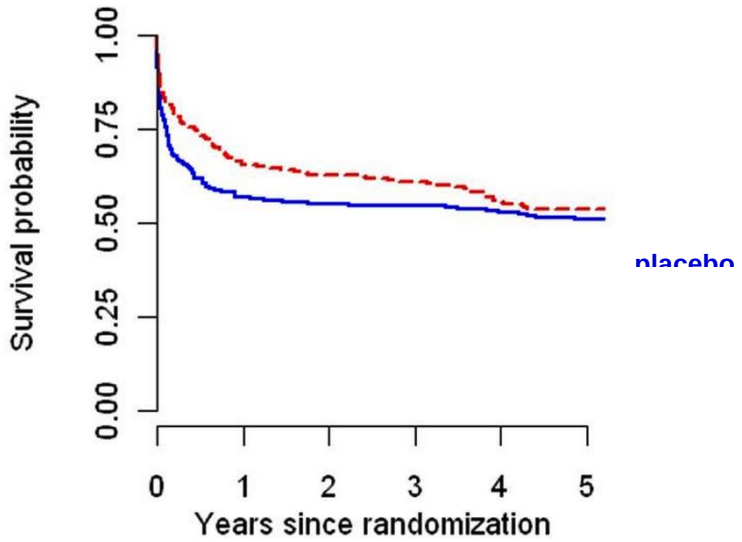
	Dexamethasone (n = 274)	**Placebo** (n = 271)
Age		
median, years	36.0	35.0

		range, years	15–88	15–84	
		Sex			
		male, n (%)	168 (61.3)	163 (60.1)	
		Diagnosis			
		definite	98 (35.8)	89 (32.8)	
		probable	130 (47.4)	131 (48.3)	
		possible	44 (16.1)	47 (17.3)	
		not tuberculous meningitis	2 (0.7)	4 (1.5)	
		Weight			
		median, kg	45.0	45.0	
		range, kg	25–75	30–70	
		Score on the Glasgow coma scale			
		median	14	14	
		range	3–15	3–15	
		Cranial nerve palsy, n (%)	82 (29.9)	74 (27.3)	
		Hemiparesis, n (%)	48 (17.5)	37 (13.7)	
		Paraparesis, n (%)	28 (10.2)	11 (4.1)	
		Severity of disease			
		stage 1, n (%)	90 (32.8)	86 (31.7)	
		stage 2, n (%)	122 (44.5)	125 (46.1)	
		stage 3, n (%)	62 (22.6)	60 (22.1)	

		HIV status		
		positive, n (%)	44 (16.1)	54 (19.9)
		negative, n (%)	227 (82.8)	209 (77.1)
		Lymphocyte count		
		CD4		
		median, /mm3	64	66
		range, /mm3	14–694	7–359
		CD8		
		median, /mm3	606	386
		range, /mm3	134–998	28–1001
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone sodium phosphate (8 weeks) stage 1 disease: received 2 weeks of intravenous therapy (0.3 mg/kg of body weight/day for week 1 and 0.2 mg/kg of body weight/day for week 2) and then 4 weeks of oral therapy (0.1 mg/kg of body weight/day for week 3, then a total of 3 mg/day, decreasing by 1 mg each week) stage 2 or 3 disease: received intravenous treatment for 4 weeks (0.4 mg/kg of body weight/day for week 1, 0.3 /kg of body weight/day for week 2, 0.2 /kg of body weight/day for week 3, and 0.1 /kg of body weight/day for week 4) and then oral treatment for 4 weeks, starting at a total of 4 mg/day and decreasing by 1 mg each week Antituberculosis chemotherapy: 3HRZS/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months			

	HIV-positive patients: 3HRZE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months previously treated patients: 3HRZSE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide, 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months None of the patients received antiretroviral drugs
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (8 weeks) stage 1 disease: received 2 weeks of intravenous therapy (0.3 mg/kg of body weight/day for week 1 and 0.2 mg/kg of body weight/day for week 2) and then 4 weeks of oral therapy (0.1 mg/kg of body weight/day for week 3, then a total of 3 mg/day, decreasing by 1 mg each week) stage 2 or 3 disease: received intravenous treatment for 4 weeks (0.4 mg/kg of body weight/day for week 1, 0.3 /kg of body weight/day for week 2, 0.2 /kg of body weight/day for week 3, and 0.1 /kg of body weight/day for week 4) and then oral treatment for 4 weeks, starting at a total of 4 mg/day and decreasing by 1 mg each week Antituberculosis chemotherapy: 3HRZS/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months HIV-positive patients: 3HRZE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months previously treated patients: 3HRZSE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide, 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months None of the patients received antiretroviral drugs

<table>
<tr><td>Location</td><td>Ho Chi Minh City, Vietnam</td></tr>
<tr><td>Bibliographic reference</td><td>Török ME, Bang ND, Chau TTH et al (2011) Dexamethasone and Long-Term Outcome of Tuberculous Meningitis in Vietnamese Adults and Adolescents. PLoS One 6(12): e27821</td></tr>
<tr><td>Length of follow up</td><td>5 years after randomisation</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality
<table>
<tr><th rowspan="2">Years after treatment initiation</th><th colspan="2">Dexamethasone (n = 274)</th><th colspan="2">Placebo (n = 271)</th><th rowspan="2">Difference in survival rate (95% CI); p-value</th></tr>
<tr><th>Number at risk</th><th>Survival rate (95% CI)</th><th>Number at risk</th><th>Survival rate (95% CI)</th></tr>
<tr><td>0</td><td>274</td><td>-</td><td>271</td><td>-</td><td>-</td></tr>
<tr><td>1</td><td>160</td><td>0.65 (0.60 to 0.71)</td><td>131</td><td>0.57 (0.51 to 0.63)</td><td>0.09 (0.00 to 0.17); p = 0.04</td></tr>
<tr><td>2</td><td>152</td><td>0.63 (0.57 to 0.69)</td><td>125</td><td>0.55 (0.49 to 0.69)</td><td>0.08 (0.00 to 0.16); p = 0.07</td></tr>
<tr><td>3</td><td>147</td><td>0.61 (0.55 to 0.67)</td><td>124</td><td>0.55 (0.49 to 0.61)</td><td>0.06 (-0.02 to 0.15); p = 0.15</td></tr>
<tr><td>4</td><td>130</td><td>0.55 (0.50 to 0.62)</td><td>117</td><td>0.53 (0.47 to 0.59)</td><td>0.03 (-0.06 to 0.11); p = 0.56</td></tr>
<tr><td>5</td><td>82</td><td>0.54 (0.48 to 0.60)</td><td>64</td><td>0.51 (0.45 to 0.57)</td><td>0.03 (-0.06 to 0.12); p = 0.51</td></tr>
</table></td></tr>
</table>



Hazard ratio 0 to 3 months after randomisation (not intent-to-treat):

HR (95% CI) = 0.62 (0.44 to 0.88)

p = 0.01

i.e. statistically significant

Hazard ratio more than 3 months after randomisation (not intent-to-treat):

HR (95% CI) = 1.50 (1.00 to 2.26)

p = 0.05

i.e. statistically significant

Number of deaths 5 years after randomisation:

dexamethasone group = 121 of 274

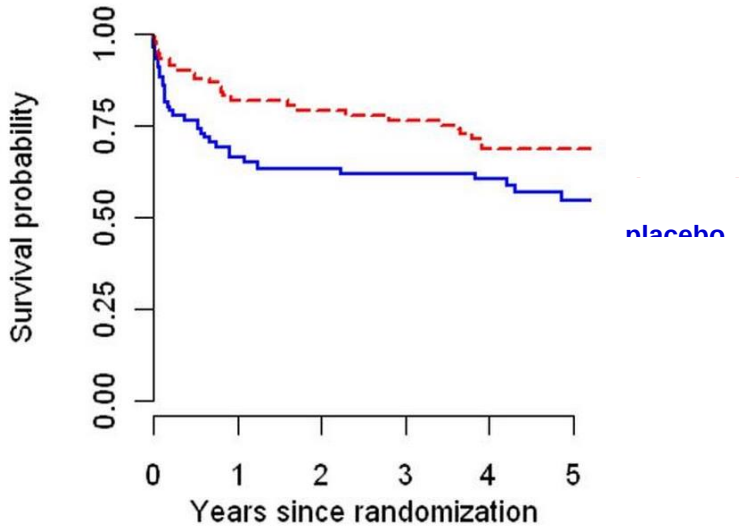
placebo group = 128 of 271

OR[1] (95% CI) = 0.88 (0.63 to 1.24)

i.e. not statistically significant

Stage 1 disease:

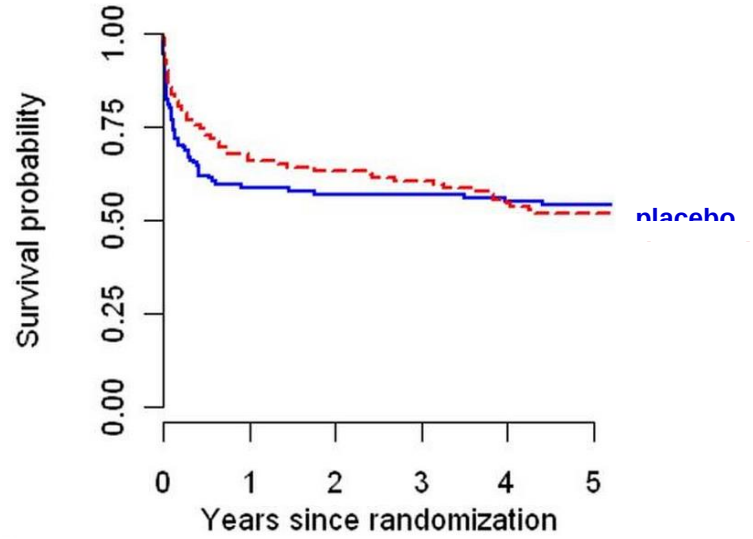
Years after treatment initiation	**Dexamethasone** (n = 90)		**Placebo** (n = 86)		**Difference in survival rate (95% CI); p-value**
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	90	-	86	-	-
1	65	0.82 (0.74 to 0.90)	46	0.66 (0.57 to 0.77)	0.15 (0.02 to 0.29); p = 0.02
2	61	0.79 (0.71 to 0.88)	42	0.63 (0.54 to 0.75)	0.16 (0.02 to 0.29); p = 0.02
3	59	0.71 (0.68 to 0.86)	41	0.62 (0.52 to 0.74)	0.15 (0.01 to 0.29); p = 0.04
4	53	0.69 (0.59 to 0.80)	39	0.60 (0.50 to 0.72)	0.08 (-0.06 to 0.23); p = 0.27
5	34	0.69 (0.59 to 0.80)	23	0.55 (0.44 to 0.68)	0.14 (-0.01 to 0.29); p = 0.07



Stage 2 disease:

Years after treatment initiation	Dexamethasone (n = 122)		Placebo (n = 125)		Difference in survival rate (95% CI); p-value
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	122	-	125	-	-
1	72	0.66 (0.58 to 0.75)	65	0.59 (0.51 to 0.68)	0.07 (-0.05 to 0.19); p = 0.25
2	69	0.63 (0.55 to 0.72)	63	0.57 (0.49 to 0.66)	0.06 (-0.06 to 0.19); p = 0.33
3	66	0.60 (0.52 to 0.70)	63	0.57 (0.49 to 0.66)	0.03 (-0.09 to 0.16); p = 0.59
4	57	0.55 (0.46 to	60	0.55 (0.47 to	0.00 (-0.18 to 0.17); p =

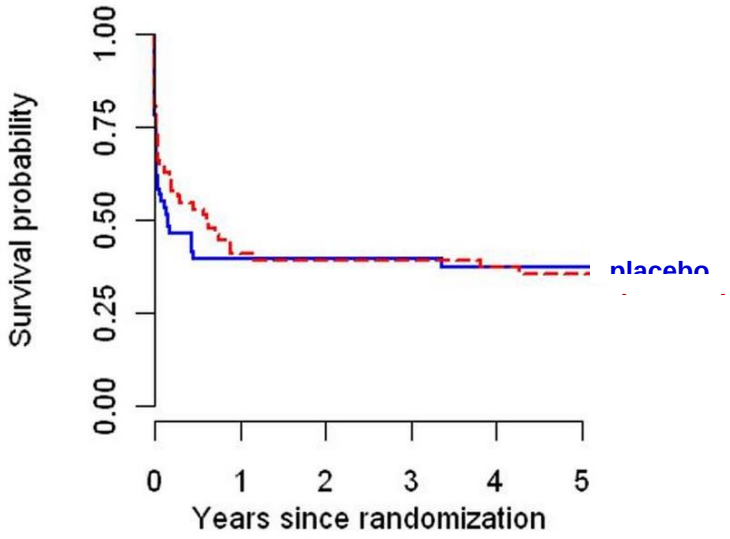
		0.65)		0.65)	0.98
5	34	0.52 (0.43 to 0.62)	33	0.54 (0.46 to 0.64)	-0.02 (-0.15 to 0.11); p = 0.73



Stage 3 disease:

Years after treatment initiation	**Dexamethasone** (n = 62)		**Placebo** (n = 60)		**Difference in survival rate (95% CI); p-value**
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	62	-	60	-	-
1	23	0.41 (0.30 to 0.55)	20	0.39 (0.29 to 0.54)	0.01 (-0.16 to 0.19); p = 0.88
2	22	0.39 (0.28 to 0.54)	20	0.39 (0.29 to 0.54)	0.00 (-0.18 to 0.17); p = 0.96

3	22	0.39 (0.28 to 0.54)	20	0.39 (0.29 to 0.54)	0.00 (-0.18 to 0.17); p = 0.96
4	20	0.37 (0.27 to 0.52)	18	0.38 (0.27 to 0.52)	0.00 (-0.18 to 0.17); p = 0.98
5	14	0.35 (0.25 to 0.50)	8	0.38 (0.27 to 0.52)	-0.02 (-0.20 to 0.15); p = 0.81



Changes in signs and symptoms – disability

Number of patients in a good disability status 5 years after randomisation:

dexamethasone group = 69 of 274

placebo group = 61 of 271

OR[1] (95% CI) = 1.14 (0.77 to 1.69)

i.e. not statistically significant

	Number of patients in an intermediate disability status 5 years after randomisation: dexamethasone group = 43 of 274 placebo group = 36 of 271 OR[1] (95% CI) = 1.22 (0.75 to 1.96) i.e. not statistically significant Number of patients in a severe disability status 5 years after randomisation: dexamethasone group = 17 of 274 placebo group = 18 of 271 OR[1] (95% CI) = 0.93 (0.47 to 1.84) i.e. not statistically significant
Bibliographic reference	Thwaites GE, Bang ND, Dung NH et al (2004) Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. New England Journal of Medicine 351: 1741-51
Length of follow up	9 months after treatment initiation
Outcomes measures and effect size	**Changes in signs and symptoms – fever** Time to fever clearance (median, days from randomisation to observation of a maximal daily temperature of less than 37.5°C for more than five consecutive days) dexamethasone group (n = 274) = 9 placebo group (n = 271) = 11 **p = 0.03** **i.e. statistically significant**
	Changes in signs and symptoms – coma Time to coma clearance (median, days from randomization until observation of a Glasgow coma score of 15 for more

	than two consecutive days) dexamethasone group (n = 274) = 9 placebo group (n = 271) = 11 p = 0.23 i.e. not statistically significant
	Changes in signs and symptoms – paresis Number of patients with hemiparesis at baseline to resolve after 9 months of treatment dexamethasone group = 36 of 48 placebo group = 30 of 37 OR[1] (95% CI) = 0.70 (0.24 to 2.00) p = 0.51 i.e. not statistically significant Number of patients without hemiparesis at baseline to be experiencing hemiparesis after 9 months of treatment dexamethasone group = 14 of 226 placebo group = 11 of 234 OR[1] (95% CI) = 1.34 (0.59 to 3.01) i.e. not statistically significant Number of patients to with paraparesis at baseline to resolve after 9 months of treatment dexamethasone group = 19 of 28 placebo group = 9 of 11 OR[1] (95% CI) = 0.47 (0.08 to 2.63)

	i.e. not statistically significant Number of patients without paraparesis at baseline to be experiencing paraparesis after 9 months of treatment dexamethasone group = 11 of 246 placebo group = 11 of 260 OR[1] (95% CI) = 1.06 (0.45 to 2.49) i.e. not statistically significant
	Relapse Defined by the onset of new focal neurologic signs or a fall in the Glasgow coma score of 2 points or more for two or more days after more than seven days of clinical stability or improvement at any time after randomization Number of patients to experience relapse dexamethasone group = 41 of 274 placebo group = 48 of 271 OR[1] (95% CI) = 0.82 (0.52 to 1.29) i.e. not statistically significant Time to relapse (median, days) dexamethasone group = 41 placebo group = 38 p = 0.12 i.e. not statistically significant
	Adverse events – 'severe' events Defined as any event causing or threatening to cause prolonged hospital stay, disability, or death

	Number of patients to experience a severe event dexamethasone group = 26 of 274 placebo group = 45 of 271 **OR[1] (95% CI) = 0.53 (0.31 to 0.88)** **i.e. statistically significant**
Bibliographic reference	Thwaites GE, Macmullen-Price J, Tran TH et al (2007) Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. Lancet Neurology 6(3): 230-6
Length of follow up	9 months after treatment initiation
Outcomes measures and effect size	**Changes in signs and symptoms – tuberculoma** Number of patients to experience a tuberculoma dexamethasone group = 9 of 274 placebo group = 5 of 271 OR[1] (95% CI) = 1.81 (0.60 to 5.46) i.e. not statistically significant
	Changes in signs and symptoms – hydrocephalus Number of patients to experience hydrocephalus dexamethasone group = 10 of 274 placebo group = 7 of 271 OR[1] (95% CI) = 1.43 (0.54 to 3.81) i.e. not statistically significant
Source of funding	Wellcome Trust

Comments	
[1] Odds ratio and 95% confidence interval calculated by reviewer Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; E, ethambutol; H, isoniazid; HR, hazard ratio; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide	

BONE & JOINT, INCLUDING SPINAL, TUBERCULOSIS

1.5.19 Cathro, 1958

Bibliographic reference	Cathro AJM (1958) A clinical trial of prednisolone in bone and joint tuberculosis. East African Medical Journal 35(1): 31-5
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* details provided are limited, but site of disease varies between the 2 groups: prednisolone group = 7 spinal, 2 knee, 1 hip; antituberculosis chemotherapy alone = 4 hip, 2 knee *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?* no – not for the full treatment period *Groups comparable for treatment completion and availability of outcome data?* yes, although follow-up not for the full treatment period and therefore completion of antituberculosis chemotherapy could not be assessed

<table>
<tr><td></td><td>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?
antituberculosis chemotherapeutic regimens lacked rifampicin, pyrazinamide and ethambutol
Have substitute outcomes been used instead of the patient-important outcomes of interest?
yes - response to treatment
Analysis followed the intent-to-treat principle?
yes</td></tr>
<tr><td>Number of patients</td><td>Randomised = 16
prednisolone group = 10
antituberculosis chemotherapy alone group = 6</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Active tuberculosis of bone and joint
Baseline
Ages ranged from 4 to 47, with an average of 16 years
<table>
<tr><th></th><th>Prednisolone</th><th>Antituberculosis chemotherapy alone</th></tr>
<tr><td>Site of disease
spinal, n (%)</td><td>
7 (70)</td><td>
0 (0)</td></tr>
</table></td></tr>
</table>

		knee, n (%)	2 (20)	4 (67)
		hip, n (%)	1 (10)	2 (33)
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (2 months) adults: 20 mg/day Antituberculosis chemotherapy: isoniazid (600 mg/day in adults) and streptomycin (1 g/day in adults); total duration of antituberculosis chemotherapy unknown Children received proportionally smaller doses according to age All patients received surgery			
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: isoniazid (600 mg/day in adults) and streptomycin (1 g/day in adults); total duration of antituberculosis chemotherapy unknown Children received proportionally smaller doses according to age All patients received surgery			
Length of follow up	3 months after treatment initiation			
Location	Nairobi, Kenya			
Outcomes measures and effect size	**Response to treatment – need for additional surgical intervention** Number of patients requiring surgery due to insufficient shrinkage of the swollen joint prednisolone group = 9 of 10 antituberculosis chemotherapy alone group = 5 of 6 OR[1] (95% CI) = 1.80 (0.09 to 35.43)			

	i.e. not statistically significant
	Changes in signs and symptoms – weight Number of patients that failed to gain weight prednisolone group = 1 of 10 antituberculosis chemotherapy alone group = 1 of 6 OR[1] (95% CI) = 0.56 (0.03 to 10.93) i.e. not statistically significant
Source of funding	Prednisolone supplied by Pfizer Ltd.
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin

PERICARDIAL TUBERCULOSIS

1.5.20 Hakim et al, 2000

Bibliographic reference	Hakim JG, Ternouth I, Mushangi E et al (2000) Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart 84: 183-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – use of a computer generated randomisation list *Allocation concealment used?* unclear *Blinding used?* double-blind: clinicians and patients were blinded to the identity of the tablets; a randomisation code list was kept sealed and was released at the end of the study *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?* 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?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – pill counts are a surrogate for adherence; improvement in cardiothoracic ratio and echocardiographic measurement of pericardial fluid are surrogates for improvement in pericardial effusion *Analysis followed the intent-to-treat principle?* unclear
Number of patients	Randomised = 58 prednisolone group = 29 antituberculosis chemotherapy alone group = 29
Patient characteristics	*Inclusion* Age 18–55 years Residence in Harare city to ensure good follow up HIV seropositive No diagnosis of tuberculosis within the past two years Large pericardial effusion on echocardiography (>1 cm anteriorly and >1 cm posteriorly Pericardial aspirate with >50% lymphocytes Protein content >30 g/l

Diagnostic criteria

Patients were admitted into the study on the basis of an echocardiographic demonstration of a large fibrinous pericardial effusion and a clinical diagnosis of tuberculous pericarditis, supported by a high lymphocyte count and a high protein content in the pericardial aspirate

Diagnostic and/or therapeutic pericardiocentesis was undertaken in all patients

The typical two dimensional (cross sectional) echocardiography appearance of tuberculous pericarditis was a thickened pericardium with layers of shaggy echoes lining both visceral and parietal pericardium, but various appearances were observed

Clinical examination and appropriate tests excluded alternative causes of pericarditis

Exclusion

Antituberculous treatment started more than 48 hours before recruitment

Corticosteroid treatment within previous one month

Presence of Kaposi's sarcoma or any other malignancy

Coexisting life threatening disease

Bacterial pneumonia

Pregnancy

Cavitating pulmonary tuberculosis

Other causes of pericardial effusion

Baseline

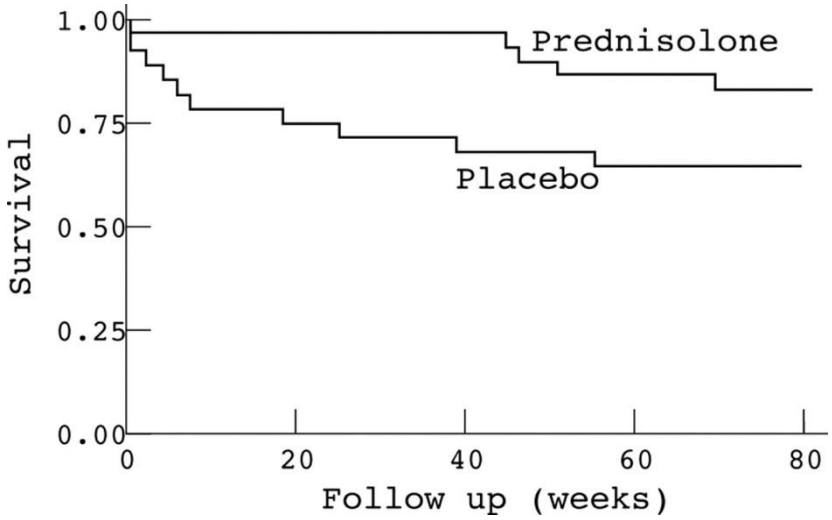
	Prednisolone (n = 29)	**Antituberculosis chemotherapy alone** (n = 29)
Age (mean (range)), years	33 (19–53)	29 (21–41)

Sex, male:female	22:7	18:11
Duration of illness		
unknown	1	1
<2 weeks, n	4	3
2–8 weeks, n	20	15
>8 weeks, n	4	10
Symptoms		
cough, n	27	28
sputum production, n	22	22
haemoptysis, n	6	3
dyspnea		
nil, n	3	5
on exertion, n	16	18
at rest, n	10	6
chest pain, n	26	23
Past medical history		
pneumonia, n	2	2
Signs		
fever (>37.7°C), n	16	18
pulse		
≤100 beats/min	0	0

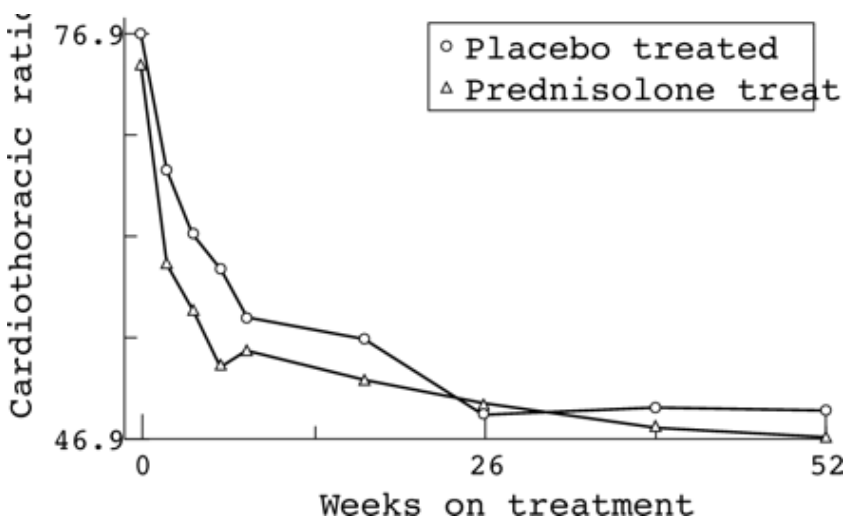
		101–120 beats/min	24	19
		>120 beats/min	5	10
		systolic blood pressure		
		<100 mm Hg	1	2
		≥100 mm Hg	28	27
		pulsus paradoxus	18	16
		jugular venous pressure		
		≤5 cm, n	4	3
		6–10 cm, n	10	14
		>10 cm, n	12	8
		Respiratory rate (mean (range)), /min	29 (18–46)	30 (18–44)
		Weight (mean (range)), kg	57 (42–75)	54 (35–67)
		Oedema		
		nil/just detectable, n	21	18
		affecting legs, n	4	5
		affecting sacrum, n	1	2
		Ascites		
		nil/just detectable, n	26	22
		shifting/dullness, n	1	3
		tense abdomen, n	0	0

		Hepatomegaly		
		≤4 cm, n	7	6
		5–8 cm, n	16	16
		>8 cm, n	4	3
		Patients' perception of wellbeing		
		completely well, n	0	0
		well, but not perfect, n	12	11
		unwell, n	17	17
		Level of physical activity		
		unrestricted, n	11	11
		out and about, but restricted, n	11	12
		restricted to home or hospital, n	6	5
		bedridden, n	1	1
		Haemoglobin <12 g/dl, n	20	19
		Total white cell count <4.0 cells/µl, n	6	1
		Platelet count <100 cells/µl, n	2	1
		CD4+ count (median (IQR))	374 (220–418)	254 (132–352)
		<200 cells/µl, n	3	5
		200–500 cells/µl, n	10	5
		>500 cells/µl, n	2	3
		Liver function tests (median (IQR))		

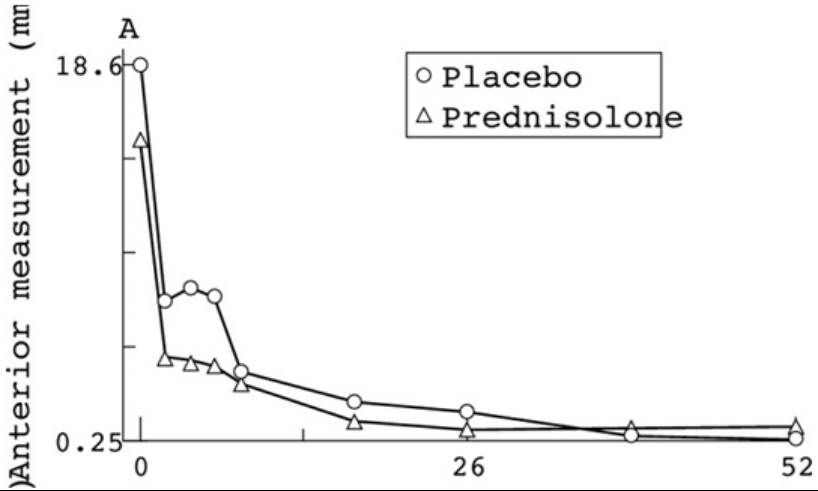
	bilirubin	11 (10–180)	11 (10–27)
	aspartate transaminase	35 (5–520)	32 (6–127)
	alkaline phosphatase	178 (145–361)	237 (100–610)
	albumin	16	12
	Cardiothoracic ratio (chest x-ray)		
	<55%	0	0
	55–75%	9	6
	>75%	5	8
	Low voltage ECG	4	5
	Pericardial effusion size (mean±SD)		
	anterior, cm	2.5±2.1	2.2±1.3
	posterior, cm	2.6±1.0	2.8±1.3
	subcostal,cm	2.7±1.0	2.7±1.0
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (6 weeks) starting at a dose of 60 mg (12 tablets) and tapering by 10 mg per week until completion at the end of the sixth week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided		
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (6 weeks)		

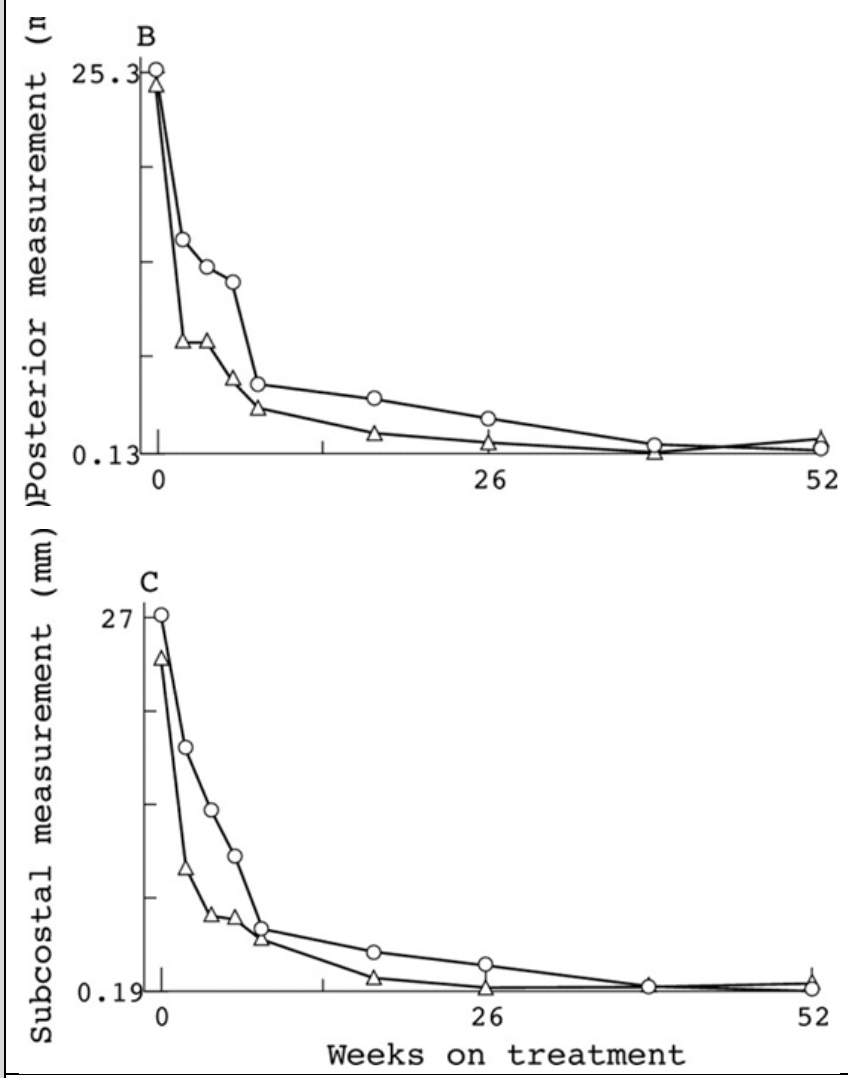
	starting at a dose of 60 mg (12 tablets) and tapering by 10 mg per week until completion at the end of the sixth week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided
Length of follow up	18 months after treatment initiation
Location	Harare, Zimbabwe
Outcomes measures and effect size	**Mortality**  Number of deaths after 18 months prednisolone group = 5 of 29 antituberculosis chemotherapy alone group = 10 of 29 p = 0.004 i.e. statistically significant OR[1] (95% CI) = 0.40 (0.12 to 1.36)

	i.e. not statistically significant
	Changes in signs and symptoms – physical activity Number of patients to experience improvement in physical activity p = 0.017 i.e. statistically significant
	Changes in signs and symptoms – constrictive pericarditis Number of patients to experience constrictive pericarditis prednisolone group = 2 of 29 antituberculosis chemotherapy alone group = 2 of 29 OR[1] (95% CI) = 1.00 (0.13 to 7.62) i.e. not statistically significant
	Changes in signs and symptoms – pericardial effusion Change in cardiothoracic ratio, as measured serially in the prednisolone and placebo treatment groups (p = 0.80, i.e. not statistically significant)[2]



Pericardial fluid regression serial echocardiographic measurements of fluid in the (A) anterior, (B) posterior, and (C) subcostal views (anterior p = 0.19; posterior p = 0.80; subcostal p = 0.39, i.e. not statistically significant)[2]





Adherence

Number of pill counts showing that >90% of tablets had been consumed

	prednisolone group = 169 of 230 antituberculosis chemotherapy alone group = 119 of 182 p = 0.008 i.e. statistically significant OR[1] (95% CI) = 1.47 (0.96 to 2.24) i.e. not statistically significant
Source of funding	CAPS(Pvt) Ltd. provided the prednisolone and placebo tablets and financial support
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Authors do not specify the statistic used (mean *vs* median etc)

Abbreviations: CI, confidence intervals; E, ethambutol; ECG, echocardiogram; H, isoniazid; IQR, interquartile range; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

1.5.21 Reuter et al, 2006

Bibliographic reference	Reuter H, Burgess LJ, Louw VJ et al (2006) Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovascular Journal of South Africa 17(5): 233-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – predetermined randomisation schedule for 100 patients on a 3:3:4 basis; numbers were drawn from a hat, stored on a list on a computer *Allocation concealment used?* yes – randomisation schedule provided to the treating physician with the assigned treatment by a non-clinical administrator

	Blinding used? double-blind: randomisation code remained concealed and was not revealed to the investigators or the study subjects until completion of the study; however, physician administering the intrapericardial steroids/placebo was unblinded *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?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes

<table>
<tr><td>Number of patients</td><td>Randomised = 57
prednisolone group = 16
triamcinolone group = 17
placebo group = 24</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Large pericardial effusion on echocardiography (epi-pericardial distance > 10 mm)
Pericardial aspirate with protein content > 30 g/l; (4) pericardial fluid adenosine deaminase (ADA) activity > 35 U/l
Aged 13 to 75 years
Exclusion
CD4 counts <200 cells/µl were excluded due to uncertainty as to the effects of corticosteroids on immunocompromised patients with TB with regard to risk for disseminated disease
Patients presenting with signs of constrictive pericarditis or requiring pericardial surgery within the first 5 days of admission
Baseline
40 of the 57 patients (70.0%) had microbiological and/or histological evidence of TB, the remaining 17 patients (30.0%) were diagnosed by clinical and supportive laboratory data
<table>
<tr><th></th><th>Prednisolone group
(n= 16)</th><th>Triamcinolone group
(n= 17)</th><th>Placebo group
(n= 24)</th></tr>
<tr><td>Sex
female, n
male, n</td><td>
7
9</td><td>
4
13</td><td>
12
12</td></tr>
<tr><td>HIV-seropositive</td><td>9</td><td>6</td><td>6</td></tr>
</table>
</td></tr>
</table>

	Age (mean±SD (range)), years	34.4±9.86 (17–58)	38.6±10.16 (22–66)	33.3±15.86 (17–66)
	Symptoms			
	fever, n (%)	13 (81)	12 (71)	18 (75)
	night sweats, n (%)	7 (44)	7 (41)	10 (42)
	weight loss, n (%)	13 (81)	13 (76)	19 (79)
	anorexia, n (%)	12 (75)	12 (71)	19 (79)
	dyspnea, n (%)	15 (94)	16 (94)	22 (92)
	chest pain, n (%)	6 (38)	4 (24)	7 (29)
	cough, n (%)	14 (88)	15 (88)	20 (83)
	Physical signs			
	lymphadenopathy, n (%)	5 (31)	4 (24)	7 (29)
	soft cardiac sounds, n (%)	13 (81)	14 (82)	20 (83)
	hepatomegaly, n (%)	10 (63)	11 (65)	16 (67)
	peripheral oedema, n (%)	6 (38)	6 (35)	11 (46)
	ascites, n (%)	2 (13)	2 (12)	3 (13)
	tachycardia, n (%)	13 (81)	13 (76)	20 (83)
	pulsus paradoxus, n (%)	3 (19)	5 (29)	7 (29)
	Kassmaul’s sign, n (%)	2 (13)	2 (12)	3 (13)
	jugular venous pressure >4 cm, n (%)	13 (81)	15 (88)	20 (83)
	systolic blood pressure <100 mm Hg, n (%)	1 (6)	1 (6)	1 (4)

Intervention 1	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (injection plus 11 weeks) oral prednisone plus intrapericardial placebo (5 ml 0.9% saline solution) intrapericardial placebo: 5 ml 0.9% saline solution oral prednisone: started at 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine with adjunctive prednisone
Intervention 2	*Antituberculosis chemotherapy plus triamcinalone* Triamcinolone (injection) 200 mg (5 ml) intrapericardial triamcinolone hexacetonide due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (injection) 200 mg (5 ml) intrapericardial placebo due to limited resources, an oral placebo was not used in conjunction with the intrapericardial placebo

	Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine
Length of follow up	1 year
Location	Western Cape, South Africa
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 0 of 16 triamcinolone group = 0 of 17 placebo group = 0 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 0.73 (0.01 to 38.15) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone* OR[2] (95% CI) = 2.06 (0.04 to 112.94) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 2.88 (0.05 to 156.88) i.e. not statistically significant
	Response to treatment – need for additional intervention Number of patients to require surgery

	prednisolone group = 2 of 16 triamcinolone group = 0 of 17 placebo group = 0 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 3.66 (0.17 to 79.63) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone* OR[2] (95% CI) = 6.18 (0.23 to 168.11) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 8.65 (0.32 to 233.13) i.e. not statistically significant
	Changes in signs and symptoms – activity levels Number of patients to experience reduced levels of activity at 1-year of follow-up prednisolone group = 2 of 16 triamcinolone group = 2 of 17 placebo group = 3 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 0.97 (0.20 to 4.78) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone*

	OR[2] (95% CI) = 1.07 (0.08 to 13.90) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 1.00 (0.09 to 11.24) i.e. not statistically significant
Source of funding	Crossley Fund and the South African Medical Research Council
Comments	

[1] Data for the 2 corticosteroid groups pooled by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer

[3] Data for prednisolone arm split in 2 to allow 2 pairwise comparisons of prednisolone *vs* triamcinolone and prednisolone *vs* placebo

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

1.5.22 Strang et al, 1987/2004

Study type	RCT
Study quality	*Appropriate method of randomisation used?* quasi-randomised: randomised in blocks of by entering names consecutively into a register *Allocation concealment used?* yes *Blinding used?* double-blind; all the clinical, radiographic, bacteriological, echocardiogram and histological data reviewed blind by an independent assessor

	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 *Intervention used is the same as the intervention of interest?* antituberculosis chemotherapeutic regimens lacked ethambutol and contained streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 143 prednisolone group = 70

	placebo group = 73 Outcome data available at 24 months = 114 prednisolone group = 53 placebo group = 61 Outcome data available at 10 years = 140 prednisolone group = 69 placebo group = 71
Patient characteristics	*Inclusion* Active tuberculous constrictive pericarditis Normal, or only moderately enlarged, cardiac shadow on x-ray 5 years and older *Diagnostic criteria* Reduced physical activity and breathlessness Increased jugular venous pressure Arterial pulsus paradoxus Tachycardia Hepatomegaly Ascites Non-specific but widespread T-wave changes and low voltage QRS complexes on the electrocardiogram Diagnosis considered definitely or probably correct in 136 of 143 patients *Exclusion*

Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year

Baseline

	Prednisolone group	**Placebo group**
Sex		
males, n (%)	23 (43)	25 (41)
Age		
<15 years, n (%)	1 (2)	1 (2)
15–34 years, n (%)	3 (6)	7 (11)
35–54 years, n (%)	24 (45)	33 (54)
≥55 years, n (%)	25 (47)	20 (33)
Pulse		
≤100/min, n (%)	18 (34)	16 (26)
101–120/min, n (%)	25 (47)	33 (54)
>120/min, n (%)	10 (19)	12 (20)
Paradoxus >10 mm Hg, n (%)	10 (20)	21 (35)
Jugular venous pressure		
≤5 cm, n (%)	2 (4)	6 (10)
6–10 cm, n (%)	25 (47)	24 (39)
>10 cm, n (%)	26 (49)	31 (51)
Liver		

	≤4 cm, n (%)	4 (8)	2 (2)
	5–8 cm, n (%)	33 (62)	29 (48)
	>8 cm, n(%)	16 (30)	30 (49)
	Ascites[1]		
	0–1, n (%)	16 (30)	14 (23)
	2, n (%)	27 (51)	40 (66)
	3, n (%)	10 (19)	7 (11)
	Oedema[2]		
	0–1, n (%)	33 (62)	25 (41)
	2, n (%)	6 (11)	10 (16)
	3, n (%)	14 (26)	26 (43)
	Activity[3]		
	1, n (%)	2 (4)	4 (7)
	2, n (%)	27 (51)	27 (44)
	3, n (%)	15 (28)	13 (21)
	4, n (%)	9 (17)	17 (28)
	Echocardiogram voltage <6 mm in V6 and <4 mm along frontal axis, n (%)	17 (34)	21 (35)
	Cardiothoracic ratio >55%, n (%)	32 (67)	36 (73)
Intervention	*Antituberculosis chemotherapy plus prednisolone*		

Prednisolone (11 weeks)

Age, years	3x daily for weeks 1 to 4 (total daily dose, mg)	3x daily for weeks 5 to 8 (total daily dose, mg)	3x daily for weeks 9 to 10 (total daily dose, mg)	1x daily for week 11 (total daily dose, mg)
5–9	30	15	7.5	2.5
10–14	45	22.5	7.5	2.5
≥15	60	30	15	5

Antituberculosis chemotherapy: 3HRZS/HR

Weight, kg	1x daily Streptomycin (total daily dose, mg)	Isoniazid (total daily dose, mg)	Rifampicin (total daily dose, mg)	Pyrazinamide (total daily dose, mg)
<20	300	150	250	500
20–29	500	250	400	1000
30–39	700	300	450	1500
40–49	900	300	450	1500
≥50	1000	300	600	2000

Every dose given under direct supervision of the hospital staff

Comparison

Antituberculosis chemotherapy plus placebo

Placebo (11 weeks)

Age, years	3x daily for weeks 1 to 4	3x daily for weeks 5 to 8	3x daily for weeks 9 to 10	1x daily for week 11 (total daily dose, mg)

		(total daily dose, mg)	(total daily dose, mg)	(total daily dose, mg)	
	5–9	30	15	7.5	2.5
	10–14	45	22.5	7.5	2.5
	≥15	60	30	15	5

Antituberculosis chemotherapy: 3HRZS/HR

Weight, kg	**1x daily**			
	Streptomycin (total daily dose, mg)	**Isoniazid** (total daily dose, mg)	**Rifampicin** (total daily dose, mg)	**Pyrazinamide** (total daily dose, mg)
<20	300	150	250	500
20–29	500	250	400	1000
30–39	700	300	450	1500
40–49	900	300	450	1500
≥50	1000	300	600	2000

Every dose given under direct supervision of the hospital staff

Location	Transkei
Bibliographic reference	Strang JIG, Nunn AJ, Johnson DA (2004) Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. Quarterly Journal of Medicine 97: 525-35
Length of follow up	10 years
Outcomes measures and effect size	**Mortality** Number of deaths during 10 years of follow-up prednisolone group = 16 of 70

	placebo group = 21 of 73 OR[4] (95% CI) = 0.73 (0.35 to 1.56) i.e. not statistically significant
	Response to treatment – need for surgical intervention Number of patients to require surgical intervention (pericardeictomy, as indicated by signs of severe constriction despite at least 3 months of antituberculosis chemotherapy) during 10 years of follow-up prednisolone group = 18 of 70 placebo group = 22 of 73 OR[4] (95% CI) = 0.80 (0.39 to 1.67) i.e. not statistically significant
	Changes in signs and symptoms – physical activity Number of patients to with unrestricted physical activity after 10 years of follow-up prednisolone group = 9 of 70 placebo group = 14 of 73 OR[4] (95% CI) = 0.62 (0.25 to 1.55) i.e. not statistically significant Number of patients to be 'out and about' but with restricted physical activity after 10 years of follow-up prednisolone group = 37 of 70 placebo group =32 of 73 OR[4] (95% CI) = 1.44 (0.74 to 2.78) i.e. not statistically significant

	Number of patients to confined to home or hospital after 10 years of follow-up prednisolone group = 5 of 70 placebo group = 2 of 73 OR[4] (95% CI) = 2.73 (0.51 to 14.56) i.e. not statistically significant
Bibliographic reference	Strang JIG, Kakaza HHS, Gibson DG et al (1987) Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 2(8573): 1418-22
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – favourable** Defined by the following criteria (or if only 1 were still abnormal): pulse rate of ≤100/min jugular vein pulse of ≤5 cm arterial pulsus paradoxus of ≤10 mm Hg ascites and oedema classified as nil or just detectable physical activity unrestricted cardiothoracic ration of ≤55% echocardiogram voltage of ≥6 mm in V6 or ≥4 mm along the frontal axis Number of patients to be considered in a favourable status after 24 months of follow-up prednisolone group = 50 of 70 placebo group = 52 of 73 OR[4] (95% CI) = 1.01 (0.49 to 2.08)

	i.e. not statistically significant
Source of funding	Grant from the Wellcome Trust; Ciba-Geigy and Gruppo Lepetit provided the rifampicin and the isoniazid; Bracco provided the pyrazinamide; Glaxo provided the prednisolone and the placebo
Comments	

[1] Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen

[2] Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum

[3] Degree of physical activity scored as follows: 0 = nil; 1 = activity unrestricted; 2 = out and about but activity restricted; 3 = confined to home or hospital; 4 = bedridden

[4] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.5.23 Strang et al, 1988/2004

Study type	RCT
Study quality	*Appropriate method of randomisation used?* quasi-randomised: randomised in blocks of by entering names consecutively into a register *Allocation concealment used?* yes *Blinding used?* double-blind; all the clinical, radiographic, bacteriological, echocardiogram and histological data reviewed blind by an independent assessor *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?* 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 chemotherapeutic regimens lacked ethambutol and contained streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 240 prednisolone group = 117 placebo group = 123 Outcome data available at 24 months = 198

<table>
<tr><td></td><td>prednisolone group = 97
placebo group = 101
Outcome data available at 10 years = 228
prednisolone group = 112
placebo group = 116</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Active tuberculous pericardial effusion confirmed by pericardiocentesis (diagnosis considered definitely or probably correct in 238 of 240 patients)
5 years and older
Exclusion
Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone
Prednisolone (11 weeks)
<table>
<tr><td rowspan="2">Age, years</td><td colspan="3">3x daily for</td><td rowspan="2">1x daily for week 11
(total daily dose, mg)</td></tr>
<tr><td>weeks 1 to 4
(total daily dose, mg)</td><td>weeks 5 to 8
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<tr><td>≥15</td><td>60</td><td>30</td><td>15</td><td>5</td></tr>
</table>
Antituberculosis chemotherapy: 3HRZS/HR
<table>
<tr><td>Weight, kg</td><td>1x daily</td></tr>
</table></td></tr>
</table>

	<table><tr><th></th><th>**Streptomycin** (total daily dose, mg)</th><th>**Isoniazid** (total daily dose, mg)</th><th>**Rifampicin** (total daily dose, mg)</th><th>**Pyrazinamide** (total daily dose, mg)</th></tr><tr><td><20</td><td>300</td><td>150</td><td>250</td><td>500</td></tr><tr><td>20–29</td><td>500</td><td>250</td><td>400</td><td>1000</td></tr><tr><td>30–39</td><td>700</td><td>300</td><td>450</td><td>1500</td></tr><tr><td>40–49</td><td>900</td><td>300</td><td>450</td><td>1500</td></tr><tr><td>≥50</td><td>1000</td><td>300</td><td>600</td><td>2000</td></tr></table> Every dose given under direct supervision of the hospital staff Patients that gave their consent were also randomised to receive complete open surgical drainage or pericardiocentesis
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (11 weeks) <table><tr><th rowspan="2">Age, years</th><th colspan="3">**3x daily for**</th><th rowspan="2">**1x daily for week 11** (total daily dose, mg)</th></tr><tr><th>**weeks 1 to 4** (total daily dose, mg)</th><th>**weeks 5 to 8** (total daily dose, mg)</th><th>**weeks 9 to 10** (total daily dose, mg)</th></tr><tr><td>5–9</td><td>30</td><td>15</td><td>7.5</td><td>2.5</td></tr><tr><td>10–14</td><td>45</td><td>22.5</td><td>7.5</td><td>2.5</td></tr><tr><td>≥15</td><td>60</td><td>30</td><td>15</td><td>5</td></tr></table> Antituberculosis chemotherapy: 3HRZS/HR <table><tr><th rowspan="2">Weight, kg</th><th colspan="4">**1x daily**</th></tr><tr><th>**Streptomycin**</th><th>**Isoniazid**</th><th>**Rifampicin**</th><th>**Pyrazinamide**</th></tr></table>

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<tr><td>Length of follow up</td><td>10 years</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality

Number of deaths during 10 years of follow-up

prednisolone group = 26 of 117

placebo group = 33 of 123

OR[4] (95% CI) = 0.78 (0.43 to 1.41)

i.e. not statistically significant

Survival analysis</td></tr>
</table>

Patient group	Variable*		Adjusted HR	95%CI
Constriction ($n=143$)	Treatment	Prednisolone	0.61	0.32–1.19
		Placebo	1.00	
	Age	1-year increase	1.03	1.00–1.06
	Gender	Male	2.80	1.39–5.63
		Female	1.00	
Effusion ($n=175$**)	Treatment	Prednisolone	0.68	0.38–1.24
		Placebo	1.00	
	Age	1-year increase	1.06	1.04–1.09
	Gender	Male	2.72	1.48–5.02
		Female	1.00	
All ($n=318$)	Pericarditis	Constriction	1.00	
		Effusion	1.02	0.66–1.57
	Treatment	Prednisolone	0.64	0.41–0.99
		Placebo	1.00	
	Age	1-year increase	1.05	1.03–1.07
	Gender	Male	2.70	1.71–4.28
		Female	1.00	

* Includes significant predictors and treatment. **One patient allocated to placebo was not included in this analysis because their age was unavailable.

Response to treatment – need for surgical intervention

Number of patients to require surgical intervention during 10 years of follow-up

prednisolone group = 11 of 117

placebo group = 7 of 123

OR[4] (95% CI) = 1.72 (0.64 to 4.60)

i.e. not statistically significant

Changes in signs and symptoms – physical activity

Number of patients to with unrestricted physical activity after 10 years of follow-up

prednisolone group = 21 of 117

	placebo group = 30 of 123 OR[4] (95% CI) = 0.68 (0.36 to 1.27) i.e. not statistically significant Number of patients to be 'out and about' but with restricted physical activity after 10 years of follow-up prednisolone group = 57 of 117 placebo group = 46 of 123 OR[4] (95% CI) = 1.59 (0.95 to 2.66) i.e. not statistically significant Number of patients to confined to home or hospital after 10 years of follow-up prednisolone group = 8 of 117 placebo group = 7 of 123 OR[4] (95% CI) = 1.22 (0.43 to 3.47) i.e. not statistically significant
Bibliographic reference	Strang JIG, Kakaza HHS, Gibson DG et al (1987) Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 2(8573): 1418-22
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – favourable** Defined by the following criteria (or if only 1 were still abnormal): pulse rate of ≤100/min jugular vein pulse of ≤5 cm arterial pulsus paradoxus of ≤10 mm Hg

	ascites and oedema classified as nil or just detectable physical activity unrestricted cardiothoracic ration of ≤55% echocardiogram voltage of ≥6 mm in V6 or ≥4 mm along the frontal axis Number of patients to be considered in a favourable status after 24 months of follow-up prednisolone group = 91 of 117 placebo group = 88 of 123 OR[4] (95% CI) = 1.39 (0.77 to 2.50) i.e. not statistically significant
Source of funding	Grant from the Wellcome Trust; Ciba-Geigy and Gruppo Lepetit provided the rifampicin and the isoniazid; Bracco provided the pyrazinamide; Glaxo provided the prednisolone and the placebo
Comments	

[1] Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen

[2] Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum

[3] Degree of physical activity scored as follows: 0 = nil; 1 = activity unrestricted; 2 = out and about but activity restricted; 3 = confined to home or hospital; 4 = bedridden

[4] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

1.5.24 Meintjes et al, 2010

Bibliographic reference	Meintjes G, Wilkinson RJ, Morroni C (2010) Randomised placebo-controlled trial of prednisolone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 24: 2381-90
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – a randomization sequence assigning participants in a 1:1 ratio was generated using Excel by the study statistician and given to an independent pharmacist *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* there was a longer period (p = 0.02) between taking antituberculosis chemotherapy and initiating ART amongst patients in the prednisolone arm (66 days) than the placebo arm (43.5 days) *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* study period only 12 weeks *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, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 110 prednisolone group = 55 antituberculosis chemotherapy alone group = 55
Patient characteristics	*Inclusion* New or recurrent tuberculosis symptoms and ≥1 of the following TB-IRIS manifestations were enrolled: infiltrate on chest radiograph enlarging lymph node/s serous effusion cold abscess *Exclusion* Age < 18 years

Known rifampicin-resistant tuberculosis

Previous glucocorticoid therapy during this tuberculosis episode

Prior ART exposure, pregnancy

Uncontrolled diabetes mellitus

Kaposi's sarcoma

Immediately life-threatening TB-IRIS, defined as: respiratory failure with arterial pO2 < 8 kPa, altered level of consciousness, new focal neurological sign/s, or compression of a vital structure

Baseline

	Prednisolone (n = 55)	**Placebo** (n = 55)
Age (mean (range)), years	31.5 (19.1–46.0)	31.6 (19.0–56.9)
Sex, male:female	17:38	23:32
Previous tuberculosis, n	15	10
CD4+ count prior to ART (mean (range)), cells/μl	56 (30–103)	48 (20–92)
WHO stage 4 at ART initiation	29	33
Duration antitubercular therapy to ART (mean (range)), days	66 (35–84)	43.5 (23.8-76)
Duration ART to TB-IRIS (mean (range)), days	14 (7–21)	10 (7–19)
Duration TB-IRIS to enrolment (mean (range)), days	12.5 (7–21)	14 (8–23.5)
TB-IRIS manifestations		

	new/recurrent lymphadenopathy, n	19	28
	new/recurrent cold abscess, n	1	1
	new/recurrent pulmonary infiltrate, n	19	16
	new/recurrent serious effusion, n	9	9
	CD4+ count (mean (range)), cells/μl	138 (78–243)	109 (55–190)
	Random glucose (mean (range)), mmol/l	5.1 (4.8–6.0)	5.3 (4.8–5.7)
	Haemoglobin (mean (range)), g/dl	9.1 (8.1–10.3)	9.2 (7.8–10.1)
	Albumin (mean (range)), g/l	23 (20–26)	23 (19.5–26.5)
	C-reactive protein (mean (range)), mg/l	104 (50–150)	106 (79–172)
	Random cortisol (mean (range)), nmol/l	471 (350–614)	559.5 (405.8–774.0)
	Hepatitis B surface antigen positive, n	3/42	3/52
	Weight (mean (range)), kg	51.6 (48.1–56.5)	52.2 (46.6–58.8)
	Hospitalised at enrolment	14	19
	Antibiotics prior to enrolment	25	19
	Karnofsky performance score (mean (range))	70 (30–80)	70 (30–80)
	MOS-HIV health survey		
	physical health summary score	36.3 (33.4–43.1)	37.9 (32.8–44.9)
	mental health summary score	49.7 (44.5–56.0)	49.8 (39.1–56.9)
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (4 weeks)		

	1.5mg/kg/day for 2 weeks followed by 0.75mg/kg/day for 2 weeks If significant clinical deterioration occurred after 2 weeks of follow up, the study protocol allowed participants to be switched to open label prednisone Antituberculosis chemotherapy: treatment-naïve: 2HRZE/4HR re-treatment: 2HRZSE/1HRZE/5HRE doses not described
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (4 weeks) 1.5mg/kg/day for 2 weeks followed by 0.75mg/kg/day for 2 weeks If significant clinical deterioration occurred after 2 weeks of follow up, the study protocol allowed participants to be switched to open label prednisone Antituberculosis chemotherapy: treatment-naïve: 2HRZE/4HR re-treatment: 2HRZSE/1HRZE/5HRE doses not described
Location	Western Cape Province, South Africa
Length of follow up	12 weeks
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 3 of 55 antituberculosis chemotherapy alone = 2 of 55

	OR[1] (95% CI) = 1.53 (0.25 to 9.53) i.e. not statistically significant
	Change in signs and symptoms – improvement/deterioration Symptom response was graded in 1 of 3 categories: deteriorated, no change, or improved/resolved; all patients who developed new TB-IRIS symptoms were graded as 'deteriorated' Number of patients in whom symptoms improved or were resolved after 4 weeks prednisolone group = 44 of 55 antituberculosis chemotherapy alone = 31 of 55 OR[1] (95% CI) = 1.81 (0.72 to 4.50) i.e. not statistically significant Number of patients in whom symptoms deteriorated after 4 weeks prednisolone group = 7 of 55 antituberculosis chemotherapy alone = 9 of 55 OR[1] (95% CI) = 0.75 (0.26 to 2.17) i.e. not statistically significant
	Change in signs and symptoms – chest radiograph Utilized a 3-point scale (deteriorated, no change, or improved/resolved Number of patients in whom chest radiographs were improved or resolved after 4 weeks prednisolone group = 40 of 55 antituberculosis chemotherapy alone = 25 of 55 **OR[1] (95% CI) = 3.20 (1.44 to 7.09)**

	i.e. statistically significant Number of patients in whom chest radiographs were deteriorated after 4 weeks prednisolone group = 4 of 55 antituberculosis chemotherapy alone = 18 of 55 **OR[1] (95% CI) = 0.16 (0.05 to 0.52)** **i.e. statistically significant**
	Adverse events Number of patients in to experience adverse drug reactions prednisolone group = 8 of 55 antituberculosis chemotherapy alone = 3 of 55 OR[1] (95% CI) = 2.95 (0.74 to 11.78) i.e. not statistically significant Number of patients in to experience infections prednisolone group = 27 of 55 antituberculosis chemotherapy alone = 17 of 55 OR[1] (95% CI) = 2.16 (0.99 to 4.70) i.e. not statistically significant
Source of funding	Financial support from Medical Research Council of South Africa, Wellcome Trust, EDCTP, Fogarty International Center, United States Agency for International Development and PEPFAR Gulf Drug Company (Durban, South Africa) donated the prednisone and placebo tablets
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: ART, antiretroviral therapy; CI, confidence intervals; E, ethambutol; H, isoniazid; IRIS, immune reconstitution inflammatory syndrome; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.6 RQ P : In people with drug susceptible, active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

1.6.1 Doğanay et al, 1995

Bibliographic reference	Doğanay M, Çalangu S, Turgut H et al (1995) Treatment of tuberculous meningitis in Turkey. Scandinavian Journal of Infectious Diseases 27: 135-8
Study type	Non-randomised controlled trial / prospective cohort (unclear from the report)
Study quality	Intervention does not exactly match the intervention of interest: different combinations used in each arm do not contain all of or just the 4 standard recommended drugs: 8-month regimen lacked ethambutol but contained streptomycin; some 12-to-16-month regimens lacked ethambutol and some contained streptomycin No randomisation or allocation concealment, and blinding is unclear Allocation was based upon which centre a patient attended – potential for differences in the way care is delivered? Allocation of patients to the 8-month regimen was prohibited for patients undergoing retreatment or who had previously defaulted; the same exclusion criteria was not applied to the group receiving 12–16 months of treatment Groups received different regimens of corticosteroids Unclear if groups were comparable at the baseline Unclear if the groups were comparable for treatment completion Unclear if groups were comparable for the availability of relapse data, although they were comparable for the availability of data for adverse events and the occurrence of residual sequelae Relapse follow-up varied widely in both groups Precise definitions were not provided for relapse or adverse events (‘side effects’), and it is unclear if a valid and reliable method was used for any of the outcomes measured
Number of patients	n = 72

	8 months = 37 12–16 months = 35
Patient characteristics	*Inclusion* Aged 15 years or older Tuberculous meningitis *Exclusion from data reporting* Death within 5 days of admission *Exclusion from 8-month regimen* Patients given a different regimen for >1 week or if therapy lapsed for 10 days during the treatment period, or if the patient had been treated for tuberculosis within the last 2 years *Diagnostic criteria* Clinical findings of sub-acute and chronic meningitis, meningeal symptoms lasting for >4 days Cerebrospinal fluid findings: clear or xanthochromic elevated cell count with a predominance of lymphocytes glucose level <400 mg/l protein level >1 g/l Demonstration of acid-fast bacilli in the cerebrospinal fluid by microscopic examination and/or culture Evidence of any associated extrameningeal tuberculous lesion *Stages of severity* Stage I: no definite neurological symptoms

	Stage II: signs of meningeal irritation with no clouding of consciousness and no neurological deficit Stage III: severe clouding of consciousness, stupor or coma, gross paresis and involuntary movements
Intervention	*8-month regimen* 2HRZS/6HR + corticosteroids Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day pyrazinamide: 1500 mg/day streptomycin: 1 g/day for 1 month, and 1 g/2 days for the following month Corticosteroids: prednisolone: given for the first 4 to 6 weeks to stage III patients
Comparison	*12-to-16-month regimens* Duration of treatment 25 patients: 12 months 2 patients: 15 months 3 patients: 16 months 5 patients: withdrawn from the study before treatment completion Combinations of drugs 19 patients: HRZE 6 patients: HRES 6 patients: HRZS

	3 patients: HRZES 1 patient: HRE Dosing: unclear Corticosteroids: e.g. prednisolone or dexamethasone: given in the presence of papilloedema, cranial nerve palsies, clouding of consciousness and/or coma
Length of follow up	Follow-up after treatment completion: 8 months (median months (IQR)) = 10 (6–24) 12–16 months (median months (IQR)) = 13 (4–36)
Location	Turkey
Outcomes measures and effect size	**Change in symptoms – residual neurological sequelae** Number of patients with residual neurological sequelae (hydrocephalus, cerebral atrophy, hemiparesis/monoparesis, visual impairment, imbalance, sense or hearing loss) 8 months = 8 of 37 12–16 months = 10 of 35 OR[1] (95% CI) = 0.69 (0.24 to 2.02) i.e. not statistically significant
	Relapse Number of patients to experience relapse 8 months = 0% 12–16 months = 0% OR[1] (95% CI) = 1.00 (0.02 to 50.89)

	i.e. not statistically significant
	Adverse effects – any Number of patients to experience side effects 8 months = 6 of 37 12–16 months = 8 of 35 OR[1] (95% CI) = 0.65 (0.20 to 2.12) i.e. not statistically significant
Source of funding	No details given
Comments	Intervention does not exactly match the intervention of interest: different combinations used in each arm do not contain all of or just the 4 standard recommended drugs: 8-month regimen lacked ethambutol but contained streptomycin; some 12-to-16-month regimens lacked ethambutol and some contained streptomycin Allocation was based upon which centre a patient attended – potential for differences in the way care is delivered? Allocation of patients to the 8-month regimen was prohibited for patients undergoing retreatment or who had previously defaulted; the same exclusion criteria was not applied to the group receiving 12–16 months of treatment Groups received different regimens of corticosteroids
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; IQR, interquartile range; OR, odds ratio; R, rifampicin; S, streptomycin; Z, pyrazinamide	

1.6.2 Jacobs et al, 1992

Bibliographic reference	Jacobs RF, Sunakorn P, Chotpitayasunonah T et al (1992) Intensive short course chemotherapy for tuberculous meningitis. Pediatric Infectious Disease Journal 11: 194-8

Study type	Non-randomised controlled trial / prospective cohort (unclear from the report)
Study quality	Intervention does not exactly match the intervention of interest: the interventions did not differ by treatment duration alone – 6-month regimen contains pyrazinamide in the initial phase, 9-month regimen does not a 12-month arm contained a regimen that did not use rifampicin; this arm was therefore not extracted the interventions did not contain all of/just the 4 drugs of the standard recommended regimen: 6-month regimen contains streptomycin but lacks ethambutol, and the 9-month regimen contains streptomycin but lacks ethambutol and pyrazinamide doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and rifampicin are slightly above those recommended; the dose of pyrazinamide is slightly below that which is recommended; the dose of streptomycin is considerably higher than that which is recommended No randomisation, allocation concealment or blinding Unclear how patients were allocated to each regimen, or if attempts were made to balance potential confounding factors Unclear if groups were comparable at the baseline Groups received the same care apart from the interventions studied Unclear of groups were followed up for the same length of time The 9 month group had a sample of just 4
Number of patients	n = 49 6-month group = 45 9-month group = 4
Patient characteristics	*Inclusion* Children

Tuberculous meningitis

Diagnostic criteria

Characteristic cerebrospinal fluid findings of pleocytosis with mononuclear predominance, and

Decrease in glucose content initially or during the course of the disease, and

Elevated protein content, and

Two or more of the following:

positive tuberculin skin test, ≥10 mm induration

radiographic evidence of pulmonary tuberculosis that included parenchymal or hilar lymph node involvement

history of contact with a known tuberculosis patient

presence of *M. tuberculosis* in the cerebrospinal fluid

Severity of disease

Stage I: clinical presentation of fever with meningeal signs; the only diagnostic clue was the cerebrospinal fluid

Stage II: findings in stage I associated with signs of increased intracranial pressure, paresis of extremities or cranial nerve palsy

Stage III: findings in stages I and II associated with severe impairment in consciousness and/or decerebrate posturing

Baseline characteristics

Treatment group	Number of patients
6-month group (n = 45)	
stage I	8
stage II	25
stage III	12

	9-month group (n = 4) stage I: 0 stage II: 1 stage III: 3
Intervention	*6-month regimen* 2HRZS/4HR + corticosteroids Dosing: streptomycin: 40 mg/kg of body weight/day isoniazid: 15 mg/kg of body weight/day rifampicin: 20 mg/kg of body weight/day pyrazinamide: 30 mg/kg of body weight/day Corticosteroids: dexamethasone (all patients): 0.3 to 0.5 mg/kg of body weight/day in the first week of treatment prednisolone (stage II and stage III patients only): 2 mg/kg of body weight/day for 3 to 4 weeks after the first week of treatment with tapering dosages Standard neurosurgical techniques and supportive and critical care were provided to all patients
Comparison	*9-month regimen* 2HRS/7HR + corticosteroids Dosing: streptomycin: 40 mg/kg of body weight/day

	isoniazid: 15 mg/kg of body weight/day rifampicin: 20 mg/kg of body weight/day Corticosteroids: dexamethasone (all patients): 0.3 to 0.5 mg/kg of body weight/day in the first week of treatment prednisolone (stage II and stage III patients only): 2 mg/kg of body weight/day for 3 to 4 weeks after the first week of treatment with tapering dosages Standard neurosurgical techniques and supportive and critical care were provided to all patients
Length of follow up	At least the full treatment period 6-month group: at least 1-year of follow-up was available for 27 of the 38 survivors, less than 1 year was available for 7 of the 38 survivors, and 7 had been lost to follow-up during treatment 9-month group: no information given
Location	Thailand
Outcomes measures and effect size	**Mortality** Number of deaths 6-month group = 7 of 45 9-month group = 2 of 4 OR[1] (95% CI) = 0.18 (0.02 to 1.53) i.e. not statistically significant
	Change in symptoms – neurological sequelae Number of patients to experience neurological sequelae (hydrocephalus, cerebral palsy with mental retardation, hemiparesis, long-term seizures, or behavioural changes) 6-month group = 11 of 45

	9-month group = 2 of 4 OR[1] (95% CI) = 0.32 (0.04 to 2.58) i.e. not statistically significant
Source of funding	No details given
Comments	Intervention does not exactly match the intervention of interest: the interventions did not differ by treatment duration alone – each regimen contained a different, though similar, combination of drugs the 12-month arm contained a regimen that did not use rifampicin; this arm was therefore not extracted the interventions did not contain all of/just the 4 drugs of the standard recommended regimen: 6-month regimen contains streptomycin but lacks ethambutol, and the 9-month regimen contains streptomycin but lacks ethambutol and pyrazinamide doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and rifampicin are slightly above those recommended; the dose of pyrazinamide is slightly below that which is recommended; the dose of streptomycin is considerably higher than that which is recommended
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; S, streptomycin; Z, pyrazinamide	

SPINAL TUBERCULOSIS

1.6.3 Medical Research Council Working Party on Tuberculosis of the Spine, 1986/1999

Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: both arms received surgery in addition to antituberculosis chemotherapy does not contain the 4 standard recommended drugs: lacks ethambutol and pyrazinamide, and contains streptomycin Population does not exactly match the population of interest:

	6 of the 43 patients tested had single or combined drug resistance Appropriate method of randomisation used: numbered series of sealed envelopes containing the allocated regimen Use of allocation concealment and blinding were unclear; it was noted that the allocation took place in London rather than Hong Kong, which may be an attempt at allocation concealment Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups not followed up for the same length of time Groups were comparable for treatment completion and availability of outcome data Favourable status at the end of treatment is a composite of cure and change in signs and symptoms; it is a substitute outcome
Number of patients	n = 60 6-month group = 31 9-month group = 29 Analysed over 36-month follow-up = 51 6-month group = 25 9-month group = 26 Analysed over 60-month follow-up = 50 6-month group = 24 9-month group = 26
Patient characteristics	*Inclusion* Clinical and radiographic evidence of tuberculosis in any vertebral body from the first thoracic to the first sacral, with evidence of activity of the disease clinically and/or radiologically

Exclusion

Serious extraspinal disease that is likely to affect the management of or response to treatment

A history of previous specific chemotherapy for 12 months or more

Paraplegia was not considered a bar to inclusion, but in practice no case was admitted

Baseline characteristics

Broadly similar in both groups

	Number of patients	
	6-month (n = 25)	***9-month (n = 26)***
Age (years)		
0 to 4	*1*	*5*
5 to 14	*5*	*2*
15 to 34	*6*	*13*
35 to 54	*6*	*3*
55+	*7*	*3*
Sinus and/or clinically evident abscess	*5*	*2*
Kyphosis present	*16*	*14*
Limitation of movement present	*11*	*12*
Central nervous system abnormality	*1*	*2*
Site of lesion		
thoracic	*11*	*8*

		thoracolumbar	*2*	*2*	
		lumbar	*12*	*15*	
		lumbosacral	*0*	*1*	
		Number of vertebrae involved			
		1	*0*	*0*	
		2	*22*	*23*	
		3	*3*	*0*	
		Total vertebral loss			
		0	*1*	*0*	
		up to 1	*23*	*24*	
		1 to 2	*1*	*2*	
		Angle of kyphosis (degrees)			
		0 to 20	*12*	*17*	
		21 to 40	*8*	*4*	
		41 to 60	*0*	*1*	
		not assessed	*5*	*4*	
		Mediastinal or psoas abscess shadows	*16*	*13*	
		Radiographic activity of disease			
		active	*16*	*15*	
		doubtfully active	*9*	*10*	

	quiescent	*0*	*1*

Intervention	*6-month regimen* $6H_7R_7S_2$ + surgery Dosing: isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg rifampicin: 15 mg/kg of body weight/day up to a maximum of 600 mg streptomycin: 20 mg/kg of body weight/day up to a maximum of 1 g intramuscularly Triple drug regimens were used because of the high levels of pretreatment drug resistance known to exist in Hong Kong Radical surgery (radical anterior resection of the tuberculous focus and subsequent reconstruction using bone grafting) was performed on all patients within 1 month of commencing chemotherapy Patients managed as inpatients for a minimum of 3 months after the initiation of chemotherapy or 2 months after surgery, after which patients were treated as outpatients, though they attended outpatient clinics daily for supervision of their chemotherapy
Comparator	*9-month regimen* $9H_7R_7S_2$ + surgery Dosing: isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg rifampicin: 15 mg/kg of body weight/day up to a maximum of 600 mg streptomycin: 20 mg/kg of body weight/day up to a maximum of 1 g intramuscularly Triple drug regimens were used because of the high levels of pretreatment drug resistance known to exist in Hong Kong

	Radical surgery (radical anterior resection of the tuberculous focus and subsequent reconstruction using bone grafting) was performed on all patients within 1 month of commencing chemotherapy Patients managed as inpatients for a minimum of 3 months after the initiation of chemotherapy or 2 months after surgery, after which patients were treated as outpatients, though they attended outpatient clinics daily for supervision of their chemotherapy
Location	Hong Kong
Bibliographic reference	Griffiths DLl et al (1986) A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. Tenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. Tubercle 67: 243-59
Length of follow up	36 months (after treatment initiation?)
Outcomes measures and effect size	**Change in signs and symptoms – sinuses** Number of patients with sinus and/or clinically evident abscesses on admission which had resolved without additional intervention[2] 6-month group = 4 of 5 9-month group = 2 of 2 OR[1] (95% CI) = 0.60 (0.02 to 20.98) i.e. not statistically significant Number of patients in whom new sinuses and/or clinically evident abscesses formed and resolved without additional intervention [2,3] 6-month group = 1 of 1 9-month group = 2 of 3 OR[1] (95% CI) = 1.80 (0.04 to 79.43) i.e. not statistically significant
	Change in signs and symptoms – nervous system involvement

Number of patients with nervous system involvement on admission which had resolved by 36 months

6-month group = 1 of 1

9-month group = 2 of 2

OR[1] (95% CI) = 0.60 (0.01 to 49.45)

i.e. not statistically significant

Change in signs and symptoms – bony fusion

Number of patients with complete bony fusion at 36 months

6-month group = 25 of 25

9-month group = 26 of 26

OR[1] (95% CI) = 0.96 (0.02 to 50.35)

i.e. not statistically significant

Cumulative occurrence of complete bony fusion over time[4]

survival time (months after treatment initiation)	**6-month group (n = 25)**		**9-month group (n = 26)**	
	number with complete bony fusion	survival probability	number with complete bony fusion	survival probability
3	4	0.84	0	1
6	9	0.64	11	0.58
9	11	0.56	20	0.23
12	14	0.44	21	0.19

<table>
<tr><td></td><td>
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<tr><td>18</td><td>17</td><td>0.32</td><td>23</td><td>0.12</td></tr>
<tr><td>24</td><td>23</td><td>0.08</td><td>25</td><td>0.04</td></tr>
<tr><td>30</td><td>24</td><td>0.04</td><td>26</td><td>0</td></tr>
<tr><td>36</td><td>25</td><td>0</td><td>26</td><td>0</td></tr>
</table>
</td></tr>
<tr><td></td><td>Adverse events – events requiring interruption and modification of the allocated regimen

Number of patients to experience adverse events that led to an interruption of treatment and subsequent modification of the allocated regimen

6-month group = 2 of 31

9-month group = 0 of 29

OR[1] (95% CI) = 5.00 (0.23 to 108.68)

i.e. not statistically significant</td></tr>
<tr><td>Bibliographic reference</td><td>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 23: 73-81</td></tr>
<tr><td>Length of follow up</td><td>60 months after the initiation of treatment</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality

Number of deaths associated with spinal tuberculosis

6-month group = 0 of 24

9-month group = 0 of 26

OR[1] (95% CI) = 1.08 (0.02 to 56.64)</td></tr>
</table>

	i.e. not statistically significant
	Response to treatment – favourable Defined as full physical activity with radiographically quiescent spinal disease, neither sinus nor clinical clinically evident abscesses, no myelopathy with functional impairment, and no modification of the allocated regimen Number of patients whose response to treatment was classified as favourable at 60 months 6-month group = 23 of 24 9-month group = 25 of 26 OR[1] (95% CI) = 0.92 (0.05 to 15.58) i.e. not statistically significant
	Response to treatment – unfavourable response requiring additional chemotherapy and/or surgery Number of patients who had an unfavourable response to treatment that required additional chemotherapy and/or during the 60-month follow-up 6-month group = 1 of 24 9-month group = 1 of 26 OR[1] (95% CI) = 1.09 (0.06 to 18.40) i.e. not statistically significant
	Change in signs and symptoms – vertebral loss Mean vertebral loss from 36 months to 60 months 6-month group (n = 24) = 0.05 9-month group (n = 25) = 0.15 MD[6] = -0.10 Mean vertebral loss from treatment initiation to 60 months[8]

	6-month group (n = 24) = 0.70 9-month group (n = 25) = 0.64 MD[6] = 0.06 % of patients with improvement in their vertebral loss (reduction in loss of more than 0.25 vertebrae) from baseline to 60 months 6-month group (n = 24) = 2 9-month group (n = 25) = 5 OR[1] (95% CI) = 0.36 (0.06 to 2.09) i.e. not statistically significant % of patients with no change in their vertebral loss (within ±0.24 vertebrae) from baseline to 60 months 6-month group (n = 24) = 13 9-month group (n = 25) = 14 OR[1] (95% CI) = 0.93 (0.30 to 2.86) i.e. not statistically significant % of patients with deterioration in their vertebral loss (further loss of more than 0.25 vertebrae) from baseline to 60 months 6-month group (n = 24) = 6 9-month group (n = 25) = 9 OR[1] (95% CI) = 0.59 (0.17 to 2.03) i.e. not statistically significant
	Change in signs and symptoms – kyphosis Mean change in angle of kyphosis in the thoracic and thoracolumbar regions from baseline to 60 months

	6-month group (n = 14) = 12.5° 9-month group (n = 14) = -1.6° MD[6] = 14.1° note: the authors note that 1 patient in the 9-month group had a particularly large decrease in their angle of kyphosis of 44°; if this outlier is removed from the analyses, the mean change in the 9-month group was an increase of 1.6°, and the mean difference between the two groups[6] was 10.9° % of patients with improvement in their angle of kyphosis (reduction of 11° or more) from baseline to 60 months 6-month group (n = 14) = 0 9-month group (n = 14) = 1 OR[1] (95% CI) = 0.31 (0.01 to 8.29) i.e. not statistically significant % of patients with no change in their angle of kyphosis (within ±10°) from baseline to 60 months 6-month group (n = 14) = 5 9-month group (n = 14) = 11 **OR[1] (95% CI) = 0.15 (0.03 to 0.81)** **i.e. statistically significant** % of patients with deterioration in their angle of kyphosis (increase of 11° or more) from baseline to 60 months 6-month group (n = 14) = 9 9-month group (n = 14) = 2 **OR[1] (95% CI) = 10.80 (1.69 to 68.94)** **i.e. statistically significant**
Source of funding	No details provided

Comments	Intervention does not exactly match the intervention of interest: both arms received surgery in addition to antituberculosis chemotherapy Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance

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

[2] Follow-up unclear; all events occurred within the treatment period, though follow-up may have been for the full 36 months

[3] Incidence of new sinus formation not analysed by reviewer as all new sinuses formed within 6 months of treatment initiation; that is, differences between the groups would not be related to the different durations of treatment

[4] Reviewer used the reported data on the cumulative occurrence of complete bony fusion to produce the survival probabilities and a Kaplan-Meier curve

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

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

[7] Mean change from baseline to 36 months not provided by authors; change in mean calculated by author

[8] Mean change from baseline to 60 months not provided by authors; change in mean calculated by author by combining with the data for baseline to 36 months from Griffiths et al (1986) with the data for 36 months to 60 months from Darbyshire (1999)

Abbreviations: CI, confidence interval; H, isoniazid; HR, hazard ratio; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin

1.6.4 Upadhyay et al, 1995

Bibliographic reference	Upadhyay SS, Saji M & Yau ACMC (1995) Duration of antituberculosis chemotherapy in conjunction with radical surgery in the management of spinal tuberculosis. Spine 21: 1898-1903
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens contain streptomycin but lack

	ethambutol and pyrazinamide 18-month regimen contained PAS - not licensed in the UK; data for this arm was not extracted all patients had surgery Population does not exactly match the population of interest: some patients also had respiratory TB Method of randomisation, and use of allocation concealment and blinding were unclear Groups were comparable at the baseline, except in terms of the incidence of neurological sequelae Groups received the same care apart from the interventions studied Groups were not followed up for the same length of time Groups were comparable for treatment completion and availability of outcome data
Number of patients	n = 51[1] 6-month group = 25 9-month group = 26
Patient characteristics	*Inclusion* Clinically and radiologic evidence of tuberculosis of the spine anywhere from T1 to S1, inclusive *Exclusion* Serious extraspinal disease that would affect the management of spinal lesion Paralysis severe enough to prevent them from walking across a room A history of previous specific chemotherapy for 12 months or more Vertebral destruction equivalent to three or more vertebral bodies *Baseline characteristics*

<table>
<tr><td></td><td>The extent of disease at entry was similar in both groups
<table>
<tr><th></th><th colspan="2">% patients</th></tr>
<tr><th></th><th>6-month</th><th>9-month</th></tr>
<tr><td>Age (mean years ± SD)</td><td></td><td></td></tr>
<tr><td>at surgery</td><td>32.6±18.3</td><td>28.5±19.6</td></tr>
<tr><td>at final follow-up</td><td>42.8±18.4</td><td>38.6±20.0</td></tr>
<tr><td>Site of lesion</td><td></td><td></td></tr>
<tr><td>thoracic</td><td>9</td><td>8</td></tr>
<tr><td>thoracolumbar</td><td>12</td><td>10</td></tr>
<tr><td>lumbar</td><td>4</td><td>8</td></tr>
<tr><td>Incidence of pulmonary tuberculosis</td><td>5/25 (20%)</td><td>13/26 (50%)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>6-month regimen
3HRS/3HR + surgery
Dosing:
isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg
rifampicin: up to 20 mg/kg of body weight/day up to a maximum of 600 mg
streptomycin: 20 mg/kg of body weight/day up to a maximum of 1.0 g
Radical surgery (Hong Kong radical resection of the tuberculous focus and subsequent reconstruction using bone grafting) was performed on all patients</td></tr>
<tr><td>Comparison</td><td>9-month regimen</td></tr>
</table>

	3HRS/6HR + surgery Dosing: isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg rifampicin: up to 20 mg/kg of body weight/day up to a maximum of 600 mg streptomycin: 20 mg/kg of body weight/day up to a maximum of 1.0 g Radical surgery (Hong Kong radical resection of the tuberculous focus and subsequent reconstruction using bone grafting) was performed on all patients
Length of follow up	Minimum of 10 years
Location	Hong Kong
Outcomes measures and effect size	**Change in signs and symptoms – neurological status (motor deficit) at 5 years after surgery** Number of patients to have motor deficit during 5-year follow-up post-surgery 6-month group = 1 of 25 (4%) 9-month group = 0 of 26 (0%) Change in the % of patients to have motor deficit from baseline to 5 years post-surgery[2] 6-month group = -4% 9-month group = -7.7%
	Change in signs and symptoms – neurological status (motor deficit) at final follow-up evaluation Number of patients to have motor deficit at final follow-up evaluation 6-month group = 1 of 25 (4%) 9-month group = 0 of 26 (0%) Change in the % of patients to have motor deficit[2]

	6-month group from baseline to final follow-up evaluation = -4% from 5 years of follow-up to final follow-up evaluation = 0% 9-month group from baseline to final follow-up evaluation = -7.7% from 5 years of follow-up to final follow-up evaluation = 0%
	Change in signs and symptoms – neurological status (sensory deficit) at 5 years after surgery Number of patients to have sensory deficit during 5-year follow-up post-surgery 6-month group = 0 of 25 (0%) 9-month group = 0 of 26 (0%) Change in the % of patients to have sensory deficit from baseline to 5 years post-surgery[2] 6-month group = -4% 9-month group = -3.8%
	Change in signs and symptoms – neurological status (sensory deficit) at final follow-up evaluation Number of patients to have sensory deficit at final follow-up evaluation 6-month group = 0 of 25 (0%) 9-month group = 0 of 26 (0%) Change in the % of patients to have sensory deficit[2] 6-month group from baseline to final follow-up evaluation = -4% from 5 years of follow-up to final follow-up evaluation = 0%

	9-month group from baseline to final follow-up evaluation = -3.8% from 5 years of follow-up to final follow-up evaluation = 0%
	Change in signs and symptoms – neurological status (abnormal reflexes) at 5 years after surgery Number of patients to have abnormal reflexes during 5-year follow-up post-surgery 6-month group = 1 of 25 (4%) 9-month group = 1 of 26 (3.8%) Change in the % of patients to have abnormal reflexes from baseline to 5 years post-surgery[1] 6-month group = -8% 9-month group = -19.3%
	Change in signs and symptoms – neurological status (abnormal reflexes) at final follow-up evaluation Number of patients to have abnormal reflexes at final follow-up evaluation 6-month group = 3 of 25 (12%) 9-month group = 2 of 26 (7.7%) Change in the % of patients to have abnormal reflexes[1] 6-month group from baseline to final follow-up evaluation = -4% from 5 years of follow-up to final follow-up evaluation = 8% 9-month group from baseline to final follow-up evaluation = -15.4% from 5 years of follow-up to final follow-up evaluation = 3.9%

	Change in signs and symptoms – kyphosis at final follow-up Changes in the mean angle of deformity (mean ± SD) at final follow-up from 6-month post-operative evaluation 6-month group (n = 25) = 3.5±7.9 9-month group (n = 26) = 4.2±8.8 MD (95% CI)[3] = -0.7 (-5.31 to 3.91) i.e. not statistically significant
	Relapse Number of patients to experience recurrence or reactivation of tuberculosis during follow-up 6-month group = 0 of 25 9-month group = 0 of 26 OR[4] (95% CI) = 1.04 (0.02 to 54.38) i.e. not statistically significant
	Adverse events Number of patients to experience adverse events during treatment 6-month group = 6 of 25 9-month group = 5 of 26 OR[4] (95% CI) = 1.33 (0.35 to 5.06) i.e. not statistically significant note: the authors note that the incidence of drug reactions is not related to the duration of chemotherapy because most of the adverse events were observed in the earlier period of drug therapy
Source of funding	No details given

Comments	Intervention does not exactly match the intervention of interest: the interventions did not differ by treatment duration alone – 18-month regimen contained PAS, the 6- and 9-month regimens contained rifampicin does not contain the 4 drugs of the standard recommended regimen – regimens contain streptomycin but lack ethambutol and pyrazinamide 18-month regimen contained PAS - not licensed in the UK; data for this arm was not extracted all patients had surgery Population does not exactly match the population of interest: some patients also had respiratory TB
[1] note: data for arm containing PAS (3SPH/15PH = 63) was not extracted [2] Calculated by the reviewer [3] 95% confidence intervals not provided by authors; calculated by reviewer [4] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence interval; H, isoniazid; MD, mean difference; OR, odds ratio; P or PAS, sodium p-aminosalicylate; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation	

BONE & JOINT TUBERCULOSIS

No papers found

PERICARDIAL TUBERCULOSIS

No papers found

LYMPH NODE TUBERCULOSIS

1.6.5 Al-Aska et al, 1992

Bibliographic	Al-Aska A, Al-Majed S, Al-Mofleh I et al (1992) Short-course chemotherapy for cervical lymph node tuberculosis. Saudi

<table>
<tr><td>reference</td><td>Medical Journal 13(2): 129-3</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Study quality</td><td>Intervention does not exactly match the intervention of interest:

the interventions did not differ by treatment duration alone: 9-month regimens have an additional drug (pyrazinamide) during the initial phase

does not contain the 4 drugs of the standard recommended regimen – 1 of the 9-month and 1 of the 12-month regimens contain streptomycin rather than ethambutol, and the 12-month regimens are lacking ethambutol

Method of randomisation, and allocation concealment and blinding were unclear

Groups were comparable at the baseline

Groups received the same care apart from the interventions studied

Groups were comparable for availability of outcome data and treatment completion

‘Favourable’ response to treatment not explicitly defined, but appears to be a substitute outcome</td></tr>
<tr><td>Number of patients</td><td>Randomised = 77

9-month group = 34

18-month group = 33</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion

Cervical tuberculous lymphadenitis microbiologically or histologically proven in lymph nodes obtained through aspiration or biopsy

Exclusion

Active pulmonary tuberculosis

Pregnancy

<table>
<tr><th></th><th>9-month</th><th>12-month</th></tr>
<tr><td>Male : female ratio</td><td>1.4:1</td><td>1.2:1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Age range (years)</td><td>17 – 51</td><td>13 – 47</td></tr>
<tr><td>Unilateral lymphadenitis</td><td>21/34</td><td>27/33</td></tr>
<tr><td>Bilateral lymphadenitis</td><td>13/34</td><td>6/33</td></tr>
<tr><td>Tuberculin positivity</td><td>30/34</td><td>26/33</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>9-month regimens[1]
2HRZS/7HR
2HRZE/7HR
Dosing:
isoniazid: 5-10 mg/kg of body weight/day
rifampicin: 10 mg/kg of body weight/day
pyrazinamide: 30 mg/kg of body weight/day
ethambutol: 20 mg/kg of body weight/day
streptomycin: 1 g/day
Patients were managed on an outpatient basis</td></tr>
<tr><td>Comparison</td><td>12-month regimens[2]
2HRS/10HR
2HRE/10HR
Dosing:
isoniazid: 5-10 mg/kg of body weight/day
rifampicin: 10 mg/kg of body weight/day</td></tr>
</table>

	ethambutol: 20 mg/kg of body weight/day streptomycin: 1 g/day Patients were managed on an outpatient basis
Length of follow up	Minimum of 36 months
Location	Saudi Arabia
Outcomes measures and effect size	**Response to treatment – favourable** Number to achieve a favourable outcome 9-month group = 30 of 34 18-month group = 32 of 33 OR[3] (95% CI) = 0.23 (0.02 to 2.22) i.e. not statistically significant
	Adverse events – hepatotoxicity Number to achieve experience hepatotoxicity 9-month group = 1 of 34 18-month group = 2 of 33 OR[3] (95% CI) = 0.47 (0.04 to 5.44) i.e. not statistically significant
Source of funding	No details provided
Comments	Intervention does not exactly match the intervention of interest: the interventions did not differ by treatment duration alone: 9-month regimens have an additional drug (pyrazinamide) during the initial phase

	does not contain the 4 drugs of the standard recommended regimen – 1 of the 9-month and 1 of the 12-month regimens contain streptomycin rather than ethambutol, and the 12-month regimens are lacking ethambutol

[1] Data for the two 9-month regimens not reported separately

[2] Data for the two 12-month regimens not reported separately

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

Abbreviations: E, ethambutol; H, isoniazid; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide

1.6.6 Campbell et al (British Thoracic Society Research Committee), 1985/1988

Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens lack pyrazinamide Method of randomisation, and use of allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for availability of outcome data, but it is unclear if they are comparable for treatment completion Did not follow the intent-to-treat principle, except for hepatotoxicity Response to treatment is a substitute outcome
Number of patients	n = 152 9-month group = 76 18-month group = 76 Analysed at 36 months = 113 9-month group = 56

<table>
<tr><td></td><td>18-month group = 57
Analysed at 5 years = 73
9-month group = 34
18-month group = 39</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Tuberculosis of the cervical, axillary or inguinal lymph nodes
Aged 15 to 80
Exclusion
Previous chemotherapy for tuberculosis
Active pulmonary tuberculosis
Pregnancy
Important impairment of visual, hepatic or renal function
Baseline characteristics
<table>
<tr><th></th><th colspan="2">9-month</th><th colspan="2">18-month</th></tr>
<tr><th></th><th>Number of patients</th><th>Mean age (years)</th><th>Number of patients</th><th>Mean age (years)</th></tr>
<tr><td>Asian</td><td></td><td></td><td></td><td></td></tr>
<tr><td>male</td><td>22</td><td>30</td><td>15</td><td>30</td></tr>
<tr><td>female</td><td>23</td><td>40</td><td>24</td><td>38</td></tr>
<tr><td>Non-Asian</td><td></td><td></td><td></td><td></td></tr>
<tr><td>male</td><td>2</td><td>65</td><td>5</td><td>41</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>female</td><td>9</td><td>47</td><td>13</td><td>42</td></tr>
<tr><td>Surgical removal of all affected nodes</td><td>18</td><td>35</td><td>14</td><td>48</td></tr>
<tr><td>Biopsy or needle aspiration of nodes for diagnostic purposes</td><td>30</td><td>37</td><td>32</td><td>37</td></tr>
<tr><td>Initial diagnosis had been clinically supported by a positive tuberculin skin test</td><td>8</td><td>32</td><td>11</td><td>30</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>9-month regimen
$2HRE_7/7HR_7$
Dosing:
isoniazid: 300 mg
rifampicin: 600 mg for patients weighing 50 kg or more, and 450 mg for patients weighing 50 kg or less
ethambutol: 15 or 25 mg/kg of body weight/day</td></tr>
<tr><td>Comparison</td><td>18-month regimen
$2HRE_7/16HR_7$
Dosing:
isoniazid: 300 mg
rifampicin: 600 mg for patients weighing 50 kg or more, and 450 mg for patients weighing 50 kg or less
ethambutol: 15 or 25 mg/kg of body weight/day</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Bibliographic</td><td>Campbell IA et al (1985) Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. British</td></tr>
</table>

reference	Thoracic Society Research Committee. BMJ 290: 1106-8
Length of follow up	36 months after treatment initiation
Outcomes measures and effect size	**Change in signs and symptoms – residual nodes** Number of patients with residual nodes at the end of treatment 9-month group = 7 of 56 18-month group = 3 of 57 OR[1] (95% CI) = 2.57 (0.63 to 10.50) i.e. not statistically significant Number of patients with residual nodes in the 36-month follow-up 9-month group = 2 of 56 18-month group = 3 of 57 OR[1] (95% CI) = 0.67 (0.11 to 4.15) i.e. not statistically significant
	Change in signs and symptoms – new nodes Number of patients with new nodes during treatment 9-month group = 5 of 56 18-month group = 8 of 57 OR[1] (95% CI) = 0.60 (0.18 to 1.96) i.e. not statistically significant Number of patients with new nodes in the 36-month follow-up 9-month group = 2 of 56

	18-month group = 0 of 57 OR[1] (95% CI) = 5.28 (0.25 to 112.39) i.e. not statistically significant
	Change in signs and symptoms – enlargement of nodes Defined as an increase in diameter of 10 mm or more Number of patients with nodes that increased in size during treatment 9-month group = 8 of 56 18-month group = 5 of 57 OR[1] (95% CI) = 1.73 (0.53 to 5.66) i.e. not statistically significant Number of patients with nodes that increased in size in the 36-month follow-up 9-month group = 6 of 56 18-month group = 4 of 57 OR[1] (95% CI) = 1.59 (0.42 to 5.97) i.e. not statistically significant
	Change in signs and symptoms – new sinuses Number of patients with sinus formation during treatment 9-month group = 0 of 56 18-month group = 3 of 57 OR[1] (95% CI) = 0.14 (0.01 to 2.73) i.e. not statistically significant

	Number of patients with sinus formation in the 36-month follow-up 9-month group = 0 of 56 18-month group = 0 of 57 OR[1] (95% CI) = 1.02 (0.02 to 52.18) i.e. not statistically significant
	Response to treatment – need for surgical intervention Number of patients needing surgical intervention (such as aspiration of pus) during treatment 9-month group = 4 of 56 18-month group = 6 of 57 OR[1] (95% CI) = 0.65 (0.17 to 2.45) i.e. not statistically significant Number of patients needing surgical intervention (such as aspiration of pus) in the 36-month follow-up 9-month group = 1 of 56 18-month group = 1 of 57 OR[1] (95% CI) = 1.02 (0.06 to 16.69) i.e. not statistically significant
	Adverse events - hepatotoxicity Number of patients to experience hepatotoxicity during treatment 9-month group = 0 of 76 18-month group = 1 of 76 OR[1] (95% CI) = 0.33 (0.01 to 8.20)

	i.e. not statistically significant
Bibliographic reference	Campbell IA et al (1988) Short course chemotherapy for tuberculosis of lymph nodes: final report at 5 years. British Thoracic Society Research Committee. British Journal of Diseases of the Chest 82: 282-4
Length of follow up	5 years
Outcomes measures and effect size	**Relapse** Number of patients to experience clinical or microbiological relapse 9-month group = 0 of 34 18-month group = 0 of 39 OR[1] (95% CI) = 1.14 (0.02 to 59.26) i.e. not statistically significant
Source of funding	Supported by grants from Ciba Geigy Pharmaceuticals and Merrel Dow Pharmaceuticals
Comments	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens lack pyrazinamide
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial	

1.6.7 Campbell et al (British Thoracic Society Research Committee), 1993

Bibliographic reference	Campbell IA et al (1993) Six months *vesrus* nine months chemotherapy for tuberculosis of the lymph nodes: final results. British Thoracic Society Research Committee. Respiratory medicine 87:621-3
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – 9-month regimens do not contain a 4th drug, 6-month regimen lack ethambutol Method of randomisation and blinding were unclear, though there appeared to be adequate allocation concealment

	It is unclear if the groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were comparable for availability of outcome data and treatment completion Did not follow the intent-to-treat principle
Number of patients	Randomised = 199 6-month group = 66 9-month groups = 133[1] Followed up to 30 months = 165 6-month group = 58 9-month groups = 107[2]
Patient characteristics	*Inclusion* Tuberculosis of the cervical, axillary or chest wall lymph nodes Aged 16 to 80 *Exclusion* Previous chemotherapy for tuberculosis Active pulmonary parenchymal tuberculosis (but not isolated mediastinal lymphadenopathy) Pregnancy Significant impairment of visual, hepatic or renal function
Intervention	*6-month regimen* $2HRZ_7/4HR_7$ Dosing:

	isoniazid: 300 mg rifampicin: 600 mg for patients weighing 50 kg or more, and 450 mg for patients weighing 50 kg or less pyrazinamide: 2.0 g for patients weighing 50 kg or more, and 1.5 g for patients weighing 50 kg or less Patients were not given corticosteroids Patients were otherwise managed according to their physician's normal practice
Comparison	*9-month regimens* $2HRE_7/7HR_7$ $2HRZ_7/7HR_7$ Dosing: isoniazid: 300 mg rifampicin: 600 mg for patients weighing 50 kg or more, and 450 mg for patients weighing 50 kg or less ethambutol: 15 mg/kg of body weight/day pyrazinamide: 2.0 g for patients weighing 50 kg or more, and 1.5 g for patients weighing 50 kg or less Patients were not given corticosteroids Patients were otherwise managed according to their physician's normal practice
Length of follow up	30 months after treatment initiation
Location	Details not given
Outcomes measures and effect size	**Change in signs and symptoms – residual nodes** Number of patients with residual nodes at 30 months 6-month group = 10 of 58 9-month groups[3] = 16 of 107

	OR[4] (95% CI) = 1.18 (0.50 to 2.81) i.e. not statistically significant
	Change in signs and symptoms – enlargement of nodes Number of patients with nodes that had increased in size by 30 months 6-month group = 4 of 58 9-month groups[3] = 8 of 107 OR[4] (95% CI) = 0.81 (0.24 to 2.77) i.e. not statistically significant
	Change in signs and symptoms – new glands Number of patients with glands formation by 30 months 6-month group = 2 of 58 9-month groups[3] = 7 of 107 OR[4] (95% CI) = 0.51 (0.10 to 2.54) i.e. not statistically significant
	Change in signs and symptoms – new sinuses Number of patients with sinus formation by 30 months 6-month group = 2 of 58 9-month groups[3] = 3 of 107 OR[4] (95% CI) = 1.24 (0.20 to 7.63) i.e. not statistically significant
	Relapse

	Number of patients to experience clinical relapse by 30 months 6-month group = 3 of 58 9-month groups[3] = 6 of 107 OR[4] (95% CI) = 0.92 (0.22 to 3.82) i.e. not statistically significant
Source of funding	Supported by a grant from Merrel Dow Pharmaceuticals
Comments	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – 9-month regimens do not contain a 4th drug, 6-month regimen lack ethambutol

[1] 2HRE/7HR = 63; 2HRZ/7HR = 70

[2] 2HRE/7HR = 49; 2HRZ/7HR = 58

[3] Pooled by reviewer

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

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

1.6.8 Yuen et al, 1997

Bibliographic reference	Yuen APW, Wong SHW, Tam CM et al (1997) Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. Otolaryngology Head and Neck Surgery 116: 189-92
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens lack ethambutol but contain streptomycin doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and pyrazinamide are above those recommended

	any abscesses were drained before treatment initiation Method of randomisation, and use of allocation concealment and blinding were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were followed up for the same length of time, and were comparable for availability of outcome data and treatment completion Did not follow the intent-to-treat principle for all outcomes Patients did not receive chemotherapy alone: abscesses were drained surgically before the commencement of treatment
Number of patients	Randomised = 113 6-month group = 49 9-month group = 64 Followed up after treatment completion = 91 6-month group = 43 9-month group = 48
Patient characteristics	*Inclusion* Tuberculous lymphadenopathy of the cervical region only *Exclusion* Patients in relapse of previously treated cervical tuberculous lymphadenopathy *Diagnostic criteria* Patients were assessed clinically with documentation of size and site of all lymph nodes All patients had fine-needle aspiration of the lymph nodes for cytology and culture for *M. tuberculosis*

Mantoux test

Chest x-ray

Excision biopsy of the most easily accessible lymph node compatible with tuberculosis lymphadenopathy was performed when necessary to confirm diagnosis and to obtain tissue for mycobacterial culture and drug sensitivity tests; no attempt was made to excise all of the involved lymph nodes

Baseline characteristics

	6-month	***9-month***	*Statistical significance*
Female : male ratio	*1.4*	*1.7*	*p = 0.67*[1]
Mean age (years) ± SD	*32±14*	*28±10*	*p = 0.08*[2]
Neck lymph node			
left side	*14*	*7*	*p = 0.125*[1]
right side	*20*	*29*	
bilateral	*9*	*12*	
Mean number of lymph nodes ± SD	*3±2.4*	*3±2.5*	*p = 0.995*[2]
Largest node size (mm) ± SD	*19±14*	*23±15*	*p = 0.181*[2]
Abscess	*4/43 (9%)*	*1/48 (2%)*	*p = 0.185*[3]
Discharging sinus	*2/43 (5%)*	*1/48 (2%)*	*p = 0.600*[3]

Intervention

6-month regimen

$4SHRZ_3/2HR_3$ + surgery

	Dosing: isoniazid: 15 mg/kg of body weight/day rifampicin: 600 mg/day pyrazinamide: 2.5 g for patients weighing 50 kg or more, and 2.0 g for patients weighing 50 kg or less streptomycin: 1 g/day Treatment was fully supervised in the chest outpatient clinic Abscesses were drained surgically before the commencement of treatment
Comparison	*9-month regimen* $4SHRZ_3/5HR_3$ + surgery Dosing: isoniazid: 15 mg/kg of body weight/day rifampicin: 600 mg/day pyrazinamide: 2.5 g for patients weighing 50 kg or more, and 2.0 g for patients weighing 50 kg or less streptomycin: 1 g/day Treatment was fully supervised in the chest outpatient clinic Abscesses were drained surgically before the commencement of treatment
Length of follow up	Median follow-up of 21 months, longest follow-up of 66 months
Location	Hong Kong
Outcomes measures and effect size	**Treatment success** Defined as the no residual lymph nodes at treatment completion, or residual lymph nodes decreasing in size or smaller than 0.5 cm diameter that require no further treatment (suspicious lymph nodes were reassessed by needle aspiration for cytology or excision biopsy for histology)

	Number of patients to experience relapse during follow-up 6-month group = 39 of 43 9-month group = 47 of 48 OR[4] (95% CI) = 0.21 (0.02 to 1.93) i.e. not statistically significant
	Treatment failure Defined as a persistent residual lymph node at the end of treatment confirmed to be persistent tuberculous lymphadenopathy by fine-needle aspiration cytology or excision biopsy Number of patients to experience relapse during follow-up 6-month group = 2 of 43 9-month group = 1 of 48 OR[4] (95% CI) = 2.29 (0.20 to 26.22) i.e. not statistically significant
	Relapse Defined as the recurrence of a residual lymph node or appearance of a new node confirmed to be tuberculous lymphadenopathy after a period of initial clinical remission Number of patients to have experienced relapse by 5 years of follow-up[5] 6-month group (n = 41) = 11% 9-month group (n = 48) = 10% OR[4] (95% CI) = 1.11 (0.45 to 2.75) i.e. not statistically significant
	Adverse events – requiring modification of treatment

	Number of patients to experience drug reactions requiring modification of treatment 6-month group = 4 of 49 9-month group = 13 of 64 OR[4] (95% CI) = 0.35 (0.11 to 1.15) i.e. not statistically significant note: drug reactions included drug-induced hepatitis, gastrointestinal upset, skin rash, tinnitus and thrombocytopenia
	Adherence – treatment default Number of patients to default treatment 6-month group = 2 of 49 9-month group = 3 of 64 OR[4] (95% CI) = 0.87 (0.14 to 5.39) i.e. not statistically significant
Source of funding	Supported by a research grant from the University of Hong Kong
Comments	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens lack ethambutol but contain streptomycin doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and pyrazinamide are above those recommended any abscesses were drained before treatment initiation

[1] Chi-square test

[2] *t*-test

[3] Fisher's exact test

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

[5] Authors provided the 'actuarial remission rate' at 5 years (6-month group = 89%; 9-month group = 10%); converted to relapse rate at 5 years by reviewer (relapse rate (%) = 100 - actuarial remission rate (%))

Abbreviations: H, isoniazid; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; Z, pyrazinamide

GASTROINTESTINAL TUBERCULOSIS

1.6.9 Kim et al, 2003

Bibliographic reference	Kim SG, Kim JS, Jung HC et al (2003) Is a 9-month treatment sufficient in tuberculosis enterocolitis? A prospective, randomised, single-centre study. Alimentary Pharmacology & Therapeutics 18: 85-91
Study type	RCT
Study quality	Population does not exactly match the population of interest: some patients also had respiratory TB Intervention does not exactly match the intervention of interest: 4 drugs used throughout, therefore more intensive the standard recommended regimen doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the dose of isoniazid above that which is recommended Appropriate method of randomisation: computer-generated Investigators were blinded, but the use of allocation concealment and blinding of participants and individuals administering care were unclear Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were not followed up for the same length of time Groups were comparable for availability of outcome data and treatment completion

<table>
<tr><td></td><td>‘Complete response’ to treatment is a composite outcome that includes both cure and change in signs and symptoms; it is a substitute outcome</td></tr>
<tr><td>Number of patients</td><td>n = 40
9-month group = 22
15-month group = 18</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Intestinal tuberculosis
Exclusion
Presence of concurrent disease which could complicate evaluation and follow-up in the study, such as known hepatic, renal, endocrine and gastrointestinal diseases, suspected or confirmed malignancies, human immunodeficiency virus infection, concurrent immunosuppressive treatment, alcoholism or drug abuse
Diagnostic criteria
At least one of the following criteria:
demonstration of acid-fast bacilli, either by stain or culture of a histological specimen
confirmation of caseating granuloma on a histological specimen
clinical, radiological and endoscopic abnormalities strongly suggestive of intestinal tuberculosis and a response to antituberculosis chemotherapy
Baseline characteristics
<table>
<tr><th></th><th>9-month</th><th>15-month</th><th>p-value</th></tr>
<tr><td>Male : female ratio</td><td>11:11</td><td>5:13</td><td>0.15</td></tr>
<tr><td>Mean age (years) ± SD</td><td>40±16</td><td>38±17</td><td>0.93</td></tr>
<tr><td>Symptom presentation
abdominal pain</td><td>21/22</td><td>14/18</td><td>0.16</td></tr>
</table></td></tr>
</table>

		weight loss	*13/22*	*12/18*	*0.62*
		diarrhea	*7/22*	*8/18*	*0.41*
		Pulmonary tuberculosis	*5/22*	*7/18*	*0.27*
Intervention	*9-month regimen* 9HREZ Dosing: isoniazid: 400 mg/day rifampicin: 450 mg/day ethambutol: 800 mg/day pyrazinamide: 500 mg 3 times daily				
Comparison	*15-month regimen* 15HREZ Dosing: isoniazid: 400 mg/day rifampicin: 450 mg/day ethambutol: 800 mg/day pyrazinamide: 500 mg 3 times daily				
Length of follow up	Mean (months) ± SD 9-month group = 23±12 15-month group = 34±19				

	MD[1] (95% CI) = -11 (-21.1 to -0.9) i.e. statistically significant
Location	South Korea
Outcomes measures and effect size	**Response to treatment – complete response** Defined as: resolution of abdominal symptoms; and endoscopic documentation of complete healing of active ulcerative or hypertrophic mucosa; and disappearance of acid-fast bacilli or caseating granuloma on histological examination Number to achieve complete response during follow-up period 9-month group = 22 of 22 15-month group = 18 of 18 OR[2] (95% CI) = 1.22 (0.02 to 64.31) i.e. not statistically significant Mean interval (months ± SD) to complete response 9-month group (n = 22) = 3.9±2.5 15-month group (n = 18) = 4.8±2.9 MD[1] (95% CI) = -0.9 (-2.6 to 0.80) i.e. not statistically significant
	Relapse Defined as the recurrence of the abdominal symptoms present at entry, and/or endoscopic documentation of active intestinal tuberculosis

	Number to experience recurrence during follow-up period 9-month group = 0 of 22 15-month group = 0 of 18 OR[2] (95% CI) = 0.82 (0.02 to 43.48) i.e. not statistically significant
Source of funding	Details not provided
Comments	Population does not exactly match the population of interest: some patients also had respiratory TB Intervention does not exactly match the intervention of interest: 4 drugs used throughout, therefore more intensive the standard recommended regimen doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the dose of isoniazid above that which is recommended

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

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

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

1.6.10 Park et al, 2009

Bibliographic reference	Park SH, Yang S-K, Yang D-H et al (2009) Prospective randomised trial of six-month versus nine-month therapy for intestinal tuberculosis. Antimicrobial Agents and Chemotherapy 53(10): 4167-71
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: continuation phase contains 3 drugs and is therefore more intensive than the 2-drug continuation phase of the

	standard recommended regimen doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and ethambutol are above those recommended, and the dose of pyrazinamide is below that which is recommended Appropriate method of randomisation: computer-generated Use of allocation concealment is unclear Open (unblinded) trial Groups were comparable at the baseline Groups received the same care apart from the interventions studied Groups were followed up for the same length of time, and were comparable for availability of outcome data and treatment completion Response to treatment is a substitute for outcome
Number of patients	n = 90 6-month group = 45 9-month group = 45
Patient characteristics	*Inclusion* Intestinal tuberculosis *Exclusion* Patients aged under 18 years or over 75 years Extrapulmonary TB other than intestinal TB Histories of antituberculosis chemotherapy within the past 5 years Immunosuppressive disorders, or chronic liver disease Pregnancy

Patients in whom poor compliance was anticipated

Diagnostic criteria

At least one of the following criteria:

demonstration of caseating granuloma upon endoscopic biopsy

identification of acid-fast bacilli in a histological specimen

positive culture of *M.* tuberculosis from a biopsy specimen

typical colonoscopic findings strongly suggestive of intestinal tuberculosis associated with active pulmonary tuberculosis, regardless of the presence of acid-fast bacilli in the sputum smear or culture

Baseline characteristics

	6-month	***9-month***	*p-value*
Male : female ratio	*18:27*	*22:23*	*0.53*
Median age (years) (range)	*36 (18 – 71)*	*42 (20 – 71)*	*0.12*
Symptom presentation			
abdominal pain	*37/45*	*35/45*	*0.79*
weight loss	*24/45*	*31/45*	*0.19*
fever	*6/45*	*10/45*	*0.41*
diarrhea	*22/45*	*18/45*	*0.53*
Laboratory findings			
anemia	*21/45*	*28/45*	*0.20*
leukocytosis	*4/45*	*5/45*	*1.00*
thrombocytosis	*15/45*	*21/45*	*0.28*

		elevated erythrocyte sedimentation rate	*26/45*	*31/45*	*0.38*	
		elevated C-reactive protein	*23/45*	*29/45*	*0.29*	
		hypalbuminemia	*15/45*	*25/45*	*0.06*	
		Location of lesions				
		ileocecal area	*38/45*	*41/45*	*0.52*	
		ascending colon	*25/45*	*28/45*	*0.67*	
		transverse colon	*10/45*	*15/45*	*0.35*	
		descending colon	*4/45*	*5/45*	*1.00*	
		sigmoid colon	*2/45*	*6/45*	*0.27*	
		rectum	*3/45*	*4/45*	*1.00*	
		Stricture	*8/45*	*10/45*	*0.79*	
Intervention	*6-month regimen* 2HREZ/4HRE Dosing: isoniazid: 300 mg/day for patients <50 kg in body weight, and 400 mg/day for patients >50 kg in body weight rifampicin: 450 mg/day for patients <50 kg in body weight, and 600 mg/day for patients >50 kg in body weight ethambutol: 1000 mg/day for patients <50 kg in body weight, and 1200 mg/day for patients >50 kg in body weight for the first 2 months, and 800 mg/day thereafter for all patients pyrazinamide: 1250 mg/day for patients <50 kg in body weight, and 1500 mg/day for patients >50 kg in body weight No corticosteroids were given to any patient, and surgery was reserved primarily for complications such as intestinal					

	obstruction, perforation and fistula
Comparison	*9-month regimen* 2HREZ/7HRE Dosing: isoniazid: 300 mg/day for patients <50 kg in body weight, and 400 mg/day for patients >50 kg in body weight rifampicin: 450 mg/day for patients <50 kg in body weight, and 600 mg/day for patients >50 kg in body weight ethambutol: 1000 mg/day for patients <50 kg in body weight, and 1200 mg/day for patients >50 kg in body weight for the first 2 months, and 800 mg/day thereafter for all patients pyrazinamide: 1250 mg/day for patients <50 kg in body weight, and 1500 mg/day for patients >50 kg in body weight No corticosteroids were given to any patient, and surgery was reserved primarily for complications such as intestinal obstruction, perforation and fistula
Length of follow up	1 year after treatment completion
Location	South Korea
Outcomes measures and effect size	**Response to treatment – complete response** Defined as endoscopically demonstrated healing of active lesions at the end of treatment Number to achieve complete response during follow-up period 6-month group = 42 of 45 9-month group = 41 of 45 OR[1] (95% CI) = 1.37 (0.29 to 6.48) i.e. not statistically significant
	Response to treatment – need for additional treatment Number to require additional chemotherapy due to incomplete response

	6-month group = 1 of 45 9-month group = 0 of 45 OR[1] (95% CI) = 3.07 (0.12 to 77.33) i.e. not statistically significant Number to require surgery due to complications such as intestinal obstruction, perforation and fistula 6-month group = 0 of 45 9-month group = 0 of 45 OR[1] (95% CI) = 1.00 (0.02 to 51.49) i.e. not statistically significant
	Relapse Defined as endoscopic documentation of recurrent lesions after complete response had been achieved Number to experience recurrence during follow-up period 6-month group = 1 of 45 9-month group = 0 of 45 OR[1] (95% CI) = 3.07 (0.12 to 77.33) i.e. not statistically significant
	Adverse events – treatment discontinuation Number to experience drug toxicity or intolerance leading to treatment discontinuation 6-month group = 2 of 45 9-month group = 4 of 45 OR[1] (95% CI) = 0.48 (0.08 to 2.74)

	i.e. not statistically significant
Source of funding	No details provided
Comments	Intervention does not exactly match the intervention of interest: continuation phase contains 3 drugs and is therefore more intensive than the 2-drug continuation phase of the standard recommended regimen doses used are not consistent with those recommended for use in UK practice by the British National Formulary: the doses of isoniazid and ethambutol are above those recommended, and the dose of pyrazinamide is below that which is recommended

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

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

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

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