

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

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## 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

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>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</p> <p>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)</p> <p>initial 3-drug phase was shorter in the daily + intermittent group (2 weeks) than in the daily group (1 month)</p> <p>The interventions do not use the 4 standard recommended drugs: the regimens contain streptomycin but are lacking ethambutol and pyrazinamide</p> <p>Randomisation, allocation concealment and blinding were unclear</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were followed up for an equal length of time</p> <p>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</p>

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

	<p>parenchymal or mediastinal lymph nodes in chest roentgenograms</p> <p>Immunologic</p> <p>tuberculin test positivity (PPD)</p> <p>Histobacteriologic</p> <p>acid-fast bacilli in the sputum, or gastric washings or in any histologic specimen</p> <p>Exclusion</p> <p>Poor “family compliance”</p> <p>Baseline</p> <table border="1"> <thead> <tr> <th></th> <th>Daily + intermittent (n = 18)</th> <th>Intermittent (n = 15)</th> </tr> </thead> <tbody> <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</td> <td></td> <td></td> </tr> <tr> <td>  clinical</td> <td>18</td> <td>15</td> </tr> <tr> <td>  epidemiologic</td> <td>14</td> <td>12</td> </tr> <tr> <td>  immunologic</td> <td>15</td> <td>12</td> </tr> <tr> <td>  radiologic</td> <td>18</td> <td>15</td> </tr> <tr> <td>  histobacteriologic</td> <td>2</td> <td>2</td> </tr> </tbody> </table>		Daily + intermittent (n = 18)	Intermittent (n = 15)	Male/female	12/6	10/5	Age (mean years ± SD)	7.6±3.9	7.7±4.0	Diagnostic criteria			clinical	18	15	epidemiologic	14	12	immunologic	15	12	radiologic	18	15	histobacteriologic	2	2
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radiologic	18	15																										
histobacteriologic	2	2																										
<b>Intervention</b>	<p>Daily regimen</p> <p>1SRH<sub>7</sub>/8RH<sub>7</sub>/3R<sub>7</sub></p>																											

	<p>daily streptomycin, isoniazid and rifampicin 1 month</p> <p>daily isoniazid and rifampicin for 8 months</p> <p>daily rifampicin for 3 months</p> <p>Dosing:</p> <p>streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g</p> <p>isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg</p> <p>rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg</p> <p>All patients were treated on an outpatient basis</p>
<b>Comparison</b>	<p>Daily + intermittent regimen</p> <p>0.5SRH<sub>7</sub>/8.5RH<sub>2</sub></p> <p>daily streptomycin, isoniazid and rifampicin for two weeks</p> <p>twice weekly isoniazid and rifampicin for 8.5 months</p> <p>Dosing:</p> <p>streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g</p> <p>isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg</p> <p>rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg</p> <p>All patients were treated on an outpatient basis</p>
<b>Length of follow up</b>	12 months after treatment completion
<b>Location</b>	Izmir, Turkey
<b>Outcomes measures and effect</b>	<p><b>Response to treatment – disease resolution</b></p> <p>Number to completely resolve (i.e. no radiologic remainder):</p>

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



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

	<p>p1 &gt; 0.05</p> <p>OR2 (95% CI) = 8.35 (0.40 to 174.51)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Details not given
<b>Comments</b>	<p>The interventions did not differ in the two groups by dosing frequency alone:</p> <p>different treatment periods – daily + intermittent group received treatment for a total of 9 months; daily group received treatment for a total of 12 months</p> <p>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)</p> <p>initial 3-drug phase was shorter in the daily + intermittent group (2 weeks) than in the daily group (1 month)</p> <p>The interventions do not use the 4 standard recommended drugs: the regimens contain streptomycin but are lacking ethambutol and pyrazinamide</p> <p>Because the interventions vary by treatment duration in addition to dosing frequency, this study is also considered for possible inclusion in review question M</p>
<p>1 Calculated by authors using the chi-square test or student’s t-test; p &lt; 0.05 was taken as significant</p> <p>2 Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>3 Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>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</p>	

### 1.1.2 Kumar et al, 1990

<b>Bibliographic reference</b>	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
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<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest: do not use the 4 standard recommended drugs: the regimens are lacking ethambutol</p> <p>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</p> <p>Allocation concealment and blinding is unclear</p> <p>By the limited characteristics reported (sex and outcomes of diagnostic tests), the groups were comparable at baseline</p> <p>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</p> <p>Groups were comparable with regards to treatment completion and availability of outcome data</p> <p>Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure)</p>
<b>Number of patients</b>	<p>n = 76</p> <p>intermittent regimen = 37</p> <p>daily + intermittent regimen = 39</p> <p>By site</p> <p>Tuberculous lymphadenopathy = 27</p> <p>intermittent regimen = 15</p> <p>daily + intermittent regimen = 12 – note: one case was subsequently shown to be M. Avium intracellulare complex and excluded (i.e. n = 11)</p> <p>Pulmonary tuberculosis = 43</p> <p>intermittent regimen = 20</p>

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

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

	<table border="1"> <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>	Positive chest roentgenogram	24	28	Smear from sputum, or gastric lavage or any discharge	15	12	Positive culture	4	3	Compatible histopathology	14	15
Positive chest roentgenogram	24	28											
Smear from sputum, or gastric lavage or any discharge	15	12											
Positive culture	4	3											
Compatible histopathology	14	15											
<b>Intervention</b>	<p>Intermittent regimen</p> <p>2HRZ<sub>2</sub>/4HR<sub>2</sub>:</p> <p>twice weekly isoniazid, rifampicin and pyrazinamide for two months</p> <p>twice weekly isoniazid and rifampicin for 4 months</p> <p>total doses = 52</p> <p>Dosing:</p> <p>isoniazid: 20 to 30 mg/kg body weight/dose</p> <p>rifampicin: 10 to 15 mg/kg body weight/dose</p> <p>pyrazinamide: 50 to 60 mg/kg body weight/dose</p> <p>Doses taken in the clinic</p>												
<b>Comparison</b>	<p>Daily + intermittent regimen</p> <p>2HRZ<sub>7</sub>/4HR<sub>2</sub>:</p> <p>daily isoniazid, rifampicin and pyrazinamide for two months</p> <p>twice weekly isoniazid and rifampicin for 4 months</p> <p>total doses = 94</p>												

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

<b>measures and effect size</b>	Cross-site <sup>1</sup>
	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	
<b>Response to treatment</b>	



	<p>Criteria for grading response to treatment</p> <p>General improvement</p> <p>normalisation of body temperature</p> <p>improvement in appetite</p> <p>weight gain</p> <p>Tuberculous lymphadenopathy</p> <p>‘Marked’</p> <p>Reduction in lymph node size within 3 to 4 months and no appearance of new lymph node enlargement, plus improvement in general condition</p> <p>‘Moderate’</p> <p>Reduction in lymph node size later than 3 to 4 months and no appearance of new lymph node enlargement, plus improvement in general condition</p> <p>‘Poor’</p> <p>Increase in lymph node size or sinus formation and appearance of new lymph node enlargement, not responding to therapy</p> <p>Pulmonary tuberculosis</p> <p>‘Marked’</p> <p>General improvement, disappearance of cough, radiologic clearance of pulmonary lesions within 3 months of therapy and no appearance of new lesions</p> <p>‘Moderate’</p> <p>General improvement, partial radiologic clearance of pulmonary lesions within 3 months of therapy and no appearance of new lesions</p> <p>‘Poor’</p>
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	<p>No significant general improvement and no radiologic clearance, or increase in size of pulmonary lesions or appearance of new lesions</p> <p>Disseminated tuberculosis</p> <p>‘Marked’</p> <p>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</p> <p>‘Moderate’</p> <p>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</p> <p>‘Poor’</p> <p>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</p> <p><i>Results</i></p> <p>Cross-site<sup>1</sup></p> <p>Marked:</p> <p>intermittent regimen = 25 of 37</p> <p>daily + intermittent regimen = 28 of 39</p> <p>OR2 (95% CI) = 0.82 (0.31 to 2.18)</p> <p>i.e. not statistically significant</p> <p>Moderate:</p> <p>intermittent regimen = 11 of 37</p> <p>daily + intermittent regimen = 3 of 39</p> <p><b>OR2 (95% CI) = 5.08 (1.29 to 20.03)</b></p>
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	<p><b>i.e. statistically significant</b></p> <p>Poor:</p> <p>intermittent regimen = 1 of 37</p> <p>daily + intermittent regimen = 1 of 39</p> <p>OR2 (95% CI) = 1.06 (0.06 to 17.52)</p> <p>i.e. not statistically significant</p> <p>Tuberculous lymphadenopathy</p> <p>Marked:</p> <p>intermittent regimen = 10 of 15</p> <p>daily + intermittent regimen = 8 of 12</p> <p>OR2 (95% CI) = 1.00 (0.20 to 5.00)</p> <p>i.e. not statistically significant</p> <p>Moderate:</p> <p>intermittent regimen = 5 of 15</p> <p>daily + intermittent regimen = 3 of 12</p> <p>OR2 (95% CI) = 1.50 (0.28 to 8.14)</p> <p>i.e. not statistically significant</p> <p>Poor:</p> <p>intermittent regimen = 0 of 15</p> <p>daily + intermittent regimen = 1 of 12</p> <p>note: this patient was later found to have <i>M. Avium intracellulare</i> complex</p>
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	<p>OR2 (95% CI) = 0.25 (0.01 to 6.64)  i.e. not statistically significant</p> <p>Pulmonary tuberculosis</p> <p>note: 4 dropouts and 1 death in intermittent group, and 6 dropouts and 1 death in daily + intermittent group</p> <p>Marked:</p> <p>intermittent regimen = 13 of 20  daily + intermittent regimen = 16 of 23</p> <p>OR2,3 (95% CI) = 0.81 (0.23 to 2.92)  i.e. not statistically significant</p> <p>Moderate:</p> <p>intermittent regimen = 1 of 20  daily + intermittent regimen = 0 of 23</p> <p>OR2,3 (95% CI) = 3.62 (0.14 to 93.85)  i.e. not statistically significant</p> <p>Poor:</p> <p>intermittent regimen = 1 of 20  daily + intermittent regimen = 0 of 23</p> <p>OR2,3 (95% CI) = 3.62 (0.14 to 93.85)  i.e. not statistically significant</p> <p>Disseminated tuberculosis</p> <p>Marked:</p>
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	<p>intermittent regimen = 2 of 2</p> <p>daily + intermittent regimen = 4 of 4</p> <p>OR2 (95% CI) = 0.56 (0.01 to 37.57)</p> <p>i.e. not statistically significant</p> <p>Moderate:</p> <p>intermittent regimen = 0 of 2</p> <p>daily + intermittent regimen = 0 of 4</p> <p>OR2 (95% CI) = 1.80 (0.03 to 121.71)</p> <p>i.e. not statistically significant</p> <p>Poor:</p> <p>intermittent regimen = 0 of 2</p> <p>daily + intermittent regimen = 0 of 4</p> <p>OR2 (95% CI) = 1.80 (0.03 to 121.71)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>Cross-site1</p> <p>Intermittent regimen = 0 of 35</p> <p>Daily + intermittent regimen = 0 of 35</p> <p>OR2 (95% CI) = 1.00 (0.02 to 51.81)</p> <p>i.e. not statistically significant</p> <p>Tuberculous lymphadenopathy</p>

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

	OR2 (95% CI) = 1.05 (0.02 to 54.45) i.e. not statistically significant
	<b>Adverse effects – hematologic effects</b> 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
<b>Source of funding</b>	Indian Council of Medical Research
<b>Comments</b>	Intervention does not exactly match the intervention of interest: do not use the 4 standard recommended drugs: the regimens are lacking ethambutol
<p>1 Data for each site pooled by reviewer</p> <p>2 Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>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)</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide</p>	

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

<b>Study type</b>	RCT
<b>Study quality</b>	<p>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</p> <p>different frameworks – daily group received 2 drugs on a daily basis throughout; intermittent group regimen was</p>

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



	<p>No more than 2 weeks of previous anti-tuberculosis treatment</p> <p>No evidence of renal or hepatic disease</p> <p>Patients with associated lymphadenitis and minimal pleural effusion not warranting a pleural tap were also considered eligible</p> <p>Diagnostic criteria</p> <p>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</p> <p>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</p> <p>Most probably TB (category A):</p> <p>patients with a primary focus plus hilar adenitis, mediastinal adenitis, miliary tuberculosis and progressive primary complex</p> <p>these patients were started on anti-tuberculosis drugs</p> <p>Probably TB (category B):</p> <p>patients with a doubtful radiological abnormality</p> <p>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.</p> <p>Treatment groups were stratified according to category of disease</p> <p>Exclusion</p> <p>Massive pleural effusion</p> <p>Extrapulmonary tuberculosis other than pleural</p> <p>Isolated bronchiectasis</p> <p>Baseline</p>
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		Daily	Intermittent
		(n = 68)	(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
<b>Intervention</b>	Daily regimen 9HR <sub>7</sub> 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
<b>Comparison</b>	<p>Intermittent regimen</p> <p>2HRZ<sub>3</sub>/4HR<sub>2</sub></p> <p>3 times weekly isoniazid, rifampicin and pyrazinamide for 2 months</p> <p>twice weekly isoniazid and rifampicin for 4 months</p> <p>Dosing:</p> <p>isoniazid: 15 mg/kg body weight/dose, up to 300 mg</p> <p>rifampicin: 12 mg/kg body weight/dose, up to 300 mg</p> <p>pyrazinamide: 45 mg/kg body weight/dose, up to 1 g</p> <p>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</p>
<b>Location</b>	Chennai, India
<b>Source of funding</b>	Details not given
<b>Bibliographic reference</b>	Ramachandran P, Kripasankar AS & Duraipandian M (1998) Short course chemotherapy for pulmonary tuberculosis in children. Indian Journal of Tuberculosis 45: 83-7
<b>Length of follow up</b>	24 months after treatment completion
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths during treatment:</p> <p>daily group = 1 of 68</p> <p>intermittent group = 2 of 69</p>

	<p>OR1 (95% CI) = 0.50 (0.04 to 5.65) i.e. not statistically significant</p>
	<p><b>Response to treatment – disease resolution</b></p> <p>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</p>
	<p><b>Adverse events – hepatotoxicity</b></p> <p>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</p>
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	<p>60 months</p> <p>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)</p>

<p><b>Outcomes measures and effect size</b></p>	<p><b>Response to treatment – disease resolution</b></p> <p>% with normal chest radiograph at treatment completion:</p> <p>daily group (n = 67) = 61%</p> <p>intermittent group (n = 67) = 48%</p> <p>OR1 (95% CI) = 1.69 (0.97 to 2.97)</p> <p>i.e. not statistically significant</p> <p>% with normal chest radiograph at 60 months:</p> <p>daily group (n = 67) = 82%</p> <p>intermittent group (n = 66) = 89.5%</p> <p>OR1 (95% CI) = 0.54 (0.20 to 1.48)</p> <p>i.e. not statistically significant</p> <p>% with residual lesions at treatment completion:</p> <p>daily group (n = 67) = 39%</p> <p>intermittent group (n = 67) = 49%</p> <p>OR1 (95% CI) = 0.67 (0.38 to 1.17)</p> <p>i.e. not statistically significant</p> <p>% with residual lesions at 60 months:</p> <p>daily group (n = 67) = 15%</p> <p>intermittent group (n = 66) = 1.5%</p> <p>p &lt; 0.01</p> <p><b>OR<sup>1</sup> (95% CI) = 11.40 (1.42 to 91.85)</b></p>
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	<p><b>i.e. statistically significant</b></p> <p><b>Relapse</b></p> <p>Number of patients in whom relapse was observed during the 60-month follow-up period:</p> <p>daily group = 1 of 67</p> <p>intermittent group = 0 of 66</p> <p>OR<sup>1</sup> (95% CI) = 3.00 (0.12 to 74.98)</p> <p><b>i.e. not statistically significant</b></p>
<b>Comments</b>	<p>The interventions did not differ in the two groups by dosing frequency alone:</p> <p>different treatment periods – daily group received treatment for a total of 9 months; intermittent group received treatment for a total of 6 months</p> <p>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)</p> <p>The interventions do not use the 4 standard recommended drugs: the regimens both lack ethambutol, and daily regimen also lacks pyrazinamide</p> <p>Because the interventions vary by treatment duration in addition to dosing frequency, this study is also considered for possible inclusion in review question M</p>
	<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>2</sup> Calculated by authors using the chi-square test; p &lt; 0.01 was taken as significant</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide</p>

#### 1.1.4 Te Water Naude et al, 2000

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

<p><b>Study quality</b></p>	<p>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</p> <p>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</p> <p>do not use the 4 standard recommended drugs: the regimens are lacking ethambutol</p> <p>Randomisation:  random number tables</p> <p>by household unit (to avoid confusion in the event of more than one child from a particular household being enrolled)</p> <p>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</p> <p>Allocation concealment unclear</p> <p>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</p> <p>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</p> <p>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.</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were followed up for an equal length of time, treatment completion was comparable and outcome data was similarly available</p> <p>Response to treatment is a substitute for an outcome of interest (cure, treatment success and treatment failure)</p> <p>Did not follow the intent-to-treat principle</p>
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<p><b>Number of patients</b></p>	<p>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</p>
<p><b>Patient characteristics</b></p>	<p>Inclusion                      Ages &lt; 14 years                      Referral to clinic for TB screening                      Exclusion                      Extrathoracic TB                      Previous treatment for TB                      &gt; 30 days hospital treatment before referral for clinic management                      Home address in a rural area  <i>Diagnostic criteria</i>                      Suspect cases:                      suspicious chest radiograph – perihilar opacification with or without parenchymal lesions, and                      suggestive clinical features – cough for &gt; 2 weeks, wheeze for &gt; 2 weeks or weight under 80th centile</p>



	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 $\geq 15$ 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			
	<i>Baseline</i>			
		<b>Intermittent</b> (n = 95)	<b>Daily</b> (n = 118)	<b>p1</b>
	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	
<b>Weight for age (median % (interquartile range))</b>	<b>89.6 (82.4 – 100.7)</b>	<b>96.6 (86.1 – 104.0)</b>	<b>0.015</b>	
Height (cm) (n = 187)	83.6 (74.0 – 95.0)	86.0 (76.0 – 94.5)	0.37	

	Height for age (median % (interquartile range))	95.0 (92.6 – 99.3)	96.2 (93.2 – 100.8)	0.09
	<b>Household contacts with pulmonary TB (n = 205)</b>	<b>78</b>	<b>74</b>	<b>0.003</b>
	Smear-positive	44	41	0.12
	<b>Culture-positive</b>	<b>38</b>	<b>66</b>	<b>0.03</b>
<b>Intervention</b>	<p>Daily regimen</p> <p>6HRZ<sub>5</sub> (Monday to Friday):</p> <p>daily isoniazid, rifampicin and pyrazinamide for six months (Monday to Friday only)</p> <p>Dosing:</p> <p>isoniazid: 10 mg/kg body weight/dose</p> <p>rifampicin: 10 mg/kg body weight/dose</p> <p>pyrazinamide: 25 mg/kg body weight/dose</p> <p>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</p>			
<b>Comparison</b>	<p>Intermittent regimen</p> <p>2HRZ<sub>2</sub>/4HR<sub>2</sub>:</p> <p>twice weekly isoniazid, rifampicin and pyrazinamide for two months</p> <p>twice weekly isoniazid and rifampicin for 4 months</p> <p>Dosing:</p> <p>isoniazid: 15 mg/kg body weight/dose</p> <p>rifampicin: 15 mg/kg body weight/dose</p>			

	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				
<b>Length of follow up</b>	30 months after the initiation of treatment				
<b>Location</b>	Local authority clinic, Western Cape Province of South Africa				
<b>Outcomes measures and effect size</b>	<b>Response to treatment</b>				
	Composite measure, assessed as follows:				
	<b>Criterion</b>	<b>-1</b>	<b>0</b>	<b>+1</b>	<b>+2</b>
	<b>Parent's assessment</b>	Worse	Not better	Better	Much better
	<b>Clinical symptoms</b>	Worse	Unchanged	Better	Much better
	<b>Weight gain</b>	Lost weight	Unchanged	Gained weight (ipsi-centile)	Significant gain (crossing centiles)
	<b>Chest radiograph</b>	Worse	Unchanged	Some clearing	Definite clearing
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 medians <sup>2</sup> = 0 Median scores (interquartile range) 6 months after treatment initiation i.e. end of treatment period:					

	<p>daily group (n = 93) = 6 (5 – 7)</p> <p>intermittent group (n = 70) = 6 (5 – 7)</p> <p>p1 = 0.90</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = 0</p> <p>Median scores (interquartile range) 12 months after treatment initiation i.e. 6 months after treatment end:</p> <p>daily group (n = 74) = 5 (4 – 6)</p> <p>intermittent group (n = 65) = 4 (3 – 5)</p> <p>p1 = 0.068</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = 1</p> <p>Median scores (interquartile range) 18-30 months after treatment initiation i.e. 12-24 months after treatment end:</p> <p>daily group (n = 74) = 4 (3 – 5)</p> <p>intermittent group (n = 71) = 4 (3 – 5)</p> <p>p1 = 0.949</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = 0</p>
	<p><b>Symptom improvement – weight gain</b></p> <p>Median weight gain on completion of treatment (interquartile range):</p> <p>daily group = 1.75 kg (1.2 – 2.3 kg)</p> <p>intermittent group = 1.5 kg (1.0 – 2.1 kg)</p>

	<p>p1 = 0.21  i.e. not statistically significant  difference in the medians2 = 0.25 kg</p>
	<p><b>Relapse</b>  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</p>
	<p><b>Adverse events</b>  No significant side effects were documented in either of the regimens (no further details provided)</p>
	<p><b>Treatment completion</b>  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</p>
	<p><b>Adherence</b></p>

	<p>Measured by nurses – dose counting</p> <p>Number of children adherent (defined as taking 75% or more of doses prescribed)</p> <p>daily group = 90 of 117</p> <p>intermittent group = 70 of 89</p> <p>p1 = 0.29</p> <p>OR3 (95% CI) = 0.90 (0.47 to 1.76)</p> <p>i.e. not statistically significant</p> <p>Number of partial adherers (defined as taking 75% or more of doses prescribed, but less than 75% during any single 4-week period)</p> <p>daily group = 30 of 117</p> <p>intermittent group = 21 of 89</p> <p>p1 = 0.69</p> <p>OR3 (95% CI) = 1.12 (0.59 to 2.12)</p> <p>i.e. not statistically significant</p> <p>Median days to default by non-adherers (interquartile range)</p> <p>daily group (n = 117) = 42 (33 – 69)</p> <p>intermittent group (n = 89) = 72 (44 – 93)</p> <p>p1 = 0.08</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = -30 days</p> <p>Median days to default by partial adherers (interquartile range)</p>
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	<p>daily group (n = 117) = 101 (40 – 132)</p> <p>intermittent group (n = 89) = 124 (74 – 144)</p> <p>p<sup>1</sup> = 0.17</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = -23 days</p> <p>Median % of prescribed doses taken (interquartile range)</p> <p>daily group = 91% (77 – 97)</p> <p>intermittent group = 93% (75 – 100)</p> <p>p<sup>1</sup> = 0.29</p> <p>i.e. not statistically significant</p> <p>difference in the medians<sup>2</sup> = -2%</p>
<b>Source of funding</b>	South African Medical Research Council
<b>Comments</b>	<p>The interventions did not differ in the two groups by dosing frequency alone:</p> <p>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</p> <p>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</p> <p>The interventions do not use the 4 standard recommended drugs: the regimens are lacking ethambutol</p>
<p><sup>1</sup> Calculated by authors using the chi-square test; p &lt; 0.05 was taken as significant</p> <p><sup>2</sup> Difference in the medians not provided by authors; calculated by reviewer as (median<sub>intermittent</sub> – median<sub>daily</sub>)</p> <p><sup>3</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; TB, tuberculosis; Z,</p>	

pyrazinamide
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## 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 coinfectd with tuberculosis and HIV

#### 1.2.1.1 Jindani et al 2004

<b>Bibliographic reference</b>	<b>Jindani A, Nunn AJ &amp; Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51</b>
<b>Study type</b>	Randomised controlled trial
<b>Study quality</b>	<p>Appropriate method of randomisation used?</p> <ul style="list-style-type: none"> <li>• yes – randomised allocation sequence was generated by computer</li> </ul> <p>Allocation concealment used?</p> <ul style="list-style-type: none"> <li>• 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)</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• no – no attempt to conceal treatment allocation after randomisation from patients, researchers, or healthcare staff</li> </ul> <p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• unclear – baseline characteristics not reported by HIV status</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• yes, although details provided limited</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• yes – 12 months after treatment completion</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• yes, although attrition rate was high in both groups</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Population studied is the same as the population of interest?</p> <ul style="list-style-type: none"> <li>• possibly some drug resistance at baseline, although unclear as baseline characteristics not reported by HIV status</li> </ul> <p>Intervention used is the same as the intervention of interest?</p>

<b>Bibliographic reference</b>	<b>Jindani A, Nunn AJ &amp; Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51</b>
	<ul style="list-style-type: none"> <li>• 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</li> <li>Have substitute outcomes been used instead of the patient-important outcomes of interest?</li> <li>• response to treatment</li> </ul>
<b>Number of patients</b>	<p>n = 127 (HIV subgroup only)</p> <ul style="list-style-type: none"> <li>• E-continuation phase, daily initial phase = 45</li> <li>• E-continuation phase, intermittent initial phase = 45</li> <li>• R-continuation phase = 37</li> </ul> <p>Data available 12 months after treatment completion = 68 (HIV subgroup only)</p> <ul style="list-style-type: none"> <li>• E-continuation phase = 49</li> <li>• R-continuation phase = 19</li> </ul>
<b>Patient characteristics</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• age 15–65 years</li> <li>• two sputum samples positive for tubercle bacilli on direct smear microscopy</li> <li>• less than a month of previous antituberculous chemotherapy</li> </ul> <p>Only data for HIV subgroup was extracted</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• patients were not eligible if they were so ill they were thought unlikely to survive the initial weeks of treatment</li> <li>• extrapulmonary tuberculosis</li> <li>• other diseases likely to prejudice the response to, or assessment of, treatment, including: diabetes, liver disease, nephritis, blood disorders, epilepsy, peripheral neuritis</li> <li>• pregnancy</li> <li>• psychiatric illness</li> <li>• alcoholism</li> </ul>
<b>Intervention</b>	<p>E-continuation phase regimen – 2HRZE<sub>7</sub>/6HE<sub>7</sub> or 2HRZE<sub>3</sub>/6HE<sub>7</sub></p> <ul style="list-style-type: none"> <li>• daily ethambutol, isoniazid, rifampicin, and pyrazinamide for 2 months, followed by daily ethambutol and isoniazid for a further 6 months; or</li> <li>• ethambutol, isoniazid, rifampicin, and pyrazinamide three times weekly for 2 months followed by daily ethambutol and isoniazid for 6 months</li> </ul> <p>Doses were according to World Health Organisation and International Union Against Tuberculosis and Lung Disease recommendations:</p>

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			
		<b>Number of tablets</b>		
		25-39 kg	40-55 kg	>55 kg
	<b>Daily intensive phase, 2HRZE<sub>7</sub></b>			
	R (150 mg) and H (100 mg) combined tablet	2	3	4
	E (400 mg)	1.5	2	3
	Z (400 mg)	2	3	4
	<b>Intermittent intensive phase, 2HRZE<sub>3</sub></b>			
	R (150 mg) and H (100 mg) combined tablet	2	3	4
	H (100 mg)	1	1	2
	E (400 mg)	1.5	2	3
	Z (400 mg)	2	3	4
	<b>E-continuation phase, 6HE<sub>7</sub></b>			
	E (400 mg) and H (100 mg) combined tablet	1.5	2	3
	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			
Comparison	R-continuation phase regimen – 2HRZE <sub>7</sub> /4HR <sub>7</sub> • 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:			
		<b>Number of tablets</b>		
		25-39 kg	40-55 kg	>55 kg
	<b>Daily intensive phase, 2HRZE<sub>7</sub></b>			
	R (150 mg) and H (100 mg) combined tablet	2	3	4
	E (400 mg)	1.5	2	3

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. <i>Lancet</i> 364:1244-51			
	Z (400 mg)	2	3	4
	<b>R-continuation phase, 4HR<sub>7</sub></b>			
	R (150 mg) and H (100 mg) combined tablet	2	3	4
	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			
<b>Length of follow up</b>	12 months after treatment completion			
<b>Location</b>	Multinational study; all HIV patients in African clinics			
<b>Outcomes measures and effect size</b>	<p>Mortality</p> <p>Number of deaths</p> <ul style="list-style-type: none"> <li>• E-continuation phase, daily initial phase = 10 of 45</li> <li>• E-continuation phase, intermittent initial phase = 3 of 45</li> <li>• R-continuation phase = 4 of 37</li> </ul> <p><i>E-continuation phase compared with R-continuation phase (any dosing schedule)</i></p> <ul style="list-style-type: none"> <li>• OR<sup>a</sup> (95% CI) = 1.39 (0.42 to 4.59)</li> </ul> <p>i.e. not statistically significant</p> <p><i>E-continuation phase compared with R-continuation phase (daily dosing only)</i></p> <ul style="list-style-type: none"> <li>• OR<sup>a</sup> (95% CI) = 2.36 (0.67 to 8.25)</li> </ul> <p>i.e. not statistically significant</p>			
	<p>Response to treatment – unfavourable outcome</p> <p>Number of patients to have an unfavourable outcome, defined as failure<sup>b</sup> or relapse<sup>c</sup>, at the end of follow-up</p> <ul style="list-style-type: none"> <li>• E-continuation phase = 13 of 90</li> <li>• R-continuation phase = 1 of 37</li> </ul> <p><i>E-continuation phase compared with R-continuation phase (any dosing schedule)</i></p> <ul style="list-style-type: none"> <li>• OR<sup>a</sup> (95% CI) = 6.08 (0.77 to 48.27)</li> </ul> <p>i.e. not statistically significant</p>			
<b>Source of funding</b>	<p>Substantial amounts of the drugs were donated by Hoechst Marion Roussel, Italy; FATOL, Arzneimittel, Germany; and BRACCO, SpA, Italy</p> <p>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</p>			

<b>Bibliographic reference</b>	<b>Jindani A, Nunn AJ &amp; Enarson DA (2004) Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 364:1244-51</b>
	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
<b>Comments</b>	
	(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

<b>Bibliographic reference</b>	<b>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</b>
<b>Study type</b>	Randomised controlled trial
<b>Study quality</b>	<p>Appropriate method of randomisation used?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Allocation concealment used?</p> <ul style="list-style-type: none"> <li>• yes – treatment instructions were contained within sealed envelopes</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• no</li> </ul> <p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• unclear – details provided were limited</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• yes – 12 months (6 months after treatment completion)</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• precise definition and reliable measure used for response to treatment, but not for relapse</li> </ul> <p>Population studied is the same as the population of interest?</p>

<b>Bibliographic reference</b>	<b>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</b>
	<ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Intervention used is the same as the intervention of interest?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Have substitute outcomes been used instead of the patient-important outcomes of interest?</p> <ul style="list-style-type: none"> <li>• response to treatment</li> </ul>
<b>Number of patients</b>	<p>n = 58 (HIV subgroup only)</p> <ul style="list-style-type: none"> <li>• HRC group = 26</li> <li>• HRZE group = 32</li> </ul>
<b>Patient characteristics</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• clinical and radiological presentations were consistent with pulmonary tuberculosis</li> <li>• acid-fast bacilli present in the sputum on direct fluorescent microscopy</li> <li>• over 18 years of age</li> </ul> <p>Only data for HIV subgroup was extracted</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• patients with a history of treatment for tuberculosis or of other exposures to any of the study drugs</li> <li>• patients with cultures positive for mycobacteria other than M. tuberculosis</li> <li>• patients with isolates of M. tuberculosis that were resistant to any of the study drugs</li> <li>• severe renal disease</li> <li>• hepatic disease</li> <li>• cardiovascular disease</li> <li>• pregnancy or lactation</li> <li>• a history of adverse reaction to one of the study drugs</li> <li>• epilepsy</li> <li>• concomitant treatment with theophylline</li> <li>• patients with severe tuberculosis who were considered unlikely to survive despite treatment</li> </ul>
<b>Intervention</b>	<p>4HRC/2HR</p> <ul style="list-style-type: none"> <li>• 300 mg of isoniazid</li> <li>• 600 mg of rifampicin</li> <li>• 750 mg of ciprofloxacin</li> <li>• all drugs were given orally once a day in the morning</li> </ul>
<b>Comparison</b>	<p>2HRZE/2HRZ/2HR</p> <ul style="list-style-type: none"> <li>• 300 mg of isoniazid</li> </ul>

<b>Bibliographic reference</b>	<b>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</b>
	<ul style="list-style-type: none"> <li>• 600 mg of rifampicin</li> <li>• 25 mg/kg of bodyweight of pyrazinamide</li> <li>• 15 mg/kg of bodyweight of ethambutol</li> <li>• all drugs were given orally once a day in the morning</li> </ul>
<b>Length of follow up</b>	12 months (6 months after treatment completion)
<b>Location</b>	Kilimanjaro, Tanzania
<b>Outcomes measures and effect size</b>	<p>Relapse</p> <p>Number of patients to experience culture-confirmed relapse</p> <ul style="list-style-type: none"> <li>• HRC group = 4 of 26</li> <li>• HRZE group = 0 of 32</li> <li>• OR<sup>a</sup> (95% CI) = 13.00 (0.67 to 253.61)</li> </ul> <p>i.e. not statistically significant</p> <p>Response to treatment – culture conversion</p> <p>Time to first negative test results (mean, median (range) (months))</p> <ul style="list-style-type: none"> <li>• HRC group (n = 26) = 2.5, 2 (1–6)</li> <li>• HRZE group (n = 32) = 1.6, 1 (1–3)</li> <li>• MD<sup>b</sup> = 0.9</li> <li>• <b>p = 0.0003</b></li> </ul> <p><b>i.e. statistically significant</b></p>

<b>Bibliographic reference</b>	<b>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</b>																					
	<p>The graph plots the percentage of patients with cultures positive for <i>M. tuberculosis</i> against the number of months of treatment (0 to 6). Two regimens are compared: HRZE (represented by solid circles) and HRC (represented by solid triangles). Both regimens start at 100% positive cultures at month 0. The HRZE group shows a steeper decline, reaching 0% positive cultures by month 3. The HRC group shows a more gradual decline, reaching 0% positive cultures by month 6.</p> <table border="1"> <thead> <tr> <th>Treatment (no. of months)</th> <th>HRZE (●) (%)</th> <th>HRC (▲) (%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>100</td> <td>100</td> </tr> <tr> <td>1</td> <td>50</td> <td>90</td> </tr> <tr> <td>2</td> <td>20</td> <td>60</td> </tr> <tr> <td>3</td> <td>0</td> <td>30</td> </tr> <tr> <td>4</td> <td>0</td> <td>15</td> </tr> <tr> <td>6</td> <td>0</td> <td>0</td> </tr> </tbody> </table>	Treatment (no. of months)	HRZE (●) (%)	HRC (▲) (%)	0	100	100	1	50	90	2	20	60	3	0	30	4	0	15	6	0	0
Treatment (no. of months)	HRZE (●) (%)	HRC (▲) (%)																				
0	100	100																				
1	50	90																				
2	20	60																				
3	0	30																				
4	0	15																				
6	0	0																				
<b>Source of funding</b>	Bayer																					
<b>Comments</b>	<p>(d) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer</p> <p>(e) Mean difference not provided by authors; calculated by reviewer</p> <p>Abbreviations: C, ciprofloxacin; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide</p>																					

### 1.2.1.3 Schwander et al, 1995

<b>Bibliographic reference</b>	<b>Schwander S, Rüscher-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</b>
<b>Study type</b>	Randomised controlled trial
<b>Study quality</b>	<p>Appropriate method of randomisation used?</p> <ul style="list-style-type: none"> <li>• yes – random selection of numbered envelopes</li> </ul> <p>Allocation concealment used?</p> <ul style="list-style-type: none"> <li>• yes – use of opaque envelopes</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul>



Bibliographic reference	Schwander S, Rüschi-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. <i>Tubercle and Lung Disease</i> 76: 210-8
	<p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• age, sex, BCG scar presence and other clinical and laboratory parameters were comparable between the 2 groups</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• both groups followed for 6 months</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• groups comparable for availability of outcome data, and unclear if groups comparable for treatment completion</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Population studied is the same as the population of interest?</p> <ul style="list-style-type: none"> <li>• no</li> </ul> <p>Intervention used is the same as the intervention of interest?</p> <ul style="list-style-type: none"> <li>• no</li> </ul> <p>Have substitute outcomes been used instead of the patient-important outcomes of interest?</p> <ul style="list-style-type: none"> <li>• response to treatment</li> </ul>
<b>Number of patients</b>	<p>n = 50</p> <ul style="list-style-type: none"> <li>• rifabutin group = 25</li> <li>• rifampicin group = 25</li> </ul> <p>Data available = 49</p> <ul style="list-style-type: none"> <li>• rifabutin group = 24</li> <li>• rifampicin group = 25</li> </ul>
<b>Patient characteristics</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• chest x-ray suggestive of pulmonary tuberculosis</li> <li>• sputum positive for acid-fast bacilli</li> <li>• HIV-1 seropositive</li> <li>• ≥15 years of age</li> <li>• use of contraceptive method</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• uric acid &gt;24 mg/dl for men, and &gt;18 mg/dl for women</li> <li>• ALT &gt;78 U/l</li> <li>• total bilirubin &gt;2.5 mg/dl</li> </ul>

Bibliographic reference	Schwander S, Rüscher-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. <i>Tubercle and Lung Disease</i> 76: 210-8		
	<ul style="list-style-type: none"> <li>• creatinine &gt;1.5 mg/dl</li> <li>• alcohol abuse</li> <li>• pregnancy or lactation</li> </ul>		
	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
Cavitary 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 <sup>3</sup> /μl)	1.5±0.8	1.8±0.7	>0.05
Neutrophils, mean±SD (10 <sup>3</sup> /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
<b>Intervention</b>	<p>Rifabutin group – 2HRbZE/4HRb</p> <ul style="list-style-type: none"> <li>• daily intake of rifabutin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifabutin and isoniazid for a further 4 months</li> <li>• treatment regimens were adapted and modified according to the World Health Organisation guidelines for tuberculosis treatment in adults</li> </ul> <p>Dosing</p> <ul style="list-style-type: none"> <li>• rifabutin: 150 mg/day for those &lt;50 kg, and 300 mg/day for those ≥50kg</li> <li>• isoniazid: 300 mg/day</li> <li>• pyrazinamide: 1500 mg/day for those &lt;50 kg, and 2000 mg/day for those ≥50kg</li> </ul>		

<b>Bibliographic reference</b>	<b>Schwander S, Rüscher-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</b>
	<ul style="list-style-type: none"> <li>• ethambutol: 80 mg/day for those &lt;50 kg, and 1200 mg/day for those ≥50kg</li> </ul>
<b>Comparison</b>	<p>Rifampicin group – 2HRZE/4HR</p> <ul style="list-style-type: none"> <li>• daily intake of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for a further 4 months</li> <li>• treatment regimens were adapted and modified according to the World Health Organisation guidelines for tuberculosis treatment in adults</li> </ul> <p>Dosing</p> <ul style="list-style-type: none"> <li>• rifampicin: 450 mg/day for those &lt;50 kg, and 600 mg/day for those ≥50kg</li> <li>• isoniazid: 300 mg/day</li> <li>• pyrazinamide: 1500 mg/day for those &lt;50 kg, and 2000 mg/day for those ≥50kg</li> <li>• ethambutol: 80 mg/day for those &lt;50 kg, and 1200 mg/day for those ≥50kg</li> </ul>
<b>Length of follow up</b>	6 months
<b>Location</b>	Kampala, Uganda
<b>Outcomes measures and effect size</b>	<p>Mortality</p> <p>Number of deaths during the study period</p> <ul style="list-style-type: none"> <li>• rifabutin group = 4 of 25</li> <li>• rifampicin group = 2 of 25</li> <li>• OR<sup>a</sup> (95% CI) = 2.19 (0.36 to 13.22)</li> </ul> <p>i.e. not statistically significant</p> <p>Changes in signs and symptoms – radiographic change</p> <p>Number of patients in whom radiographic improvement was observed</p> <ul style="list-style-type: none"> <li>• rifabutin group = 24 of 25</li> <li>• rifampicin group = 25 of 25</li> <li>• OR<sup>a</sup> (95% CI) = 0.32 (0.01 to 8.25)</li> </ul> <p>i.e. not statistically significant</p> <p>Response to treatment – sputum conversion</p> <p>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</p> <ul style="list-style-type: none"> <li>• rifabutin group = 22 of 25</li> <li>• rifampicin group = 22 of 25</li> <li>• OR<sup>a</sup> (95% CI) = 1.00 (0.18 to 5.51)</li> </ul> <p>i.e. not statistically significant</p>

<b>Bibliographic reference</b>	<b>Schwander S, Rüscher-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</b>
	Time to sputum conversion (median, days) <sup>b</sup> , 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 <ul style="list-style-type: none"> <li>• rifabutin group (n = 25) = Not reported</li> <li>• rifampicin group (n = 25) = Not reported</li> </ul> <p>Difference in the medians<sup>c</sup> = Not reported</p>
<b>Source of funding</b>	Study partially supported by Farmitalia Carlo Erba, Freiburg, Germany
<b>Comments</b>	<p>(f) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer</p> <p>(g) Not provided by authors; read off Kaplan-Meier plot by reviewer</p> <p>(h) Difference not provided by authors; calculated by reviewer</p> <p>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</p>

#### 1.2.1.4 HIV/TB Study Writing Group, 2009

<b>Bibliographic reference</b>	<b>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</b>
<b>Study type</b>	Prospective cohort
<b>Study quality</b>	<p>Method of allocation to treatment groups unrelated to potential confounding factors?</p> <ul style="list-style-type: none"> <li>• unclear, though unlikely</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• unclear, though unlikely</li> </ul> <p>Attempts made within the design or analysis to balance the groups for potential confounders?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• unclear – details of treatment and other care received were limited</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p>

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
	<ul style="list-style-type: none"> <li>• yes – 1 year</li> </ul> Groups comparable for treatment completion and availability of outcome data? <ul style="list-style-type: none"> <li>• unclear</li> </ul> Study used precise definitions and reliable measures of outcome? <ul style="list-style-type: none"> <li>• yes</li> </ul> Population studied is the same as the population of interest? <ul style="list-style-type: none"> <li>• no – some drug resistance was present at baseline (7% of patients in Central/Northern Europe, 13% in Southern Europe and 50% in Eastern Europe)</li> </ul> Intervention used is the same as the intervention of interest? <ul style="list-style-type: none"> <li>• unclear – details of treatment and other care received were limited</li> </ul> Have substitute outcomes been used instead of the patient-important outcomes of interest? <ul style="list-style-type: none"> <li>• no</li> </ul>
<b>Number of patients</b>	n = 784 <ul style="list-style-type: none"> <li>• non-rifampicin group = 117</li> <li>• rifampicin group = 667</li> </ul>
<b>Patient characteristics</b>	Inclusion criteria <ul style="list-style-type: none"> <li>• initiation of antituberculosis therapy between January 2004 and December 2006</li> <li>• known to be infected with HIV at diagnosis of tuberculosis, or diagnosed with HIV infection within 6 months of tuberculosis diagnosis</li> <li>• aged 16 years or older</li> </ul> Diagnosis of tuberculosis <ul style="list-style-type: none"> <li>• confirmed tuberculosis = M. tuberculosis cultured or M. tuberculosis DNA demonstrated by PCR</li> <li>• probable tuberculosis = acid-fast bacilli or granulomatous inflammation present</li> <li>• presumptive tuberculosis = antituberculosis therapy initiated in the absence of supportive microbiological or histological evidence and diagnosis of tuberculosis not subsequently ruled out</li> </ul>
<b>Intervention</b>	Non-rifampicin group <ul style="list-style-type: none"> <li>• regimens contained at least isoniazid and pyrazinamide, but not rifampicin</li> </ul>
<b>Comparison</b>	Rifampicin group <ul style="list-style-type: none"> <li>• regimens contained at least rifampicin (or any other rifamycin), isoniazid and pyrazinamide</li> </ul>
<b>Length of follow up</b>	1 year
<b>Location</b>	Argentina, Italy, Spain, Denmark, France, Switzerland, Belarus, Latvia, Romania, Russia, Ukraine and the UK
<b>Outcomes measures and</b>	Mortality – univariate analysis

<b>Bibliographic reference</b>	<b>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</b>
<b>effect size</b>	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 <sup>a</sup> RR (95% CI) (non-rifampicin compared to rifampicin group) = 1.21 (0.74 to 1.97); p = 0.447 i.e. not statistically significant
<b>Source of funding</b>	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
<b>Comments</b>	
	(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

<b>Bibliographic reference</b>	<b>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</b>
<b>Study type</b>	Prospective cohort
<b>Study quality</b>	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

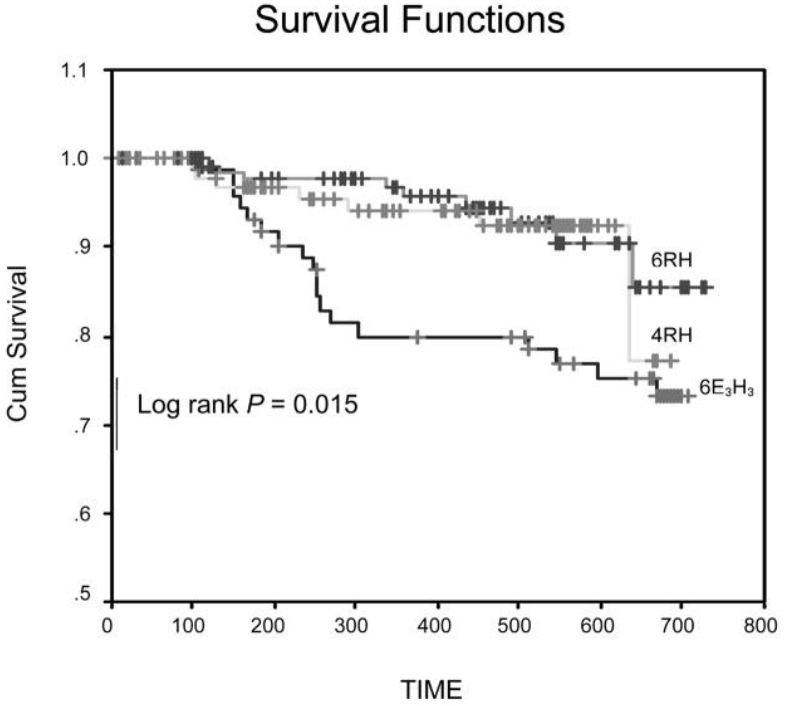
Bibliographic reference	Okwera A, Johnson JL, Luzze H et al (2006) Comparison of intermittent ethambutol with rifampicin-based regimens in HIV-infected adults with PTB, Kampala. <i>International Journal of Tuberculosis and Lung Disease</i> 10(1): 39-44
	<p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• no – rifampicin regimens (2HRZE/4HR and 2HRZE/6HR) were self-administered, non-rifampicin regimen (2HRZE/6HE) was directly observed</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• no definitions provided for culture-negative at 2 months, treatment failure or treatment completion</li> </ul> <p>Population studied is the same as the population of interest?</p> <ul style="list-style-type: none"> <li>• population appears to match the population of interest, although unclear if there was any drug resistance at baseline</li> </ul> <p>Intervention used is the same as the intervention of interest?</p> <ul style="list-style-type: none"> <li>• 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)</li> </ul> <p>Have substitute outcomes been used instead of the patient-important outcomes of interest?</p> <ul style="list-style-type: none"> <li>• culture-negative at 2 months – an indicator of response to treatment, a surrogate for cure</li> </ul>
Number of patients	<p>n = 549</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 136</li> <li>• 2HRZE/6HR group = 266</li> <li>• 2HRZE/4HR group = 147</li> </ul>
Patient characteristics	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• adults with initial episodes of smear-positive pulmonary tuberculosis</li> <li>• HIV-positive</li> </ul> <p>Diagnosis of tuberculosis</p> <ul style="list-style-type: none"> <li>• acid-fast bacilli smear-positive</li> <li>• at least one sputum culture-positive for <i>M. tuberculosis</i></li> <li>• chest X-ray findings consistent with tuberculosis</li> </ul> <p>Exclusion criteria</p>

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			
	<ul style="list-style-type: none"> <li>• suspected miliary and meningeal tuberculosis</li> <li>• previous treatment of tuberculosis</li> <li>• pregnant women</li> <li>• no antiretroviral therapy during the course of the study</li> </ul>			
	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 <sup>2</sup> )	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 <sup>3</sup> )	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	
<b>Intervention</b>	Ethambutol-containing continuation phase - 2HRZE/6HE <ul style="list-style-type: none"> <li>• isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months</li> <li>• followed by isoniazid and ethambutol 3 times a week for 6 months</li> </ul> Dosing: <ul style="list-style-type: none"> <li>• 900 mg isoniazid</li> <li>• 1800 mg ethambutol</li> <li>• no dosing information given for rifampicin and pyrazinamide</li> </ul> Directly observed therapy					
<b>Comparison</b>	Rifampicin-containing continuation phase - 2HRZE/4HR or 2HRZE/6HR <ul style="list-style-type: none"> <li>• isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months</li> <li>• followed by isoniazid and rifampicin daily for 4 or 6 months</li> </ul> Dosing: <ul style="list-style-type: none"> <li>• 300 mg isoniazid</li> <li>• 600 mg ethambutol</li> <li>• no dosing information given for pyrazinamide and ethambutol</li> </ul> Self-administered therapy					
<b>Length of follow up</b>	Median follow-up: <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 661 days</li> <li>• 2HRZE/6HR group = 533 days</li> <li>• 2HRZE/4HR group = 512 days</li> </ul>					
<b>Location</b>	Kampala, Uganda					
<b>Outcomes measures and</b>	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	<p>Number of people to die within 2 years</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 27 of 136</li> <li>• 2HRZE/6HR group = 62 of 266</li> <li>• 2HRZE/4HR group = 51 of 147</li> <li>• OR<sup>a</sup> (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.66 (0.41 to 1.06) i.e. not statistically significant</li> <li>• OR<sup>a</sup> (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</li> </ul> <p>Treatment failure</p> <p>Number of patients to experience treatment failure</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 8 of 136</li> <li>• 2HRZE/6HR group = 7 of 266</li> <li>• 2HRZE/4HR group = 5 of 147</li> <li>• OR<sup>a</sup> (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 2.09 (0.84 to 5.22) i.e. not statistically significant</li> <li>• OR<sup>a</sup> (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</li> </ul> <p>Relapse</p> <p>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</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 23 of 136</li> <li>• 2HRZE/6HR group = 14 of 266</li> <li>• 2HRZE/4HR group = 16 of 147</li> <li>• <b>OR<sup>a</sup> (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 2.60 (1.45 to 4.65)</b> <b>i.e. statistically significant</b></li> <li>• <b>OR<sup>a</sup> (95% CI) (6-month E-containing continuation phase compared to 6-month R-containing continuation phase) = 3.66 (1.82 to 7.38)</b> <b>i.e. statistically significant</b></li> </ul>

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
	<p style="text-align: center;"><b>Survival Functions</b></p>  <p>Kaplan Meier curve showing time to relapse of patients in the three cohorts; '6E<sub>3</sub>H<sub>3</sub>' = 2HRZE/6HE group, '6RH' = 2HRZE/6HR group, '4RH' = 2HRZE/4HR group</p> <p>Response to treatment – culture conversion          Number of patients to be culture-negative after 2 months of treatment</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 101 of 136</li> <li>• 2HRZE/6HR group = 238 of 266</li> <li>• 2HRZE/4HR group = 126 of 147</li> </ul> <p>• <b>OR<sup>a</sup> (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.39 (0.24 to 0.63)</b>  <b>i.e. statistically significant</b></p> <p>Adherence – treatment completion          Number of patients to complete therapy</p> <ul style="list-style-type: none"> <li>• 2HRZE/6HE group = 89 of 136</li> </ul>

<b>Bibliographic reference</b>	<b>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</b>
	<ul style="list-style-type: none"> <li>• 2HRZE/6HR group = 195 of 266</li> <li>• 2HRZE/4HR group = 122 of 147</li> <li>• <b>OR<sup>a</sup> (95% CI) (E-containing continuation phase compared to R-containing continuation phase) = 0.57 (0.39 to 0.87) i.e. statistically significant</b></li> <li>• OR<sup>a</sup> (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</li> </ul>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<i>(j) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer</i>	
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

<b>Bibliographic reference</b>	<b>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</b>
<b>Study type</b>	Randomised controlled trial
<b>Study quality</b>	<p>Appropriate method of randomisation used?</p> <ul style="list-style-type: none"> <li>• yes – random number table</li> </ul> <p>Allocation concealment used?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• no</li> </ul> <p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• unclear – limited details provided</li> </ul>

<b>Bibliographic reference</b>	<b>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</b>
	<p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• yes – 3 months after treatment was stopped</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Population studied is the same as the population of interest?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Intervention used is the same as the intervention of interest?</p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p>Have substitute outcomes been used instead of the patient-important outcomes of interest?</p> <ul style="list-style-type: none"> <li>• no</li> </ul>
<b>Number of patients</b>	<p>n = 31</p> <ul style="list-style-type: none"> <li>• ofloxacin group = 16</li> <li>• rifampicin group = 15</li> </ul>
<b>Patient characteristics</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• proven chronic liver disease</li> <li>• diagnosis of tuberculosis</li> </ul> <p>Screening for tuberculosis</p> <ul style="list-style-type: none"> <li>• fever</li> <li>• cough for &gt;2 weeks</li> <li>• haemoptysis</li> <li>• unexplained weight loss</li> <li>• increasing ascites not responding to diuretics</li> <li>• unexplained bowel symptoms, such as diarrhoea, constipation or subacute intestinal obstructions</li> <li>• radiological lesions suggestive of tuberculosis</li> <li>• past or family history of tuberculosis</li> </ul> <p>Diagnosis of tuberculosis</p> <ul style="list-style-type: none"> <li>• based on a good clinical response to chemotherapy, and one or more of the following:</li> </ul>

<b>Bibliographic reference</b>	<b>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</b>
	<ul style="list-style-type: none"> <li>– histological evidence of caseating granulomas</li> <li>– sputum positivity for acid-fast bacilli</li> <li>– growth of M. tuberculosis on culture</li> <li>– positive PCR for M. tuberculosis in tissues</li> <li>• diagnosis of pleural or peritoneal tuberculosis was established if 3 of the following criteria were met: <ul style="list-style-type: none"> <li>– raised ascite fluid cell count with lymphocyte predominance</li> <li>– raised ascetic fluid albumin (&gt;2.5 g/dl)</li> <li>– raised adenosine deaminase (&gt;33 U/l)</li> </ul> </li> <li>– positive PCR for M. tuberculosis</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• serum bilirubin &gt;5 mg/dl</li> <li>• baseline ALT/AST &gt;200 IU/l</li> <li>• serum creatinine &gt;2.5 mg/dl</li> <li>• increase in ALT/AST over 1 week prior to initiation of antituberculosis chemotherapy was &gt;2-fold the baseline levels</li> </ul>
<b>Intervention</b>	<p>Ofloxacin group – 2HZEO/10HEO</p> <ul style="list-style-type: none"> <li>• isoniazid, pyrazinamide, ethambutol and ofloxacin for 2 months</li> <li>• followed by isoniazid, ethambutol and ofloxacin for a further 10 months</li> </ul> <p>Dosing:</p> <ul style="list-style-type: none"> <li>• ofloxacin was given in a dose of 400 mg once daily</li> <li>• no further dosing information provided</li> </ul>
<b>Comparison</b>	<p>Rifampicin group – 2HRE/7HR</p> <ul style="list-style-type: none"> <li>• isoniazid, rifampicin and ethambutol for 2 months</li> <li>• followed by isoniazid and rifampicin for a further 7 months</li> </ul> <p>Dosing:</p> <ul style="list-style-type: none"> <li>• no dosing information provided</li> </ul>
<b>Length of follow up</b>	3 months after treatment was stopped
<b>Location</b>	New Delhi, India
<b>Outcomes measures and effect size</b>	<p>Mortality – all cause</p> <p>Number of patients to die from any cause</p> <ul style="list-style-type: none"> <li>• ofloxacin group = 1 of 16<sup>a</sup></li> <li>• rifampicin group = 0 of 15</li> </ul>

<b>Bibliographic reference</b>	<b>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</b>
	<ul style="list-style-type: none"> <li>• OR<sup>b</sup> (95% CI) = 3.00 (0.11 to 79.50) i.e. not statistically significant</li> </ul>
	<p>Mortality – tuberculosis-related</p> <p>Number of tuberculosis-related deaths</p> <ul style="list-style-type: none"> <li>• ofloxacin group = 0 of 16</li> <li>• rifampicin group = 0 of 15</li> <li>• OR<sup>b</sup> (95% CI) = 0.94 (0.02 to 50.32) i.e. not statistically significant</li> </ul>
	<p>Mortality – hepatotoxicity-related</p> <p>Number of hepatotoxicity-related deaths</p> <ul style="list-style-type: none"> <li>• ofloxacin group = 0 of 16</li> <li>• rifampicin group = 0 of 15</li> <li>• OR<sup>b</sup> (95% CI) = 0.94 (0.02 to 50.32) i.e. not statistically significant</li> </ul>
	<p>Adverse events - hepatotoxicity</p> <p>Number of patients to experience hepatotoxicity, defined as ALT/AST levels &gt;5-fold the baseline level or &gt;400 IU/L, or if bilirubin increased by 2.5 mg/dl after exclusion of superimposed acute hepatitis</p> <ul style="list-style-type: none"> <li>• ofloxacin group = 0 of 16</li> <li>• rifampicin group = 4 of 15</li> <li>• OR<sup>b</sup> (95% CI) = 0.08 (0.00 to 1.58) i.e. not statistically significant</li> </ul>
<b>Source of funding</b>	No details provided
<b>Comments</b>	<p>(k) Death resulted from intracranial bleeding unrelated to the antituberculosis chemotherapy during the follow-up</p> <p>(l) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer</p> <p>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</p>

### 1.2.2.2 Pan et al, 2005

<b>Bibliographic reference</b>	<b>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</b>
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<b>Bibliographic reference</b>	<b>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</b>
<b>Study type</b>	Prospective cohort
<b>Study quality</b>	<p>Method of allocation to treatment groups unrelated to potential confounding factors?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Blinding used?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Attempts made within the design or analysis to balance the groups for potential confounders?</p> <ul style="list-style-type: none"> <li>• no</li> </ul> <p>Groups comparable at baseline?</p> <ul style="list-style-type: none"> <li>• yes – authors state that the ‘general conditions of the 2 groups were not distinguishable (<math>p &gt; 0.05</math>)’, although no further details are provided</li> </ul> <p>Groups received the same care apart from the intervention(s) studied?</p> <ul style="list-style-type: none"> <li>• unclear – details provided were limited</li> </ul> <p>Groups followed up for an equal and appropriate length of time?</p> <ul style="list-style-type: none"> <li>• unclear</li> </ul> <p>Groups comparable for treatment completion and availability of outcome data?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Study used precise definitions and reliable measures of outcome?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Population studied is the same as the population of interest?</p> <ul style="list-style-type: none"> <li>• yes</li> </ul> <p>Intervention used is the same as the intervention of interest?</p> <ul style="list-style-type: none"> <li>• 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)</li> </ul> <p>Have substitute outcomes been used instead of the patient-important outcomes of interest?</p> <ul style="list-style-type: none"> <li>• no</li> </ul>
<b>Number of patients</b>	<p>n = 47</p> <ul style="list-style-type: none"> <li>• HRbAOL group = 23</li> <li>• HRZS/E group = 24</li> </ul>
<b>Patient characteristics</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• pulmonary tuberculosis</li> <li>• patients carrying HBV whose liver function was normal when they suffered from pulmonary tuberculosis; values of ALT were all <math>&lt;60</math> U/L before antituberculosis chemotherapy was initiated</li> </ul>



<b>Bibliographic reference</b>	<b>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</b>
	Diagnosis of tuberculosis <ul style="list-style-type: none"> <li>• made by chest x-ray, medical history, acid-fast bacilli in the phlegm and tuberculosis PCR</li> </ul> Exclusion criteria <ul style="list-style-type: none"> <li>• infection with other hepatitis viruses</li> <li>• alcoholic liver ailment</li> <li>• other chronic liver ailment</li> </ul>
<b>Intervention</b>	HRbAOL <ul style="list-style-type: none"> <li>• 0.3 g isoniazid once a day</li> <li>• 0.6 g rifabutin once a week</li> <li>• 0.2 g amikacin twice a day</li> <li>• 0.2 g ofloxacin twice a day</li> <li>• 0.2 g levofloxacin twice a day</li> </ul>
<b>Comparison</b>	HRZS/E <ul style="list-style-type: none"> <li>• 0.3 g isoniazid once a day</li> <li>• 0.45 g rifampicin once a day</li> <li>• 1.0 g pyrazinamide once a day</li> <li>• 1.0 g ethambutol and/or 0.75 g streptomycin once a day</li> </ul>
<b>Length of follow up</b>	Unclear
<b>Location</b>	Shaanxi Province, China
<b>Outcomes measures and effect size</b>	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 <ul style="list-style-type: none"> <li>• HRbAOL group = 7 of 23</li> <li>• HRZS/E group = 19 of 24</li> <li>• <b>OR<sup>a</sup> (95% CI) = 0.12 (0.03 to 0.43)</b></li> </ul> <b>i.e. statistically significant</b>
<b>Source of funding</b>	No details provided
<b>Comments</b>	<i>(m) Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer</i> 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**

<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population does not exactly match the population of interest: 3.4% drug resistance at baseline</p> <p>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</p> <p>Method of randomisation, although allocation concealment was possible ("random allocations of treatment were made centrally by coordinators")</p> <p>Radiologists were blinded, although unclear if other investigators, patients or those administering care were blinded</p> <p>Groups were comparable at the baseline</p> <p>Unclear if groups received the same care apart from the interventions studied</p> <p>Groups were not followed up for an equal length of time: 'follow-up' was timed from treatment initiation; therefore,</p>

	<p>since treatment durations were of different duration, follow-up for outcomes that were measured after treatment completion was not equal</p> <p>Groups were statistically comparable for treatment completion, although this occurred in more patients in the 6M group</p> <p>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</p>
<p><b>Number of patients</b></p>	<p><i>Patients without cavities or no cavity &gt;2 cm</i></p> <p>Randomised = 431<sup>1</sup></p> <p>6-month regimens = 214<sup>2</sup></p> <p>12-month regimens = 217<sup>3</sup></p> <p>Data available at treatment completion = 384</p> <p>6-month regimens = 194<sup>4</sup></p> <p>12-month regimens = 190<sup>5</sup></p> <p>Data available at 54 months after treatment initiation = 295<sup>6</sup></p> <p>6-month regimens = 144</p> <p>12-month regimens = 151</p> <p><i>Patients with cavities &gt;2 cm</i></p> <p>Randomised = 381<sup>1</sup></p> <p>9-month regimens = 187<sup>7</sup></p> <p>18-month regimens = 194<sup>8</sup></p> <p>Data available at treatment completion = 312</p> <p>9-month regimens = 157<sup>9</sup></p> <p>18-month regimens = 155<sup>10</sup></p>

	<p>Data available at 54 months after treatment initiation = 253<sup>6</sup></p> <p>9-month regimens = 132</p> <p>18-month regimens = 121</p>																																																														
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Culture-positive pulmonary tuberculosis</p> <p>Patients aged 15 to 70 years</p> <p><i>Exclusion</i></p> <p>Previous antituberculosis therapy for more than 2 weeks at any time</p> <p>Pregnant</p> <p>Impaired renal, hepatic or visual function</p> <p><i>Baseline characteristics</i></p> <p>Balanced in terms of mean age, sex and pretreatment radiographic characteristics</p> <table border="1" data-bbox="600 890 2087 1417"> <thead> <tr> <th colspan="7"><b>Patients without cavities or no cavity &gt;2 cm</b></th> </tr> <tr> <th rowspan="2"></th> <th colspan="4">Age &lt;60 years</th> <th colspan="2">Age &gt;60 years</th> </tr> <tr> <th><b>6EHR</b></th> <th><b>6SHR</b></th> <th><b>12EHR</b></th> <th><b>12SHR</b></th> <th><b>6EHR</b></th> <th><b>12EHR</b></th> </tr> </thead> <tbody> <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> </tbody> </table>	<b>Patients without cavities or no cavity &gt;2 cm</b>								Age <60 years				Age >60 years		<b>6EHR</b>	<b>6SHR</b>	<b>12EHR</b>	<b>12SHR</b>	<b>6EHR</b>	<b>12EHR</b>	Total	78	83	76	81	33	33	Mean age (years)	40	37	38	36	65	64	Sex							male	57	58	49	58	25	27	female	21	25	27	23	8	6	Radiographic extent of the						
<b>Patients without cavities or no cavity &gt;2 cm</b>																																																															
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female	21	25	27	23	8	6																																																									
Radiographic extent of the																																																															

	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	
	<b>Patients with cavities &gt;2 cm</b>							
		Age <60 years				Age >60 years		
		<b>9EHR</b>	<b>9SHR</b>	<b>18EHR</b>	<b>18SHR</b>	<b>9EHR</b>	<b>18EHR</b>	
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	
<b>Intervention</b>	<b>Patients without cavities or no cavity &gt;2 cm: 6-month regimens<sup>11</sup></b>						
	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						
	<b>Patients with cavities &gt;2 cm: 9-month regimens<sup>11</sup></b>						
	Patients aged less than 60 years – randomised to either:						
	9EHR: 9 months of ethambutol, isoniazid and rifampicin						

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



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

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

	<p>Number of participants with cavities &gt;2 cm to experience relapse during the 54 month of follow-up</p> <p>9-month regimens = 0 of 187</p> <p>18-month regimens = 0 of 194</p> <p>OR<sup>12</sup> (95% CI) = 1.04 (0.02 to 52.55)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Ciba Laboratories and Lepetit Pharmaceuticals provided financial support
<b>Comments</b>	<p>Population does not exactly match the population of interest:</p> <p>3.4% drug resistance at baseline</p> <p>Intervention does not exactly match the intervention of interest:</p> <p>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</p>
<p><sup>1</sup> Reviewer calculated number randomised by adding together those who did not complete allocated treatment to the number remaining for analysis</p> <p><sup>2</sup> 6EHR (age &lt; 60 years) = 86; 6SHR (age &lt; 60 years) = 92; 6EHR (age &gt; 60 years) = 36</p> <p><sup>3</sup> 12EHR (age &lt; 60 years) = 90; 12SHR (age &lt; 60 years) = 90; 12EHR (age &gt; 60 years) = 37</p> <p><sup>4</sup> 9EHR (age &lt; 60 years) = 77; 9SHR (age &lt; 60 years) = 84; 9EHR (age &gt; 60 years) = 26</p> <p><sup>5</sup> 18EHR (age &lt; 60 years) = 78; 18SHR (age &lt; 60 years) = 84; 18EHR (age &gt; 60 years) = 32</p> <p><sup>6</sup> Reviewer included patients that “absconded/emigrated”; authors ‘analysed’: 6-month regimens = 130; 12-month regimens = 140; 9-month regimens = 116; 18-month regimens = 108</p> <p><sup>7</sup> 6EHR (age &lt; 60 years) = 78; 6SHR (age &lt; 60 years) = 83; 6EHR (age &gt; 60 years) = 33</p> <p><sup>8</sup> 12EHR (age &lt; 60 years) = 76; 12SHR (age &lt; 60 years) = 81; 12EHR (age &gt; 60 years) = 33</p> <p><sup>9</sup> 9EHR (age &lt; 60 years) = 65; 9SHR (age &lt; 60 years) = 72; 9EHR (age &gt; 60 years) = 20</p>	

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

<sup>11</sup> Data for regimens of the same length were pooled by the reviewer

<sup>12</sup> 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

<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>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</p> <p>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</p> <p>Method of randomisation was unclear</p> <p>Allocation concealment unclear, although allocation 'was made centrally 2 coordinators'</p> <p>Blinding was unclear, although radiographs were read by an observer without knowledge of the regimen allocated to the patients</p> <p>Groups were comparable at the baseline</p> <p>Unclear if groups received the same care apart from the interventions studied</p> <p>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</p> <p>Did not follow the intent-to-treat principle</p>
<b>Number of patients</b>	<p>Randomised = 593</p> <p>Analysed = 511</p>

	<p>6-month regimens = 344<sup>1</sup>                  9-month regimen = 177                  Completed treatment = 444                  6-month regimens = 287<sup>2</sup>                  9-month regimen = 157                  Data available at 36 months = 373                  6-month regimens = 246<sup>3</sup>                  9-month regimen = 127</p>																	
<b>Patient characteristics</b>	<p><i>Inclusion</i>                  Culture-positive pulmonary tuberculosis                  Aged 18 to 60 years</p> <p><i>Exclusion</i>                  &gt;2 weeks antituberculosis therapy at any time                  Pregnancy                  Clinical evidence of impaired renal or hepatic function, gout or impaired vision</p> <p><i>Baseline characteristics</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;"></th> <th style="width: 25%; text-align: center;">6-month group</th> <th style="width: 25%; text-align: center;">9-month group</th> </tr> </thead> <tbody> <tr> <td>Sex</td> <td></td> <td></td> </tr> <tr> <td style="padding-left: 20px;">male</td> <td style="text-align: center;">59.1%</td> <td style="text-align: center;">67.8%</td> </tr> <tr> <td style="padding-left: 20px;">female</td> <td style="text-align: center;">40.1%</td> <td style="text-align: center;">32.2%</td> </tr> <tr> <td>Age (mean, years)</td> <td style="text-align: center;">37</td> <td style="text-align: center;">38</td> </tr> </tbody> </table>				6-month group	9-month group	Sex			male	59.1%	67.8%	female	40.1%	32.2%	Age (mean, years)	37	38
	6-month group	9-month group																
Sex																		
male	59.1%	67.8%																
female	40.1%	32.2%																
Age (mean, years)	37	38																

		<b>Radiographic extent of disease</b> slight limited moderate extensive and gross not classified	31.4% 33.1% 14.8% 16.6% 1.2%	27.7% 37.3% 16.4% 16.3% 2.3%
		<b>Radiographic extent of cavitation</b> nil slight moderate extensive not classified	49.1% 27.9% 16.9% 2.3% 0.9%	50.3% 23.1% 21.4% 2.8% 2.3%
		<b>Bacteriological status</b> smear-positive, culture-positive smear-negative, culture-positive	56.1% 41.0%	57.6% 42.4%
<b>Intervention</b>	<i>6-month regimens</i> 2SHRZ <sub>7</sub> /4HR <sub>7</sub> isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months			

	<p>2EHRZ<sub>7</sub>/4HR<sub>7</sub></p> <p>isoniazid, rifampicin, ethambutol and pyrazinamide daily for 2 months</p> <p>isoniazid and rifampicin daily for a further 4 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg</p> <p>streptomycin: 750 mg intramuscularly, 6 days/week</p> <p>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</p> <p>ethambutol: 25 mg/kg of body weight/day</p> <p>Chemotherapy was administered on an outpatient or inpatient basis according to the usual practice of the physician</p>
<b>Comparison</b>	<p><i>9-month regimen</i></p> <p>2EHR<sub>7</sub>/7HR<sub>7</sub></p> <p>isoniazid, rifampicin and ethambutol daily for 2 months</p> <p>isoniazid and rifampicin daily for a further 7 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg</p> <p>ethambutol: 25 mg/kg of body weight/day</p> <p>Chemotherapy was administered on an outpatient or inpatient basis according to the usual practice of the physician</p>
<b>Location</b>	UK

<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	Minimum of 3 years after treatment completion
<b>Outcomes measures and effect size</b>	<p><b>Relapse</b></p> <p>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</p> <p>The following were not considered to be indicative relapse:</p> <p>isolated positive culture – a culture that was preceded and followed by several successive negative cultures</p> <p>smear positive, but culture negative</p> <p>Number of participants to experience bacteriological or radiographic recurrence</p> <p>6-month regimens = 6 of 287</p> <p>9-month regimen = 2 of 157</p> <p>OR<sup>4</sup> (95% CI) = 1.65 (0.33 to 8.30)</p> <p>i.e. not statistically significant</p>
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	24 months after treatment completion
<b>Outcomes measures and effect size</b>	<p><b>Adverse events - hepatotoxicity</b></p> <p>Number of participants to experience hepatotoxicity</p> <p>6-month regimens = 14 of 287</p>



	<p>9-month regimen = 7 of 157</p> <p>OR<sup>4</sup> (95% CI) = 1.10 (0.43 to 2.78)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events - rash</b></p> <p>Number of participants to experience rash</p> <p>6-month regimens = 13 of 287</p> <p>9-month regimen = 1 of 157</p> <p>OR<sup>4</sup> (95% CI) = 7.40 (0.96 to 57.12)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events - arthralgia</b></p> <p>Number of participants to experience arthralgia</p> <p>6-month regimens = 2 of 287</p> <p>9-month regimen = 0 of 157</p> <p>OR<sup>4</sup> (95% CI) = 2.76 (0.13 to 57.82)</p> <p>i.e. not statistically significant</p>
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	Full treatment period
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – culture-negative at 6 months</b></p> <p>Number of participants to be culture-negative at 6 months</p> <p>6-month regimens = 287 of 287</p>

	<p>9-month regimen = 157 of 157</p> <p>OR<sup>4</sup> (95% CI) = 1.83 (0.04 to 92.44)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – requiring modification or withdrawal of chemotherapy</b></p> <p>Number of participants to experience adverse reactions to 1 or more drugs leading to modification or withdrawal of chemotherapy</p> <p>6-month regimens = 19 of 344</p> <p>9-month regimen = 7 of 177</p> <p>OR<sup>4</sup> (95% CI) = 1.42 (0.59 to 3.44)</p> <p>i.e. not statistically significant</p>
	<p><b>Adherence – treatment default</b></p> <p>Number of participants to default before treatment completion</p> <p>6-month regimens = 11 of 344</p> <p>9-month regimen = 4 of 177</p> <p>OR<sup>4</sup> (95% CI) = 1.43 (0.45 to 4.55)</p> <p>i.e. not statistically significant</p>
	<p><b>Adherence – isoniazid metabolites in urine</b></p> <p>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</p> <p>Number of urine samples that were positive for isoniazid metabolites</p> <p>6-month regimens = 1334 of 1379</p>

	<p>9-month regimen = 1128 of 1166</p> <p>OR<sup>4</sup> (95% CI) = 1.00 (0.64 to 1.55)</p> <p>i.e. not statistically significant</p> <p>Authors' interpretation: the majority of patients took their drugs as prescribed</p>
<b>Source of funding</b>	British Medical Research Council
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>varies by more than duration (different combinations in each arm)</p> <p>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</p>
<p><sup>1</sup> 2SHRZ/4HR = 170; 2EHRZ/4HR = 164</p> <p><sup>2</sup> 2SHRZ/4HR = 146; 2EHRZ/4HR = 141</p> <p><sup>3</sup> 2SHRZ/4HR = 119; 2EHRZ/4HR = 127</p> <p><sup>4</sup> 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</p> <p>Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide</p>	

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

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

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

	<p>Sputum-smear-negative on at least 5 pretreatment samples in the course of 1 week</p> <p>Aged 15-75 years</p> <p><i>Exclusion</i></p> <p>Patients whose lesions were considered to be fibrotic and inactive</p> <p>Previous anti-tuberculosis treatment</p>
<b>Intervention</b>	<p><i>2-month regimen</i></p> <p>2SHRZ<sub>7</sub></p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg daily</p> <p>rifampicin: 450 mg daily</p> <p>streptomycin: 750 mg daily</p> <p>pyrazinamide: 1500 mg daily, or 2000 mg daily for patients weighing 50 kg or more</p> <p>All treatment was directly supervised by outpatient clinic or hospital staff</p>
<b>Comparison</b>	<p><i>3-month regimen</i></p> <p>3SHRZ<sub>7</sub></p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide daily for 3 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg daily</p> <p>rifampicin: 450 mg daily</p> <p>streptomycin: 750 mg daily</p>

	<p>pyrazinamide: 1500 mg daily, or 2000 mg daily for patients weighing 50 kg or more</p> <p>All treatment was directly supervised by outpatient clinic or hospital staff</p>
<b>Location</b>	Hong Kong / UK
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	60 months after treatment initiation
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – negative culture at the end of chemotherapy</b></p> <p>Number of smear negative patients to have a negative culture at the end of chemotherapy<sup>3</sup></p> <p>2-month group = 303 of 303</p> <p>3-month group = 307 of 307</p> <p>OR<sup>4</sup> (95% CI) = 0.98 (0.02 to 49.90)</p> <p>i.e. not statistically significant</p> <p>Number of smear negative patients with 1 or more initial positive culture<sup>2</sup> to have a negative culture at the end of chemotherapy</p> <p>2-month group = 71 of 71</p> <p>3-month group = 68 of 68</p> <p>OR<sup>4</sup> (95% CI) = 1.04 (0.02 to 53.35)</p> <p>i.e. not statistically significant</p> <p>Number of smear negative patients with all cultures initially negative<sup>3</sup> to have a negative culture at the end of chemotherapy</p> <p>2-month group = 161 of 161</p> <p>3-month group = 161 of 161</p>

	<p>OR<sup>4</sup> (95% CI) = 1.00 (0.02 to 50.71)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>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</p> <p>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</p> <p>Number of smear negative patients to experience relapse<sup>3</sup></p> <p>2-month group = 45 of 303</p> <p>3-month group = 21 of 307</p> <p><b>OR<sup>4</sup> (95% CI) = 2.38 (1.38 to 4.10)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of smear negative patients to experience bacteriologically confirmed relapse<sup>3</sup></p> <p>2-month group = 30 of 303</p> <p>3-month group = 13 of 307</p> <p><b>OR<sup>4</sup> (95% CI) = 2.49 (1.27 to 4.86)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of smear negative patients with 1 or more initial positive culture<sup>2</sup> to experience relapse</p> <p>2-month group = 23 of 71</p> <p>3-month group = 9 of 68</p> <p><b>OR<sup>4</sup> (95% CI) = 3.14 (1.33 to 7.42)</b></p>

	<p><b>i.e. statistically significant</b></p> <p>Number of smear negative patients with 1 or more initial positive culture<sup>2</sup> to experience bacteriologically confirmed relapse</p> <p>2-month group = 16 of 71</p> <p>3-month group = 7 of 68</p> <p>OR<sup>4</sup> (95% CI) = 2.54 (0.97 to 6.62)</p> <p>i.e. not statistically significant</p> <p>Number of smear negative patients with all cultures initially negative<sup>3</sup> to experience relapse</p> <p>2-month group = 17 of 161</p> <p>3-month group = 11 of 161</p> <p>OR<sup>4</sup> (95% CI) = 1.61 (0.73 to 3.55)</p> <p>i.e. not statistically significant</p> <p>Number of smear negative patients with all cultures initially negative<sup>3</sup> to experience bacteriologically confirmed relapse</p> <p>2-month group = 10 of 161</p> <p>3-month group = 5 of 161</p> <p>OR<sup>4</sup> (95% CI) = 2.07 (0.69 to 6.19)</p> <p>i.e. not statistically significant</p>
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	Full treatment period
<b>Outcomes</b>	<b>Adverse events – any</b>



<p><b>measures and effect size</b></p>	<p>Number of smear negative patients<sup>3</sup> to experience any adverse reaction</p> <p>2-month group = 76 of 303</p> <p>3-month group = 98 of 307</p> <p>OR<sup>4</sup> (95% CI) = 0.71 (0.50 to 1.02)</p> <p>i.e. not statistically significant</p> <p>note: most adverse reactions were reported by the authors to be “trivial or mild cutaneous, vestibular or gastrointestinal episodes”</p> <hr/> <p><b>Adverse events – requiring withdrawal of one or more drug</b></p> <p>Number of smear negative patients<sup>3</sup> to experience any adverse reaction requiring the withdrawal of one or more drug</p> <p>2-month group = 6 of 303</p> <p>3-month group = 9 of 307</p> <p>OR<sup>4</sup> (95% CI) = 0.67 (0.24 to 1.90)</p> <p>i.e. not statistically significant</p>
<p><b>Source of funding</b></p>	<p>No details given</p>
<p><b>Comments</b></p>	<p>Population does not exactly match the population of interest:</p> <p>children also included</p> <p>some cases were drug resistant at baseline (4.1%)</p> <p>Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol</p>
<p><sup>1</sup> Data not extracted for the ‘selective chemotherapy’ or 12 month (3SPH<sub>7</sub>/9SH<sub>2</sub>) groups as they both used regimens containing PAS, a drug not licensed for use in the UK</p> <p><sup>2</sup> Extracted only data for those with drug susceptible tuberculosis</p> <p><sup>3</sup> This population may include both drug susceptible and drug resistant cases</p>	

<sup>4</sup> 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

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population does not exactly match the population of interest:</p> <ul style="list-style-type: none"> <li>may be some children included (inclusion criteria = ages 15 to 75 years)</li> <li>may be some drug resistant cases amongst the culture negative patients</li> <li>some possibly 'inactive' tuberculosis at baseline</li> </ul> <p>Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol</p> <p>Randomisation, allocation concealment and blinding were unclear</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Unclear if groups were comparable for treatment completion and availability of outcome data</p> <p>Did not follow the intent-to-treat principle</p>
<b>Number of patients</b>	<p>Admitted = 2020</p> <p>Analysed = 1692<sup>1</sup></p> <p>3-month regimens = 759<sup>2</sup></p> <p>4-month regimens = 743<sup>2</sup></p>

	<p>6-month regimen = 190</p> <p>Patients with one or more of their initial cultures positive that were drug susceptible = 502</p> <p>4-month regimens = 325<sup>2</sup></p> <p>6-month regimen = 177</p> <p>Patients with all cultures initially negative = 1118<sup>3</sup></p> <p>3-month regimens = 759<sup>2</sup></p> <p>4-month regimen = 359</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Presented at chest clinic with respiratory symptoms</p> <p>Radiographically active</p> <p>Sputum-smear-negative on at least 5 pretreatment samples in the course of 1 week</p> <p>Aged 15-75 years</p> <p>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</p> <p><i>Exclusion</i></p> <p>Patients whose lesions were considered to be fibrotic and inactive</p> <p>Previous anti-tuberculosis treatment</p>
<p><b>Intervention 1</b></p>	<p><i>3-month regimens</i></p> <p>3SHRZ<sub>7</sub></p> <p>only patients with all cultures initially negative</p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide daily for 3 months</p>

	<p>3SHRZ<sub>3</sub></p> <p>only patients with all cultures initially negative</p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide thrice-weekly for 3 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg</p> <p>rifampicin: 450 mg, or 600 mg for patients weighing 50 kg or more</p> <p>streptomycin: 750 mg</p> <p>pyrazinamide: 1500 mg, or 2000 mg for patients weighing 50 kg or more</p> <p>All treatment was directly supervised by outpatient clinic or hospital staff</p>
<p><b>Intervention 2</b></p>	<p><i>4-month regimens</i></p> <p>4SHRZ<sub>7</sub></p> <p>patients with all cultures initially negative <i>or</i> patients with one or more of their initial cultures positive</p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide daily for 4 months</p> <p>4SHRZ<sub>3</sub></p> <p>only patients with one or more of their initial cultures positive</p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide thrice-weekly for 4 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg</p> <p>rifampicin: 450 mg, or 600 mg for patients weighing 50 kg or more</p> <p>streptomycin: 750 mg</p> <p>pyrazinamide: 1500 mg, or 2000 mg for patients weighing 50 kg or more</p>

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

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

	<p>6-month regimen = 4 of 190</p> <p>&lt;6 months<sup>4</sup> vs 6 months:</p> <p>OR<sup>5</sup> (95% CI) = 1.01 (0.35 to 2.89)</p> <p>i.e. not statistically significant</p> <p>Number of participants with 1 or more initial positive culture<sup>2</sup> to experience relapse</p> <p>4-month group = 7 of 325</p> <p>6-month group = 8 of 177</p> <p>OR<sup>5</sup> (95% CI) = 0.47 (0.17 to 1.30)</p> <p>i.e. not statistically significant</p> <p>Number of participants with 1 or more initial positive culture<sup>2</sup> to experience bacteriologically confirmed relapse</p> <p>4-month group = 5 of 325</p> <p>6-month group = 3 of 177</p> <p>OR<sup>5</sup> (95% CI) = 0.90 (0.21 to 3.84)</p> <p>i.e. not statistically significant</p> <p>Number of participants with all cultures initially negative<sup>3</sup> to experience relapse</p> <p>3-month group = 48 of 759</p> <p>4-month group = 12 of 359</p> <p><b>OR<sup>5</sup> (95% CI) = 1.95 (1.02 to 3.72)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of participants with all cultures initially negative<sup>3</sup> to experience bacteriologically confirmed relapse</p> <p>3-month group = 20 of 759</p>
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	<p>4-month group = 4 of 359</p> <p>OR<sup>5</sup> (95% CI) = 2.40 (0.81 to 7.08)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – any</b></p> <p>Number of participants<sup>3</sup> to experience any adverse reaction</p> <p>3-month regimens = 212 of 759<sup>2</sup></p> <p>4-month regimens = 250 of 743<sup>2</sup></p> <p>6-month regimen = 81 of 190</p> <p>&lt;6 months<sup>4</sup> vs 6 months:</p> <p><b>OR<sup>5</sup> (95% CI) = 0.60 (0.44 to 0.81)</b></p> <p><b>i.e. statistically significant</b></p>
	<p><b>Adverse events – requiring withdrawal of one or more drug</b></p> <p>Number of participants<sup>3</sup> to experience any adverse reaction requiring the withdrawal of one or more drug</p> <p>3-month regimens = 37 of 759<sup>2</sup></p> <p>4-month regimens = 34 of 743<sup>2</sup></p> <p>6-month regimen = 6 of 190</p> <p>&lt;6 months<sup>4</sup> vs 6 months:</p> <p>OR<sup>5</sup> (95% CI) = 1.52 (0.65 to 3.55)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – requiring temporary interruption of treatment</b></p> <p>Number of participants<sup>3</sup> to experience any adverse reaction requiring temporary interruption of treatment</p>



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

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

	<p>may be some children included (inclusion criteria = ages 15 to 75 years)</p> <p>may be some drug resistant cases amongst the culture negative patients</p> <p>some possibly 'inactive' tuberculosis at baseline</p> <p>Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol</p>
<p><sup>1</sup> Includes some drug resistant tuberculosis</p> <p><sup>2</sup> Data for regimens of the same duration were pooled by the author</p> <p><sup>3</sup> Population may include both drug susceptible and drug resistant cases</p> <p><sup>4</sup> Reviewer pooled the 3- and 4- month arms to produce a comparison of 6 months to less than 6 months of treatment</p> <p><sup>5</sup> Odds ratio and 95% confidence intervals calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide</p>	

### 1.3.5 Mehotra, 1982

<b>Bibliographic reference</b>	Mehotra ML (1982) Agra study of short-course chemotherapy in pulmonary tuberculosis patients. Indian Journal of Tuberculosis 29(1): 29-39
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>interventions contain streptomycin but lack ethambutol</p> <p>Method of randomisation, allocation concealment and blinding were unclear</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>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</p>

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

	<p>Dosing:</p> <p>isoniazid: 5–8 mg/kg of body weight/day</p> <p>rifampin: 10 mg/kg of body weight/day</p> <p>streptomycin: 750 mg/day</p> <p>pyrazinamide: 25–35 mg/kg of body weight/day</p> <p>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 (&lt;35 kg):</p> <p>isoniazid: 200 mg/day</p> <p>rifampin: 300 mg/day</p> <p>pyrazinamide: 10 g/day</p> <p>streptomycin: 500mg/day</p> <p>until the patient achieved a weight of 36 kg</p> <p>All treatment was directly supervised and ambulatory</p> <p>After treatment completion and during follow-up, patients received placebo tablets of calcium lactate</p>
<p><b>Comparison</b></p>	<p><i>4.5-month regimen</i></p> <p>3RSZH<sub>6</sub>/1.5RH<sub>6</sub></p> <p>isoniazid, rifampicin, streptomycin and pyrazinamide 6 days/week for 3 months</p> <p>isoniazid and rifampicin 6 days/week for 1.5 months</p> <p>Dosing:</p> <p>isoniazid: 5–8 mg/kg of body weight/day</p> <p>rifampin: 10 mg/kg of body weight/day</p>

	<p>streptomycin: 750 mg/day</p> <p>pyrazinamide: 25–35 mg/kg of body weight/day</p> <p>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 (&lt;35 kg):</p> <p>isoniazid: 200 mg/day</p> <p>rifampin: 300 mg/day</p> <p>pyrazinamide: 10 g/day</p> <p>streptomycin: 500mg/day</p> <p>until the patient achieved a weight of 36 kg</p> <p>All treatment was directly supervised and ambulatory</p> <p>After treatment completion and during follow-up, patients received placebo tablets of calcium lactate</p>
<b>Location</b>	India
<b>Length of follow up</b>	1 year after treatment completion
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – culture conversion</b></p> <p>Number of patients to be culture-negative after 3 months of chemotherapy</p> <p>3-month regimen = 58 of 58</p> <p>4.5-month regimen = 68 of 68</p> <p>OR<sup>2</sup> (95% CI) = 0.85 (0.02 to 43.72)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 0.54 (0.28 to 1.04)</p>

	<p>i.e. not statistically significant</p> <p><b>Changes in signs and symptoms – radiographic status</b></p> <p>Number of patients to experience deterioration in radiographic appearance 6 months after treatment initiation</p> <p>3-month regimen = 0 of 55</p> <p>4.5-month regimen = 0 of 64</p> <p>OR<sup>2</sup> (95% CI) = 1.16 (0.02 to 59.54)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 0.98 (0.02 to 49.83)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience no change in radiographic appearance 6 months after treatment initiation</p> <p>3-month regimen = 0 of 55</p> <p>4.5-month regimen = 1 of 64</p> <p>OR<sup>2</sup> (95% CI) = 0.38 (0.02 to 9.55)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 0.32 (0.01 to 8.02)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience moderate regression in radiographic appearance 6 months after treatment initiation</p> <p>3-month regimen = 31 of 55</p> <p>4.5-month regimen = 39 of 64</p>
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	<p>OR<sup>2</sup> (95% CI) = 0.83 (0.40 to 1.72)  i.e. not statistically significant  <i>Intent-to-treat analysis</i><sup>3</sup>  OR<sup>2</sup> (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<sup>2</sup> (95% CI) = 1.29 (0.62 to 2.69)  i.e. not statistically significant  <i>Intent-to-treat analysis</i><sup>3</sup>  OR<sup>2</sup> (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<sup>2</sup> (95% CI) = 0.95 (0.35 to 2.61)  i.e. not statistically significant  <i>Intent-to-treat analysis</i><sup>3</sup>  OR<sup>2</sup> (95% CI) = 1.30 (0.61 to 2.76)  i.e. not statistically significant</p>
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	<p>Number of patients to experience marked regression in radiographic appearance 18 months after treatment initiation</p> <p>3-month regimen = 20 of 35</p> <p>4.5-month regimen = 16 of 27</p> <p>OR<sup>2</sup> (95% CI) = 0.92 (0.33 to 2.54)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 1.29 (0.62 to 2.68)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>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)</p> <p>Number of patients to experience relapse</p> <p>3-month regimen = 1 of 40</p> <p>4.5-month regimen = 1 of 34</p> <p>OR<sup>2</sup> (95% CI) = 0.85 (0.05 to 14.06)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 0.98 (0.06 to 15.88)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – requiring treatment interruption</b></p>

	<p>Criteria used to identify drug toxicity were extreme intolerance, challenge, and clinical observation of toxic reactions</p> <p>Number of patients to experience adverse events requiring treatment interruption</p> <p>3-month regimen = 5 of 71</p> <p>4.5-month regimen = 2 of 68</p> <p>OR<sup>2</sup> (95% CI) = 2.50 (0.47 to 13.35)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 2.53 (0.48 to 13.39)</p> <p>i.e. not statistically significant</p>
	<p><b>Adherence – treatment default</b></p> <p>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</p> <p>Number of patients to default</p> <p>3-month regimen = 8 of 71</p> <p>4.5-month regimen = 7 of 68</p> <p>OR<sup>2</sup> (95% CI) = 1.11 (0.38 to 3.24)</p> <p>i.e. not statistically significant</p> <p><i>Intent-to-treat analysis</i><sup>3</sup></p> <p>OR<sup>2</sup> (95% CI) = 1.13 (0.39 to 3.26)</p> <p>i.e. not statistically significant</p>
<p><b>Source of funding</b></p>	<p>Pfizer Limited, India, supplied the placebo tablets</p>

<b>Comments</b>	Intervention does not exactly match the intervention of interest: interventions contain streptomycin but lack ethambutol
<p><sup>1</sup> Regimens that did not contain rifampicin throughout (3RSZH/1.5SHZ) or that contained ethionamide (3RSZHE<sup>ide</sup> and 3RSZHE<sup>ide</sup>/1.5RH), which is not licensed for use in the UK, were not extracted by the reviewer</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals calculated by reviewer</p> <p><sup>3</sup> 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</p> <p>Abbreviations: CI, confidence interval; E<sup>ide</sup>, ethionamide; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide</p>	

### 1.3.6 Nayar et al, 1988

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT (field study)
<b>Study quality</b>	<p>Age of participants is not clear</p> <p>Interventions do not use the 4 standard recommended drugs: the regimens are missing ethambutol</p> <p>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</p> <p>Randomisation, allocation concealment and blinding were unclear</p> <p>Unclear if groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for treatment completion and availability of outcome data</p> <p>Did not follow the intent-to-treat principle</p> <p>Relapse was the only outcome that could be extracted because the authors reported all other outcomes such that the</p>

	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
<b>Number of patients</b>	<p>Eligible for intake = 381<sup>1</sup></p> <p>Available for assessment = 206</p> <p>6-month regimen = 98</p> <p>8-month regimen = 108</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Symptomatic pulmonary tuberculosis - identified during door-to-door survey</p> <p><i>Diagnostic criteria</i></p> <p>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</p> <p>Samples were subjected to direct microscopy by Ziehl Neelson's method and cultured on Lowenstein Jensen medium</p> <p>For analysis, symptomatics positive by culture only were considered as bacillary-positive cases</p> <p>Those culture-negative at one examination but positive subsequently were categorised as positive</p>
<b>Intervention</b>	<p><i>6-month regimen</i></p> <p>2HRZ<sub>2</sub>/4HR<sub>2</sub></p> <p>for participants in rural areas</p> <p>isoniazid, rifampicin and pyrazinamide twice-weekly for 2 months</p> <p>isoniazid and rifampicin twice-weekly for a further 4 months</p> <p>Dosing:</p> <p>isoniazid: 600 mg/day</p> <p>rifampicin: 600 mg/day</p>

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

	i.e. not statistically significant
<b>Source of funding</b>	Indian Council of Medical Research
<b>Comments</b>	Age of participants is not clear Interventions do not use the 4 standard recommended drugs: the regimens are missing ethambutol
<p><sup>1</sup> 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</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals have been calculated by the reviewer</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide</p>	

### 1.3.7 Perriens et al, 1995

<b>Bibliographic reference</b>	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. <i>New England Journal of Medicine</i> 332(12): 779-84
<b>Study type</b>	RCT
<b>Study quality</b>	<p>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</p> <p>Method of randomisation and allocation concealment unclear</p> <p>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)</p> <p>Only participants were blinded</p> <p>Groups were statistically comparable at the baseline, although the median CD4+ count was higher in the 12-month group (413 vs 338 cells/mm<sup>3</sup>)</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for treatment completion and availability of outcome data</p>

	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												
<b>Number of patients</b>	<p>Randomised = 247</p> <p>6-month regimen = 123</p> <p>12-month regimen = 124</p> <p>Relapse data available = 240</p> <p>6-month regimen = 121</p> <p>12-month regimen = 119</p>												
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>HIV-seropositive patients</p> <p>First episode of smear- and culture-positive pulmonary tuberculosis</p> <p><i>Baseline characteristics</i></p> <table border="1"> <thead> <tr> <th></th> <th><b>6-month regimen</b></th> <th><b>12-month regimen</b></th> </tr> </thead> <tbody> <tr> <td>Male sex – no. (%)</td> <td>52 (43.0)</td> <td>45 (37.8)</td> </tr> <tr> <td>Mean (<math>\pm</math> SD) age – years</td> <td>31.7<math>\pm</math>7.2</td> <td>29.8<math>\pm</math>6.5</td> </tr> <tr> <td>Median CD4+ count at the start of treatment – cells/mm<sup>3</sup></td> <td>413</td> <td>338</td> </tr> </tbody> </table>		<b>6-month regimen</b>	<b>12-month regimen</b>	Male sex – no. (%)	52 (43.0)	45 (37.8)	Mean ( $\pm$ SD) age – years	31.7 $\pm$ 7.2	29.8 $\pm$ 6.5	Median CD4+ count at the start of treatment – cells/mm <sup>3</sup>	413	338
	<b>6-month regimen</b>	<b>12-month regimen</b>											
Male sex – no. (%)	52 (43.0)	45 (37.8)											
Mean ( $\pm$ SD) age – years	31.7 $\pm$ 7.2	29.8 $\pm$ 6.5											
Median CD4+ count at the start of treatment – cells/mm <sup>3</sup>	413	338											
<b>Intervention</b>	<p><i>6-month regimen</i></p> <p>2HRZE<sub>7</sub>/4HR<sub>7</sub>/6placebo</p> <p>isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months</p>												

	<p>isoniazid and rifampicin twice-weekly for a further 4 months</p> <p>placebo for the final 6 months</p> <p>Dosing:</p> <p>initial phase:</p> <p>combination tablets (120 mg rifampicin, 50 mg isoniazid and 300 mg pyrazinamide per tablet): 1 tablet/10 kg of body weight/day</p> <p>ethambutol: 3 400 mg tablets/day, or 2 if the body weight was less than 50 kg</p> <p>continuation phase:</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the body weight was less than 50 kg</p> <p>isoniazid: 15 mg/kg of body weight/day</p> <p>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</p> <p>No patients received ART at any time during the study</p>
<p><b>Comparison</b></p>	<p><i>12-month regimen</i></p> <p>2HRZE<sub>7</sub>/10HR<sub>7</sub></p> <p>isoniazid, rifampicin, pyrazinamide and ethambutol daily for 2 months</p> <p>isoniazid and rifampicin twice-weekly for a further 10 months</p> <p>Dosing:</p> <p>initial phase:</p> <p>combination tablets (120 mg rifampicin, 50 mg isoniazid and 300 mg pyrazinamide per tablet): 1 tablet/10 kg of body weight/day</p> <p>ethambutol: 3 400 mg tablets/day, or 2 if the body weight was less than 50 kg</p>



	<p>continuation phase:</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the body weight was less than 50 kg</p> <p>isoniazid: 15 mg/kg of body weight/day</p> <p>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</p> <p>No patients received ART at any time during the study</p>
<b>Length of follow up</b>	24 months after treatment initiation
<b>Location</b>	Zaire
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of patients to die from tuberculosis</p> <p>6-month regimen = 1 of 123</p> <p>12-month regimen = 0 of 124</p> <p>OR<sup>1</sup> (95% CI) = 3.05 (0.12 to 75.58)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>Number of patients to experience relapse</p> <p>6-month regimen = 1 of 123</p> <p>12-month regimen = 9 of 124</p> <p><b>OR<sup>1</sup> (95% CI) = 0.10 (0.01 to 0.84)</b></p> <p><b>i.e. statistically significant</b></p>
<b>Source of funding</b>	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)
<b>Comments</b>	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
<p><sup>1</sup> Odds ratio and 95% confidence intervals have been calculated by the reviewer</p> <p>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</p>	

### 1.3.8 Research Committee of the Tuberculosis Association of India, 1984

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>some regimens contain streptomycin, and all regimens lack ethambutol</p> <p>doses used are inconsistent with those listed in the British National Formulary – isoniazid dose is higher than recommended</p> <p>Method of randomisation, allocation concealment and blinding were unclear</p> <p>Unclear if groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Unclear if groups were comparable for treatment completion and availability of outcome data</p> <p>Did not follow the intent-to-treat principle</p>
<b>Number of patients</b>	<p>Total cases 'inducted' = 175<sup>1</sup></p> <p>Smear-negative patients for whom data is available at treatment completion = 126</p> <p>3-month regimens = 56<sup>2</sup></p>

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

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

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

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

<b>Source of funding</b>	Lepetit Laboratories, Italy, and Ranbaxy Laboratories, Delhi, supplied the rifampicin Brocco Industries, Italy, supplied the pyrazinamide
<b>Comments</b>	Intervention does not exactly match the intervention of interest: some regimens contain streptomycin, and all regimens lack ethambutol
<p><sup>1</sup> 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</p> <p><sup>2</sup> 2HRZ/1HR/3pla = 29; 2HRZS/1HR/3pla = 27</p> <p><sup>3</sup> 2HRZ/4HR = 37; 2HRZS/4HR = 33</p> <p><sup>4</sup> 2HRZ/1HR/3pla = 22; 2HRZS/1HR/3pla = 30</p> <p><sup>5</sup> 2HRZ/4HR = 25; 2HRZS/4HR = 25</p> <p><sup>6</sup> Data for regimens of the same duration were pooled by the reviewer</p> <p><sup>7</sup> Odds ratio and 95% confidence intervals calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; pla, placebo; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide</p>	

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

<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population does not exactly match the population of interest: some children may also have been included</p> <p>some cases were drug resistant; data for these were not extracted by the reviewer</p> <p>Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol</p> <p>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)</p>

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



	<p>2SHRZ<sub>7</sub>/2HR<sub>7</sub> isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months</p> <p>2SHRZ<sub>7</sub>/2HRZ<sub>7</sub> isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid, rifampicin and pyrazinamide daily for a further 2 months</p> <p>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</p> <p>All patients received every dose of chemotherapy under the direct supervision of hospital or outpatient clinic staff</p>
<p><b>Comparison</b></p>	<p><i>6-month regimens</i><sup>7</sup></p> <p>2SHRZ<sub>7</sub>/4HR<sub>7</sub> isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid and rifampicin daily for a further 4 months</p> <p>2SHRZ<sub>7</sub>/4HRZ<sub>7</sub> isoniazid, rifampicin, streptomycin and pyrazinamide daily for 2 months isoniazid, rifampicin and pyrazinamide daily for a further 2 months</p> <p>Dosing: isoniazid: 300 mg/day</p>

	<p>rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 50 kg on admission</p> <p>streptomycin: 750 mg intramuscularly</p> <p>pyrazinamide: 2000 mg/day, or 1500 mg/day if the patient weighed less than 50 kg on admission</p> <p>All patients received every dose of chemotherapy under the direct supervision of hospital or outpatient clinic staff</p>
<b>Location</b>	Singapore
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	Full treatment period
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – favourable response</b></p> <p>Number of participants whose response to chemotherapy was defined as 'favourable' at the end of treatment</p> <p>4-month regimens = 161 of 161</p> <p>6-month regimens = 169 of 169</p> <p>OR<sup>6</sup> (95% CI) = 0.95 (0.02 to 48.31)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events</b></p> <p>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"</p> <p>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</p>
<b>Bibliographic reference</b>	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

<b>Length of follow up</b>	5 to 8 years after treatment initiation
<b>Outcomes measures and effect size</b>	<p><b>Relapse</b></p> <p>Defined as a culture growing 10 or more colonies in 2 different months during any 3-month period during follow-up</p> <p>Number of participants to experience relapse during follow-up</p> <p>4-month regimens = 20 of 131</p> <p>6-month regimens = 3 of 138</p> <p><b>OR<sup>6</sup> (95% CI) = 8.11 (2.35 to 28.00)</b></p> <p><b>i.e. statistically significant</b></p>
<b>Source of funding</b>	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
<b>Comments</b>	<p>Population does not exactly match the population of interest:</p> <p>some children may also have been included</p> <p>some cases were drug resistant; data for these were not extracted by the reviewer</p> <p>Intervention does not exactly match the intervention of interest: interventions contain streptomycin and lack ethambutol</p>
<p><sup>1</sup> Includes both drug susceptible and drug resistant cases</p> <p><sup>2</sup> 2SHRZ/2HR = 81; 2SHRZ/2HRZ = 80</p> <p><sup>3</sup> 2SHRZ/4HR = 84; 2SHRZ/4HRZ = 85</p> <p><sup>4</sup> 2SHRZ/2HR = 70; 2SHRZ/2HRZ = 61</p> <p><sup>5</sup> 2SHRZ/4HR = 67; 2SHRZ/4HRZ = 71</p> <p><sup>6</sup> Odds ratio and 95% confidence intervals calculated by the reviewer</p> <p><sup>7</sup> Data for regimens of the same length were pooled by the reviewer</p>	

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

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population did not exactly match the population of interest:</p> <ul style="list-style-type: none"> <li>may be some children in the included population (inclusion criteria = 15 years or more)</li> <li>some extrapulmonary tuberculosis, although limited to pleural or lymph node tuberculosis</li> <li>some drug resistant tuberculosis</li> </ul> <p>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</p> <p>Doses of antituberculosis drugs used are inconsistent with those listed in the British National Formulary – isoniazid and ethambutol doses are higher than recommended</p> <p>Appropriate method of randomisation used: computer-generated random allocation sequence</p> <p>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</p> <p>Unblinded</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>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</p>

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

	<b>Laboratory criteria</b>		
	haemoglobin >7 g/l		
	granulocyte count >1.1 x 10 <sup>9</sup> /l		
	platelet count > 100 x 10 <sup>9</sup> /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			
<i>Diagnostic criteria</i>			
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			
<i>Exclusion</i>			
Moribund condition			
Pregnancy			
<i>Baseline characteristics</i>			
		<b>6-month regimen</b>	<b>9-month regimen</b>
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 <sup>3</sup>	152 (80–304)	167 (88–280)
	CD4+ count <200 cells/mm <sup>3</sup> – %	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)

	<table border="1"> <tr> <td>hilar adenopathy – n (%)</td> <td>29 (25)</td> <td>15 (14)</td> </tr> <tr> <td>miliary tuberculosis – n (%)</td> <td>7 (6)</td> <td>7 (6)</td> </tr> <tr> <td>cavities – n (%)</td> <td>19 (16)</td> <td>20 (18)</td> </tr> <tr> <td>others – n (%)</td> <td>10 (9)</td> <td>7 (6)</td> </tr> </table>	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)
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)											
<b>Intervention</b>	<p><i>6-month regimen</i></p> <p>2HRZE/4HR</p> <p>isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months</p> <p>isoniazid and rifampicin thrice-weekly for a further 4 months</p> <p>Dosing:</p> <p>isoniazid: 600 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 60 kg</p> <p>pyrazinamide: 1500 mg/day</p> <p>ethambutol: 1200 mg/day</p> <p>Co-trimoxazole prophylaxis was given to all patients with CD4+ counts &lt;250 cells/mm<sup>3</sup></p> <p>Patients did not receive ART during antituberculosis chemotherapy</p> <p>The taking of all doses in the intensive phase was directly observed by the study staff</p> <p>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</p>												
<b>Comparison</b>	<p><i>9-month regimen</i></p> <p>2HRZE/7HR</p>												



	<p>isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months</p> <p>isoniazid and rifampicin thrice-weekly for a further 7 months</p> <p>Dosing:</p> <p>isoniazid: 600 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day if the patient weighed less than 60 kg</p> <p>pyrazinamide: 1500 mg/day</p> <p>ethambutol: 1200 mg/day</p> <p>Co-trimoxazole prophylaxis was given to all patients with CD4+ counts &lt;250 cells/mm<sup>3</sup></p> <p>Patients did not receive ART during antituberculosis chemotherapy</p> <p>The taking of all doses in the intensive phase was directly observed by the study staff</p> <p>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</p>
<b>Length of follow up</b>	36 months after treatment initiation
<b>Location</b>	India
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p><i>'Modified ITT analysis'</i><sup>1</sup></p> <p>Number of deaths (all cause)</p> <p>6-month regimen = 33 of 167</p> <p>9-month regimen = 37 of 160</p> <p>OR<sup>2</sup> (95% CI) = 0.82 (0.48 to 1.38)</p> <p>i.e. not statistically significant</p>

	<p><i>Drug sensitive cases only</i></p> <p>Number of deaths (all cause)</p> <p>6-month regimen = 3 of 100</p> <p>9-month regimen = 10 of 97</p> <p>OR<sup>2</sup> (95% CI) = 0.27 (0.07 to 1.01)</p> <p>i.e. not statistically significant</p>
	<p><b>Cure ('favourable response')</b></p> <p>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</p> <p>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</p> <p><i>'Modified ITT analysis'</i></p> <p>Number of patients to achieve a 'favourable response' at the end of treatment</p> <p>6-month regimen = 138 of 167</p> <p>9-month regimen = 122 of 160</p> <p>RR (95% CI) = 1.08 (0.97 to 1.21)</p> <p>p = 0.15</p> <p>OR<sup>2</sup> (95% CI) = 1.48 (0.86 to 2.55)</p> <p>i.e. not statistically significant</p> <p><i>Drug sensitive cases only</i></p> <p>Number of patients to achieve a 'favourable response' at the end of treatment</p> <p>6-month regimen = 85 of 100</p>

	<p>9-month regimen = 75 of 97</p> <p>OR<sup>2</sup> (95% CI) = 1.66 (0.80 to 3.44)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture positive at baseline<sup>1</sup></i></p> <p>Number of patients to achieve a ‘favourable response’ at the end of treatment</p> <p>6-month regimen = 96 of 117</p> <p>9-month regimen = 81 of 110</p> <p>OR<sup>2</sup> (95% CI) = 1.64 (0.87 to 3.09)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture negative at baseline<sup>1</sup></i></p> <p>Number of patients to achieve a ‘favourable response’ at the end of treatment</p> <p>6-month regimen = 28 of 34</p> <p>9-month regimen = 31 of 38</p> <p>OR<sup>2</sup> (95% CI) = 1.05 (0.32 to 3.51)</p> <p>i.e. not statistically significant</p>
	<p><b>Treatment failure</b></p> <p>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+)</p> <p><i>‘Modified ITT analysis’<sup>1</sup></i></p> <p>Number of patients to experience bacteriological failure of chemotherapy</p> <p>6-month regimen = 8 of 167</p>

	<p>9-month regimen = 11 of 160</p> <p>OR<sup>2</sup> (95% CI) = 0.68 (0.27 to 1.74)</p> <p>i.e. not statistically significant</p> <p><i>Drug sensitive cases only</i></p> <p>Number of patients to experience bacteriological failure of chemotherapy</p> <p>6-month regimen = 3 of 100</p> <p>9-month regimen = 7 of 97</p> <p>OR<sup>2</sup> (95% CI) = 0.40 (0.10 to 1.58)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture positive at baseline<sup>1</sup></i></p> <p>Number of patients to experience bacteriological failure of chemotherapy</p> <p>6-month regimen = 8 of 117</p> <p>9-month regimen = 11 of 110</p> <p>OR<sup>2</sup> (95% CI) = 0.66 (0.26 to 1.71)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture negative at baseline<sup>1</sup></i></p> <p>Number of patients to experience bacteriological failure of chemotherapy</p> <p>6-month regimen = 0 of 34</p> <p>9-month regimen = 0 of 38</p> <p>OR<sup>2</sup> (95% CI) = 1.12 (0.02 to 57.77)</p> <p>i.e. not statistically significant</p>
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	<p><b>Relapse</b></p> <p>Bacteriological recurrence was defined by at least 2 positive cultures (at least 1 with a grade of more than 1+)</p> <p>Recurrence was only recorded for those who successfully completed treatment (i.e. achieved a favourable status)</p> <p>Recurrences were classified as:</p> <p>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)</p> <p>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</p> <p><i>'Modified ITT analysis'</i></p> <p>Number of patients to experience bacteriological recurrence</p> <p>6-month regimen = 21 of 167</p> <p>9-month regimen = 8 of 160</p> <p><b>OR<sup>2</sup> (95% CI) = 2.73 (1.17 to 6.36)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of patients who successfully completed treatment to experience bacteriological recurrence</p> <p>6-month regimen = 21 of 138</p> <p>9-month regimen = 8 of 122</p> <p>RR (95% CI) = 2.07 (1.33 to 3.23)</p> <p>p = 0.03</p> <p><b>OR<sup>2</sup> (95% CI) = 2.56 (1.09 to 6.01)</b></p> <p><b>i.e. statistically significant</b></p>
	<b>Adverse events – drug toxicity</b>

	<p><i>'Modified ITT analysis'</i><sup>1</sup></p> <p>Number of patients to experience drug toxicity</p> <p>6-month regimen = 1 of 167</p> <p>9-month regimen = 1 of 160</p> <p>OR<sup>2</sup> (95% CI) = 0.96 (0.06 to 15.45)</p> <p>i.e. not statistically significant</p> <p><i>Drug sensitive cases only</i></p> <p>Number of patients to experience drug toxicity</p> <p>6-month regimen = 1 of 100</p> <p>9-month regimen = 0 of 97</p> <p>OR<sup>2</sup> (95% CI) = 2.93 (0.12 to 73.05)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture positive at baseline</i><sup>1</sup></p> <p>Number of patients to experience drug toxicity</p> <p>6-month regimen = 1 of 117</p> <p>9-month regimen = 0 of 110</p> <p>OR<sup>2</sup> (95% CI) = 2.85 (0.11 to 70.60)</p> <p>i.e. not statistically significant</p> <p><i>Pulmonary tuberculosis only - culture negative at baseline</i><sup>1</sup></p> <p>Number of patients to experience drug toxicity</p> <p>6-month regimen = 0 of 34</p>
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	<p>9-month regimen = 1 of 38  OR<sup>2</sup> (95% CI) = 0.36 (0.01 to 9.20)  i.e. not statistically significant</p>
	<p><b>Adherence – treatment default</b>  <i>‘Modified ITT analysis’<sup>1</sup></i>  Number of patients to default of their treatment for &gt;1 month  6-month regimen = 11 of 167  9-month regimen = 16 of 160  OR<sup>2</sup> (95% CI) = 0.63 (0.29 to 1.41)  i.e. not statistically significant  <i>Drug sensitive cases only</i>  Number of patients to default of their treatment for &gt;1 month  6-month regimen = 5 of 100  9-month regimen = 4 of 97  OR<sup>2</sup> (95% CI) = 1.22 (0.32 to 4.70)  i.e. not statistically significant</p>
<b>Source of funding</b>	<p>None of the authors had a financial relationship with a commercial entity that has an interest in the subject of this paper</p>
<b>Comments</b>	<p>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</p>

	<p>some drug resistant tuberculosis</p> <p>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</p>
<p><sup>1</sup> Data extracted by reviewer from a 'trial profile' flow diagram; diagram was generally difficult to interpret</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals have been calculated by the reviewer</p> <p>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</p>	

### 1.3.11 Teo et al, 2002

<b>Bibliographic reference</b>	Teo SK, Tan KK & Khoo TK (2002) Four-month chemotherapy in the treatment of smear-negative pulmonary tuberculosis: results at 30 and 60 months. <i>Annals, Academy of Medicine Singapore</i> 31: 175-81
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>regimens lack ethambutol</p> <p>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</p> <p>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</p> <p>Unclear if groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for treatment completion and availability of outcome data</p> <p>Did not follow the intent-to-treat principle</p>
<b>Number of patients</b>	<p>Randomised = 113</p> <p>4-month regimen = 59</p>



	<p>6-month regimen = 54</p> <p>Data available after 60 months of follow-up = 79</p> <p>4-month regimen = 41</p> <p>6-month regimen = 38</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>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</p> <p>Positive culture<sup>1</sup></p> <p><i>Exclusion</i></p> <p>Recent or past history of treatment pulmonary tuberculosis</p> <p>History of mental disorder, alcohol or drug abuse</p> <p>Pregnancy</p>
<p><b>Intervention</b></p>	<p><i>4-month regimen</i></p> <p>2HRZ<sub>7</sub>/2HR<sub>7</sub></p> <p>isoniazid, rifampicin and pyrazinamide daily for 2 months</p> <p>isoniazid and rifampicin daily for 2 months</p> <p>Dosing:</p> <p>isoniazid: 300 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg</p> <p>pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg</p> <p>Treatment was given under direct supervision</p>

<b>Comparison</b>	<p><i>6-month regimen</i></p> <p>2HRZ<sub>7</sub>/4HR<sub>3</sub></p> <p>isoniazid, rifampicin and pyrazinamide daily for 2 months</p> <p>isoniazid and rifampicin 3-times weekly for 4 months</p> <p>Dosing:</p> <p>initial phase</p> <p>isoniazid: 300 mg/day</p> <p>rifampicin: 600 mg/day, or 450 mg/day in those weighing less than 50 kg</p> <p>pyrazinamide: 2000 mg/day, or 1500 mg/day in those weighing less than 50 kg</p> <p>continuation phase</p> <p>isoniazid: 15 mg/kg of body weight/day</p> <p>rifampicin: 600 mg/day</p> <p>Treatment was given under direct supervision</p>
<b>Location</b>	Singapore
<b>Length of follow up</b>	60 months after treatment initiation
<b>Outcomes measures and effect size</b>	<p><b>Treatment failure</b></p> <p>Defined as failure of sputum culture conversion towards the end of therapy</p> <p>Number of smear-negative culture-positive patients to experience treatment failure</p> <p>4-month regimen = 0 of 59</p> <p>6-month regimen = 1 of 54</p> <p>OR<sup>2</sup> (95% CI) = 0.30 (0.01 to 7.52)</p>

	<p>i.e. not statistically significant</p> <p><b>Changes in signs and symptoms – radiographic status</b></p> <p>Number of smear-negative culture-positive patients to show no change in radiological status by the end of chemotherapy</p> <p>4-month regimen = 0 of 59</p> <p>6-month regimen = 0 of 54</p> <p>OR<sup>7</sup> (95% CI) = 0.92 (0.02 to 4.97)</p> <p>i.e. not statistically significant</p> <p>Number of smear-negative culture-positive patients to show less than 50% radiological clearing by the end of chemotherapy</p> <p>4-month regimen = 0 of 59</p> <p>6-month regimen = 0 of 54</p> <p>OR<sup>7</sup> (95% CI) = 0.92 (0.02 to 4.97)</p> <p>i.e. not statistically significant</p> <p>Number of smear-negative culture-positive patients to show more than 50% radiological clearing by the end of chemotherapy</p> <p>4-month regimen = 52 of 59</p> <p>6-month regimen = 52 of 54</p> <p>OR<sup>7</sup> (95% CI) = 0.29 (0.06 to 1.44)</p> <p>i.e. not statistically significant</p> <p>Number of smear-negative culture-positive patients to show complete radiological clearing by the end of chemotherapy</p> <p>4-month regimen = 5 of 59</p>
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	<p>6-month regimen = 1 of 54</p> <p>OR<sup>7</sup> (95% CI) = 4.91 (0.55 to 43.42)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>Defined as a clinical and radiological deterioration following therapy with or without bacteriological confirmation</p> <p>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</p> <p>Number of smear-negative culture-positive patients to experience relapse</p> <p>4-month regimen = 0 of 59</p> <p>6-month regimen = 0 of 54</p> <p>OR<sup>2</sup> (95% CI) = 0.92 (0.02 to 4.97)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Supported by a grant from the Ministry of Health, Singapore
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>regimens lack ethambutol</p> <p>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</p>
<p><sup>1</sup> 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)</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide</p>	

**1.3.12 Ziaullah et al, 2004**

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population does not exactly match the population of interest: children also included (for more details, see 'patient characteristics' below)</p> <p>Randomisation, allocation concealment and blinding were unclear</p> <p>Unclear if groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for treatment completion and availability of outcome data, though rate of attrition was high in both groups</p> <p>Sputum conversion, a measure of response to treatment, is a substitute for an outcome of interest (cure, treatment success and treatment failure)</p> <p>Did not follow the intent-to-treat principle</p>
<b>Number of patients</b>	<p>Randomised = 200</p> <p>6-month group = 93</p> <p>9-month group = 107</p> <p>Data available for 'cure' = 95</p> <p>6-month group = 44</p> <p>9-month group = 51</p> <p>Data available for 'treatment failure' = 113</p> <p>6-month group = 44</p> <p>9-month group = 69</p>

	<p>Data available for 'response to treatment - sputum conversion' = 133</p> <p>6-month group = 64</p> <p>9-month group = 69</p> <p>Data available for 'relapse' = 39</p> <p>6-month group = 19</p> <p>9-month group = 24</p>																								
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Pulmonary tuberculosis</p> <p><i>Diagnostic criteria</i></p> <p>Chest x-ray</p> <p>Sputum microscopy</p> <p><i>Exclusion</i></p> <p>Previous anti-tuberculosis treatment</p> <p><i>Baseline characteristics</i></p> <table border="1"> <thead> <tr> <th>Age (years)</th> <th>Male</th> <th>Female</th> <th>Total</th> </tr> </thead> <tbody> <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> </tbody> </table>	Age (years)	Male	Female	Total	5-14	34	32	66	15-29	38	28	66	30-44	13	9	22	45-59	11	11	22	60+	14	10	24
Age (years)	Male	Female	Total																						
5-14	34	32	66																						
15-29	38	28	66																						
30-44	13	9	22																						
45-59	11	11	22																						
60+	14	10	24																						

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

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



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**

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>The interventions did not differ in the two groups by treatment duration alone:</p> <p>initial 3-drug phase was shorter in the 9-month regimen (2 weeks) than in the 12-month regimen (1 month)</p> <p>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</p> <p>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</p> <p>Interventions do not use the 4 standard recommended drugs: the regimens are missing pyrazinamide and ethambutol, and they contain streptomycin</p> <p>Prescribed doses of isoniazid and streptomycin are above that recommended by the British National Formulary</p> <p>A number of outcomes could not be extracted as they were not reported at or after treatment completion:</p>

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

<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Ages 5 months to 13 years</p> <p>Pulmonary TB</p> <p><i>Diagnostic criteria</i></p> <p>Clinical:</p> <p>afternoon fever</p> <p>excessive sweating</p> <p>cough</p> <p>anorexia</p> <p>weight loss</p> <p>Epidemiologic</p> <p>direct contact with a tuberculous adult (bacillary positive or negative)</p> <p>Radiologic</p> <p>parenchymal or mediastinal lymph nodes in chest roentgenograms</p> <p>Immunologic</p> <p>tuberculin test positivity (PPD)</p> <p>Histobacteriologic</p> <p>acid-fast bacilli in the sputum, or gastric washings or in any histologic specimen</p> <p><i>Exclusion</i></p> <p>Poor “family compliance”</p> <p><i>Baseline</i></p>
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		<b>9-month</b> (n = 18)	<b>12-month</b> (n = 15)
	Male/female	12/6	10/5
	Age (mean years $\pm$ SD)	7.6 $\pm$ 3.9	7.7 $\pm$ 4.0
	Diagnostic criteria		
	clinical	18	15
	epidemiologic	14	12
	immunologic	15	12
	radiologic	18	15
	histobacteriologic	2	2
<b>Intervention</b>	<p><i>9-month regimen</i></p> <p>0.5SRH<sub>7</sub>/8.5RH<sub>2</sub></p> <p>daily streptomycin, isoniazid and rifampicin for two weeks</p> <p>twice weekly isoniazid and rifampicin for 8.5 months</p> <p>Dosing:</p> <p>streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g</p> <p>isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg</p> <p>rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg</p> <p>All patients were treated on an outpatient basis</p>		
<b>Comparison</b>	<i>12-month regimen</i>		

	<p>1SRH<sub>7</sub>/8RH<sub>7</sub>/3R<sub>7</sub></p> <p>daily streptomycin, isoniazid and rifampicin 1 month</p> <p>daily isoniazid and rifampicin for 8 months</p> <p>daily rifampicin for 3 months</p> <p>Dosing:</p> <p>streptomycin: 20 mg/kg body weight/dose, intramuscularly, up to 1 g</p> <p>isoniazid: 15 mg/kg body weight/dose, in two divided oral doses, up to 400 mg</p> <p>rifampicin: 15 mg/kg body weight/dose, as a single oral dose, up to 600 mg</p> <p>All patients were treated on an outpatient basis</p>
<b>Length of follow up</b>	12 months after treatment completion
<b>Location</b>	Izmir, Turkey
<b>Outcomes measures and effect size</b>	<p><b>Recurrence</b></p> <p>Number to experience recurrence (based on clinical or radiologic examination) in 12 months after treatment completion:</p> <p>9-month group = 0 of 18</p> <p>12-month group = 0 of 18</p> <p>OR<sup>2</sup> (95% CI) = 1.00 (0.02 to 53.12)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – hepatotoxicity</b></p> <p>Defined as elevated serum aspartate aminotransferase and alanine aminotransferase (note: thresholds not given)</p> <p>Number to experience hepatotoxicity:</p>

	<p>9-month group = 0 of 18            12-month group = 1 of 18            OR<sup>2</sup> (95% CI) = 0.32 (0.01 to 8.27)            i.e. not statistically significant</p> <hr/> <p><b>Adherence</b>            Number excluded due to “poor compliance” (note: definition not provided):            9-month group = 0 of 18            12-month group = 3 of 18            p<sup>1</sup> &gt; 0.05            OR<sup>2</sup> (95% CI) = 0.12 (0.01 to 2.50)            i.e. not statistically significant</p>
<b>Source of funding</b>	Details not given
<b>Comments</b>	<p>Because the interventions vary by dosing frequency in addition to treatment duration, this study is also considered for possible inclusion in review question I</p> <p>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)</p> <p>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</p> <p>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</p> <p>Interventions do not use the 4 standard recommended drugs: the regimens are missing pyrazinamide and ethambutol, and they contain streptomycin</p> <p>A number of outcomes could not be extracted as they were not reported at or after treatment completion:</p>

	<p>therapy period for early clinical response – not relevant to the effectiveness of treatment duration</p> <p>number of participants to show clinical improvement – recorded after 6 months of treatment</p> <p>number of participants to completely resolve – recorded after 6 months of treatment</p> <p>weight gain – recorded after 6 months of treatment</p> <p>note: the data for these can be seen in the evidence tables for review question I</p>
<p><sup>1</sup> Calculated by authors using the chi-square test or student's t-test; <math>p &lt; 0.05</math> was taken as significant</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis</p>	



**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

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> only laboratory staff and those reading chest scans were blinded</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> follow-up period was appropriate (1 to 3 years), although it is unclear if it was the same in each group</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p>

	<p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> antituberculosis regimens do not use all of or just the 4 standard recommended drugs</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> yes – change in bacillary count is a surrogate for cure/treatment success/treatment failure</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>
<b>Number of patients</b>	<p>Randomised = 178</p> <p>prednisolone group = 91</p> <p>antituberculosis chemotherapy alone group = 87</p> <p>Outcome data available for = 178</p> <p>prednisolone group = 91</p> <p>antituberculosis chemotherapy alone group = 87</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Advanced pulmonary tuberculosis causing persistent high-grade fever (<math>\geq 38^{\circ}\text{C}</math>), weight loss (<math>\geq 2</math> kg/week) and/or low serum albumin levels (<math>&lt; 3</math> g/dL)</p> <p>HIV-negative</p> <p><i>Diagnostic criteria</i></p> <p>Confirmed by acid-fast bacilli positivity on smear or culture, and/or granulomatous inflammation with caseous necrosis in the pulmonary biopsy specimen</p> <p>Other febrile causes were excluded by serial blood culture, sputum and urine culture, total body gallium-67</p>

	scintigraphy for occult abscesses, screening for occult malignancy, withholding antituberculosis treatment for 3 days to monitor temperature response, and a trial of intravenous broad-spectrum antibiotics for the same 3 days		
	<i>Exclusion</i>		
	Accompanying uncontrollable hypertension, recalcitrant diabetes, active or recent peptic ulcer or gastrointestinal bleeding, resistant hypokalemia or florid sepsis		
	<i>Baseline</i>		
		<b>Prednisolone group</b> (n = 91)	<b>Antituberculosis chemotherapy alone group</b> (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	
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus prednisolone</i>		

	<p>Prednisolone (40 days)</p> <p>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</p> <p>Antituberculosis chemotherapy:</p> <p>drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR</p> <p>drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given</p> <p>doses not stated</p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy:</p> <p>drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR</p> <p>drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given</p> <p>doses not stated</p>
<b>Length of follow up</b>	1 to 3 years
<b>Location</b>	Izmir, Turkey
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>prednisolone group = 0 of 91</p> <p>antituberculosis chemotherapy alone group = 0 of 87</p> <p>OR<sup>1</sup> (95% CI) = 0.96 (0.02 to 48.73)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – bacillary count</b></p> <p>Number of to experience a drop in bacillary count 50 days after prednisolone was initiated<sup>3</sup></p>

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

	<p>MD<sup>2</sup> = 3.0</p> <p><b>p = 0.002</b></p> <p><b>i.e. statistically significant</b></p>
	<p><b>Changes in signs and symptoms – radiographic improvement</b></p> <p>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):</p> <p>marked (&gt;90%)</p> <p>moderate (50–89%)</p> <p>slight (10–49%)</p> <p>no improvement (&lt;10%)</p> <p>Number of to experience radiographic improvement (marked, moderate or slight) 50 days after prednisolone initiation<sup>3</sup></p> <p>prednisolone group = 91 of 91</p> <p>antituberculosis chemotherapy alone group = 83 of 87</p> <p>OR<sup>1</sup> (95% CI) = 9.86 (0.52 to 185.96)</p> <p>i.e. not statistically significant</p> <p>Number of to experience marked radiographic improvement 50 days after prednisolone initiation<sup>3</sup></p> <p>prednisolone group = 15 of 91</p> <p>antituberculosis chemotherapy alone group = 8 of 87</p> <p>OR<sup>1</sup> (95% CI) = 1.95 (0.78 to 4.86)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p>

	<p>Number of patients to experience radiographic, bacteriologic or clinical relapse during follow-up</p> <p>prednisolone group = 0 of 91</p> <p>antituberculosis chemotherapy alone group = 0 of 87</p> <p>OR<sup>1</sup> (95% CI) = 0.96 (0.02 to 48.73)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Mean difference and 95% confidence interval calculated by reviewer</p> <p><sup>3</sup> Read off graph by reviewer</p> <p>Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; Z, pyrazinamide</p>

### 1.5.2 Mayanja-Kizza et al, 2005

<b>Bibliographic reference</b>	Mayanja-Kizza H, Jones-Lopez E, Okwera A et al (2005) Immuno-adjunct prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. <i>Journal of Infectious Diseases</i> 191(6): 856-65
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>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</p> <p><i>Allocation concealment used?</i></p> <p>assignments were placed in sealed envelopes and drawn sequentially by a study nurse who was not involved with patient care</p>



	<p><i>Blinding used?</i></p> <p>double-blind</p> <p><i>Groups comparable at baseline?</i></p> <p>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</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>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</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
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<p><b>Number of patients</b></p>	<p>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</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i>  Initial episodes of acid fast smear–positive pulmonary tuberculosis  HIV-infected patients  &gt;18 years of age  <i>Exclusion</i>  Previous treatment for tuberculosis  Advanced HIV infection (World Health Organization stage IV)  Karnofsky performance score &lt;80  Peripheral blood CD4+ T cell count &lt;200 cells/μL  Kaposi sarcoma  Active herpes zoster  Glucose level &gt;160 mg/dL or diabetes mellitus by history</p>

	Serum aminotransferase level >65 IU/L		
	Potassium level >5.5 mmol/L		
	Positive $\beta$ -urinary human chorionic gonadotrophin test		
	Previous use of immunomodulators		
	Presence or history of hypertension		
	Psychiatric disease		
	Peptic ulcer disease		
	Pancreatitis		
	<i>Baseline</i>		
	<b>Prednisolone group</b> (n = 93)	<b>Placebo group</b> (n = 94)	
Sex			
males, n (%)	55 (59)	58 (62)	
BCG scar present, n (%)	40 (44)	42 (46)	
PPD induration			
$\geq 5$ mm, n (%)	83 (89)	79 (84)	
mean $\pm$ SD, mm	16 $\pm$ 5.4	16 $\pm$ 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 <sup>2</sup>	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 <sup>3</sup>	8±2.8	7.8±2.8
	Lymphocyte count (mean±SD), cells/mm <sup>3</sup>	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)	
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (8 weeks)</p> <p>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</p> <p>Antituberculosis chemotherapy: HRZE – duration and dosing unclear</p>				

	Medications were self-administered
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (8 weeks)</p> <p>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</p> <p>Antituberculosis chemotherapy: HRZE – duration and dosing unclear</p> <p>Medications were self-administered</p>
<b>Length of follow up</b>	36 months
<b>Location</b>	Uganda
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>prednisolone group = 17 of 93</p> <p>placebo group = 14 of 94</p> <p>OR<sup>1</sup> (95% CI) = 1.28 (0.59 to 2.77)</p> <p>i.e. not statistically significant</p>
	<p><b>Event-free survival</b></p> <p>Number of patients to survive to 36 months without significant adverse event</p> <p>prednisolone group = 36 of 93</p> <p>placebo group = 40 of 94</p> <p>OR<sup>1</sup> (95% CI) = 0.85 (0.48 to 1.53)</p> <p>i.e. not statistically significant</p>

	<p><b>Treatment failure</b></p> <p>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</p> <p>Number of patients to experience treatment failure</p> <p>prednisolone group = 1 of 93</p> <p>placebo group = 1 of 94</p> <p>OR<sup>1</sup> (95% CI) = 1.01 (0.06 to 16.41)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – sputum conversion</b></p> <p>Number of patients to have a sputum culture negative for <i>M. tuberculosis</i> after 1 month of treatment</p> <p>prednisolone group = 58 of 93</p> <p>placebo group = 35 of 94</p> <p><b>OR<sup>1</sup> (95% CI) = 2.79 (1.54 to 5.05)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of patients to have a sputum culture negative for <i>M. tuberculosis</i> after 2 months of treatment</p> <p>prednisolone group = 80 of 93</p> <p>placebo group = 80 of 94</p> <p>OR<sup>1</sup> (95% CI) = 1.08 (0.48 to 2.44)</p> <p>i.e. not statistically significant</p>
	<p><b>Recurrence</b></p> <p>Defined as the recurrence of active TB after the establishment of cure</p>

	<p>Number of patients to experience recurrence within 2 years of initiating treatment</p> <p>prednisolone group = 8 of 93</p> <p>placebo group = 11 of 94</p> <p>OR<sup>1</sup> (95% CI) = 0.71 (0.27 to 1.85)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events</b></p> <p>Number of patients to experience any adverse event</p> <p>prednisolone group = 87 of 93</p> <p>placebo group = 82 of 94</p> <p>OR<sup>1</sup> (95% CI) = 2.55 (0.86 to 7.54)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience a severe or life-threatening adverse event</p> <p>prednisolone group = 22 of 93</p> <p>placebo group = 18 of 94</p> <p>OR<sup>1</sup> (95% CI) = 1.31 (0.65 to 2.64)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>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</p>	



## 1.5.3 Park et al, 1997

<b>Bibliographic reference</b>	Park IW, Choi BW & Hue SH (1997) Prospective study of corticosteroid as an adjunct in the treatment of endobronchial tuberculosis in adults. <i>Respirology</i> 2: 275-81
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> unclear</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> not for the full treatment period: only 2 months</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes</p>

	<p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although some patients received streptomycin instead of ethambutol</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>unclear</p>					
<b>Number of patients</b>	<p>Randomised = 34</p> <p>prednisolone group= 17</p> <p>antituberculosis chemotherapy alone group = 17</p>					
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Endobronchial tuberculosis</p> <p><i>Diagnostic criteria</i></p> <p>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</p> <p><i>Exclusion</i></p> <p>Systemic disease or infection</p> <p>History of previous tuberculosis</p> <p>Patients who have stopped antituberculosis medications or corticosteroids due to severe side effects</p> <p>Pregnancy</p> <p><i>Baseline</i></p> <table border="1" data-bbox="618 1366 2078 1422"> <tr> <td data-bbox="618 1366 1361 1422"></td> <td data-bbox="1361 1366 1720 1422"><b>Prednisolone group</b></td> <td data-bbox="1720 1366 2078 1422"><b>Antituberculosis</b></td> </tr> </table>				<b>Prednisolone group</b>	<b>Antituberculosis</b>
	<b>Prednisolone group</b>	<b>Antituberculosis</b>				

	(n = 17)	<b>chemotherapy alone group</b> (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

	<table border="1"> <tr> <td>stenosis with fibrosis, n</td> <td>5</td> <td>2</td> </tr> <tr> <td>non-specific bronchitic, n</td> <td>5</td> <td>6</td> </tr> <tr> <td>glandular, n</td> <td>2</td> <td>4</td> </tr> <tr> <td>granular, n</td> <td>2</td> <td>2</td> </tr> <tr> <td>ulcerative, n</td> <td>0</td> <td>0</td> </tr> </table>	stenosis with fibrosis, n	5	2	non-specific bronchitic, n	5	6	glandular, n	2	4	granular, n	2	2	ulcerative, n	0	0
stenosis with fibrosis, n	5	2														
non-specific bronchitic, n	5	6														
glandular, n	2	4														
granular, n	2	2														
ulcerative, n	0	0														
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (4 to 8 weeks)</p> <p>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</p> <p>Antituberculosis chemotherapy: HRZS, HRZE or HRZSE</p> <p>dosing and duration not specified</p>															
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: HRZS, HRZE or HRZSE</p> <p>dosing and duration not specified</p>															
<b>Length of follow up</b>	2 months after treatment initiation															
<b>Location</b>	Seoul, Korea															
<b>Outcomes measures and effect size</b>	<p><b>Change in signs and symptoms – endobronchial lesions</b></p> <p>Including actively caseating lesions, stenosis with and without fibrosis, glandular-type lesions and granular-type lesions</p> <p>Number of endobronchial lesions identified using bronchoscopy before treatment to have improved after 2 months of treatment</p> <p>prednisolone group= 24 of 35</p>															

	<p>antituberculosis chemotherapy alone group = 22 of 30</p> <p>OR<sup>1</sup> (95% CI) = 0.79 (0.27 to 2.33)</p> <p>i.e. not statistically significant</p>
	<p><b>Change in signs and symptoms – pulmonary lesions</b></p> <p>Including atelectasis, patchy infiltration, fibrostriky density, hilar mass shadow, nodular lesions and cavitory lesions</p> <p>Number of lesions identified using chest-x-ray before treatment to have improved after 2 months of treatment</p> <p>prednisolone group= 22 of 29</p> <p>antituberculosis chemotherapy alone group = 23 of 28</p> <p>OR<sup>1</sup> (95% CI) = 0.68 (0.19 to 2.48)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; Z, pyrazinamide</p>	

#### 1.5.4 Tuberculosis Research Centre (Madras), 1983

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>unclear</p>

	<p><i>Allocation concealment used?</i></p> <p>unclear</p> <p><i>Blinding used?</i></p> <p>unclear</p> <p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>unclear</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>yes – sputum conversion is a substitute for cure/treatment failure</p> <p><i>Analysis followed the intent-to-treat principle?</i></p>
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	unclear
<b>Number of patients</b>	<p>Randomised = 530</p> <p>prednisolone group = 261</p> <p>antituberculosis chemotherapy alone group = 269</p> <p>Outcome data available at 24 months = 530</p> <p>prednisolone group = 261</p> <p>antituberculosis chemotherapy alone group = 269</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Newly diagnosed pulmonary tuberculosis</p> <p>Aged <math>\geq 12</math> years</p> <p><i>Diagnostic criteria</i></p> <p>At least 2 positive sputum cultures</p> <p><i>Baseline</i></p> <p>Unclear</p>
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (8 weeks)</p> <p>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<sup>th</sup> week and 5 mg daily in the eighth week</p> <p>Antituberculosis chemotherapy: 2SHRZ<sub>7</sub>/3SHZ<sub>2</sub>, 2SHRZ<sub>7</sub>/5SHZ<sub>2</sub> or 2SHZ<sub>7</sub>/5SHZ</p> <p>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</p>

	Treated as outpatients, though were given their drugs under close supervision by a clinic nurse
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: 2SHRZ<sub>7</sub>/3SHZ<sub>2</sub>, 2SHRZ<sub>7</sub>/5SHZ<sub>2</sub> or 2SHZ<sub>7</sub>/5SHZ</p> <p>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</p> <p>Treated as outpatients, though were given their drugs under close supervision by a clinic nurse</p>
<b>Location</b>	Madras, India
<b>Length of follow up</b>	24 months
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – sputum conversion</b></p> <p>Number of patients with all cultures negative after 1 month of treatment</p> <p>prednisolone group = 81 of 261</p> <p>antituberculosis chemotherapy alone = 80 of 269</p> <p>OR<sup>1</sup> (95% CI) = 1.06 (0.73 to 1.54)</p> <p>i.e. not statistically significant</p> <p>Number of patients with all cultures negative after 2 months of treatment</p> <p>prednisolone group = 167 of 261</p> <p>antituberculosis chemotherapy alone = 167 of 269</p> <p>OR<sup>1</sup> (95% CI) = 1.09 (0.76 to 1.54)</p> <p>i.e. not statistically significant</p> <p>Number of patients with all cultures negative after 3 months of treatment</p> <p>prednisolone group = 187 of 261</p>



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

	<p>examinations up to 24 months after treatment initiation, or in any 4 consecutive monthly examinations beyond 24 months</p> <p>Number to experience bacteriological relapse requiring treatment</p> <p>prednisolone group = 5 of 261</p> <p>antituberculosis chemotherapy alone = 6 of 269</p> <p>OR<sup>1</sup> (95% CI) = 0.86 (0.26 to 2.84)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis</p>	

## PLEURAL TUBERCULOSIS

### 1.5.5 Elliott et al, 2004

<b>Bibliographic reference</b>	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. <i>Journal of Infectious Diseases</i> 190: 869-78
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>yes – computer-generated randomisation sequence</p> <p><i>Allocation concealment used?</i></p> <p>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</p> <p><i>Blinding used?</i></p> <p>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</p> <p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p>

	<p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>yes – recurrence is a substitute for relapse</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
<p><b>Number of patients</b></p>	<p>Randomised = 297</p> <p>prednisolone group = 99</p> <p>antituberculosis chemotherapy alone group = 98</p> <p>Outcome data available at 24 weeks for anorexia, weight and cough = 151</p> <p>prednisolone group = 80</p> <p>antituberculosis chemotherapy alone group = 71</p> <p>Outcome data available at 24 weeks for residual effusion = 148</p> <p>prednisolone group = 76</p>

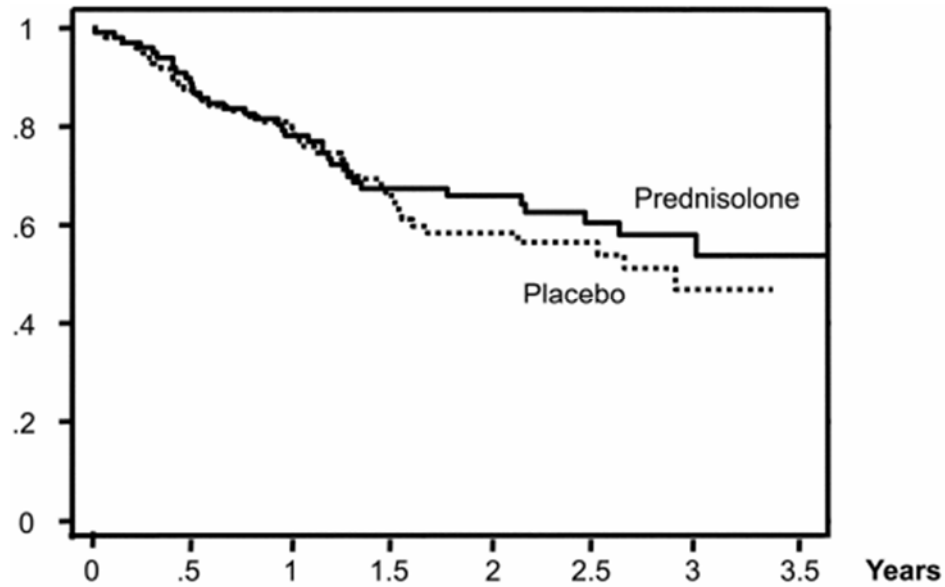
	antituberculosis chemotherapy alone group = 72		
<b>Patient characteristics</b>	<i>Inclusion</i>		
	Presented with clinical features suggesting pleural tuberculosis, with a pleural effusion occupying at least one-third of 1 hemithorax (as determined by a radiograph)		
	≥18 years old		
	HIV-1-associated		
	Residents of Kampala		
	<i>Diagnostic criteria</i>		
	Pleural tuberculosis was considered to be confirmed if a patient had a positive culture for <i>Mycobacterium tuberculosis</i> from pleural biopsy tissue, pleural fluid, or sputum or if histopathologic analysis of pleural tissue was consistent with tuberculous pleurisy		
	<i>Exclusion</i>		
	Previous treatment or prophylaxis for tuberculosis		
	Recent treatment with glucocorticoids		
	Pregnant or breast-feeding		
	<i>Baseline</i>		
		<b>Prednisolone group</b> (n = 98)	<b>Placebo group</b> (n = 99)
	Sex		
	males, n	54	60
	females, n	45	38
	Age (mean±SD), years	34±9	34±8

	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 thrush, 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	

		isoniazid resistance, n	5	5	
		pyrazinamide resistance, n	1	0	
		Radiography findings			
		1 zone affected, n	14	18	
		2 zones affected, n	49	46	
		≥3 zones affected, n	33	33	
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (8 weeks)</p> <p>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</p> <p>Antituberculosis chemotherapy: 2HRZE/4HR</p> <p>doses were adjusted according to each patient's weight, using the American Thoracic Society's standard criteria</p> <p>Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week</p>				
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (8 weeks)</p> <p>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</p> <p>Antituberculosis chemotherapy: 2HRZE/4HR</p> <p>doses were adjusted according to each patient's weight, using the American Thoracic Society's standard criteria</p>				

	Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week
<b>Length of follow up</b>	42 months
<b>Location</b>	Kampala, Uganda
<b>Outcomes measures and effect size</b>	<b>Mortality</b> 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**

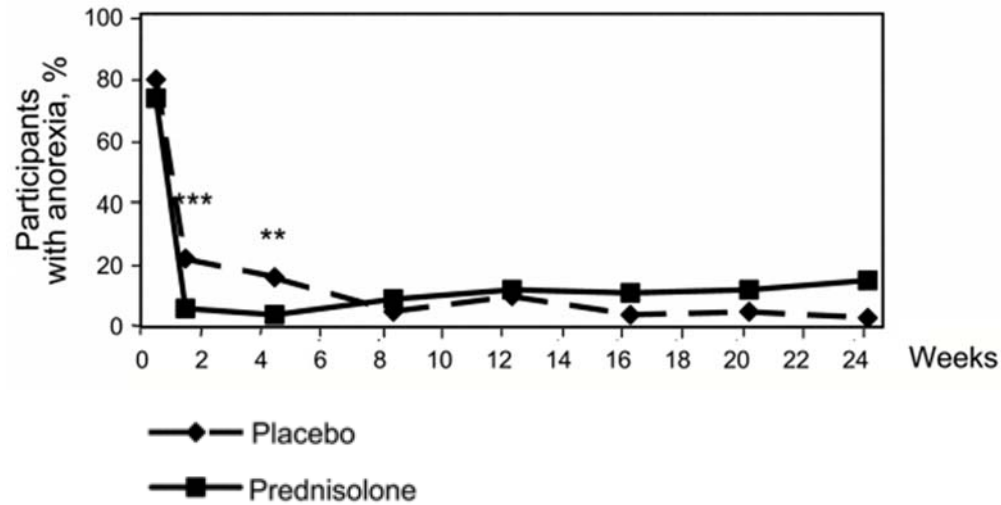
Number of patients to be anorexic after 24 weeks of treatment<sup>2</sup>

prednisolone group = 12 of 99

antituberculosis chemotherapy alone group = 3 of 98

**OR<sup>1</sup> (95% CI) = 4.37 (1.19 to 16.00)**

**i.e. statistically significant**



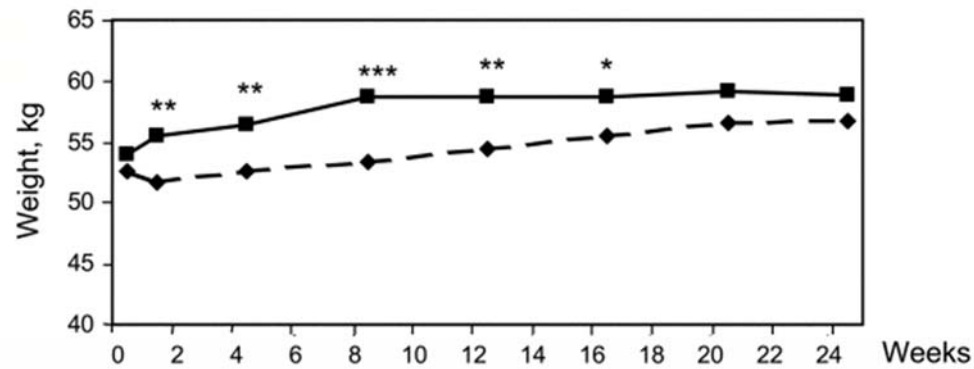
**Changes in signs and symptoms – weight**

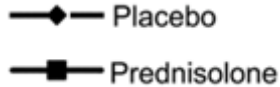
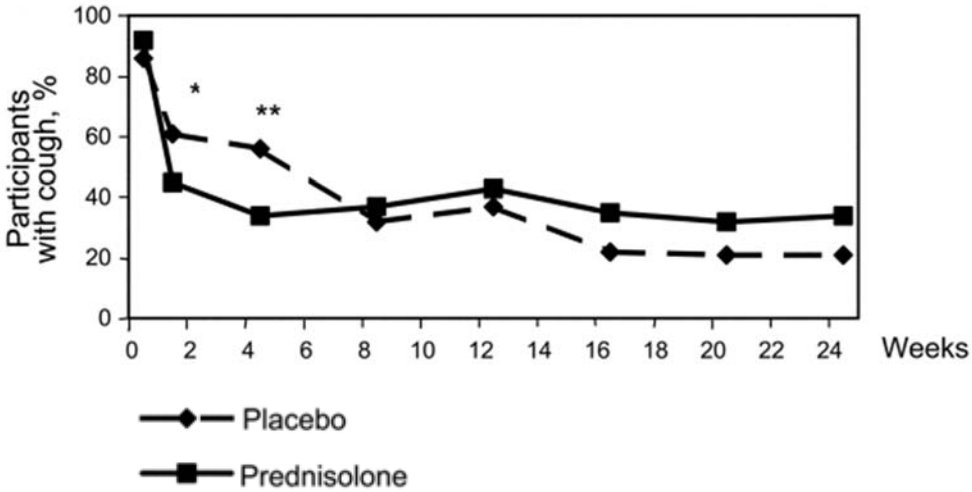
Weight (mean, kg) after 24 weeks of treatment<sup>2</sup>

prednisolone group = 59

antituberculosis chemotherapy alone group = 56

MD<sup>3</sup> = 3 kg

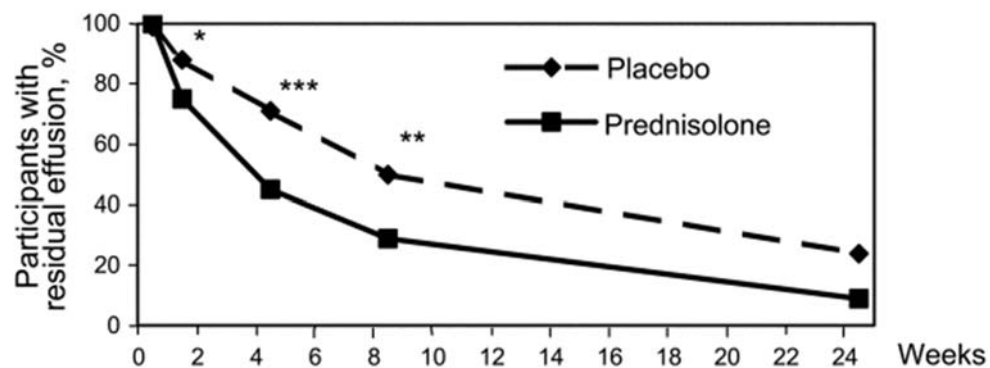


	<p>  </p>																											
	<p><b>Changes in signs and symptoms – cough</b></p> <p>Number of patients with a cough after 24 weeks of treatment<sup>2</sup></p> <p>prednisolone group = 26 of 99</p> <p>antituberculosis chemotherapy alone group = 14 of 98</p> <p><b>OR<sup>1</sup> (95% CI) = 2.14 (1.04 to 4.40)</b></p> <p><b>i.e. statistically significant</b></p>  <table border="1"> <caption>Data for Cough Symptom Graph</caption> <thead> <tr> <th>Weeks</th> <th>Placebo (%)</th> <th>Prednisolone (%)</th> </tr> </thead> <tbody> <tr><td>0</td><td>85</td><td>92</td></tr> <tr><td>2</td><td>60</td><td>45</td></tr> <tr><td>4</td><td>55</td><td>35</td></tr> <tr><td>8</td><td>35</td><td>38</td></tr> <tr><td>12</td><td>38</td><td>42</td></tr> <tr><td>16</td><td>22</td><td>35</td></tr> <tr><td>20</td><td>20</td><td>32</td></tr> <tr><td>24</td><td>20</td><td>33</td></tr> </tbody> </table>	Weeks	Placebo (%)	Prednisolone (%)	0	85	92	2	60	45	4	55	35	8	35	38	12	38	42	16	22	35	20	20	32	24	20	33
Weeks	Placebo (%)	Prednisolone (%)																										
0	85	92																										
2	60	45																										
4	55	35																										
8	35	38																										
12	38	42																										
16	22	35																										
20	20	32																										
24	20	33																										
	<p><b>Changes in signs and symptoms – pleural effusion</b></p> <p>Number of patients with pleural effusion after 24 weeks of treatment<sup>2</sup></p> <p>prednisolone group = 7 of 99</p>																											

antituberculosis chemotherapy alone group = 17 of 98

**OR<sup>1</sup> (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<sup>1</sup> (95% CI) = 4.80 (1.01 to 22.82)**

	<p><b>i.e. statistically significant</b></p> <p><b>Adverse events – incidence of HIV-related disease</b></p> <p>Number of patients to experience Kaposi sarcoma</p> <p>prednisolone group = 6 of 99</p> <p>antituberculosis chemotherapy alone group = 0 of 98</p> <p>OR<sup>1</sup> (95% CI) = 13.70 (0.76 to 246.52)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience cryptococcal meningitis</p> <p>prednisolone group = 3 of 99</p> <p>antituberculosis chemotherapy alone group = 5 of 98</p> <p>OR<sup>1</sup> (95% CI) = 0.58 (0.14 to 2.50)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience oesophageal candidiasis</p> <p>prednisolone group = 35 of 99</p> <p>antituberculosis chemotherapy alone group = 23 of 98</p> <p>OR<sup>1</sup> (95% CI) = 1.78 (0.96 to 3.32)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience herpes zoster</p> <p>prednisolone group = 22 of 99</p> <p>antituberculosis chemotherapy alone group = 19 of 98</p> <p>OR<sup>1</sup> (95% CI) = 1.19 (0.60 to 2.37)</p>
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	<p>i.e. not statistically significant</p> <p>Number of patients to experience oral or genital herpes simplex</p> <p>prednisolone group = 22 of 99</p> <p>antituberculosis chemotherapy alone group = 20 of 98</p> <p>OR<sup>1</sup> (95% CI) = 1.11 (0.56 to 2.21)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience oral thrush</p> <p>prednisolone group = 31 of 99</p> <p>antituberculosis chemotherapy alone group = 31 of 98</p> <p>OR<sup>1</sup> (95% CI) = 1.43 (0.79 to 2.56)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience gastroenteritis</p> <p>prednisolone group = 34 of 99</p> <p>antituberculosis chemotherapy alone group = 28 of 98</p> <p>OR<sup>1</sup> (95% CI) = 1.31 (0.72 to 2.39)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Details not provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Read off graph by reviewer</p> <p><sup>3</sup> Mean difference calculated by reviewer</p>	

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

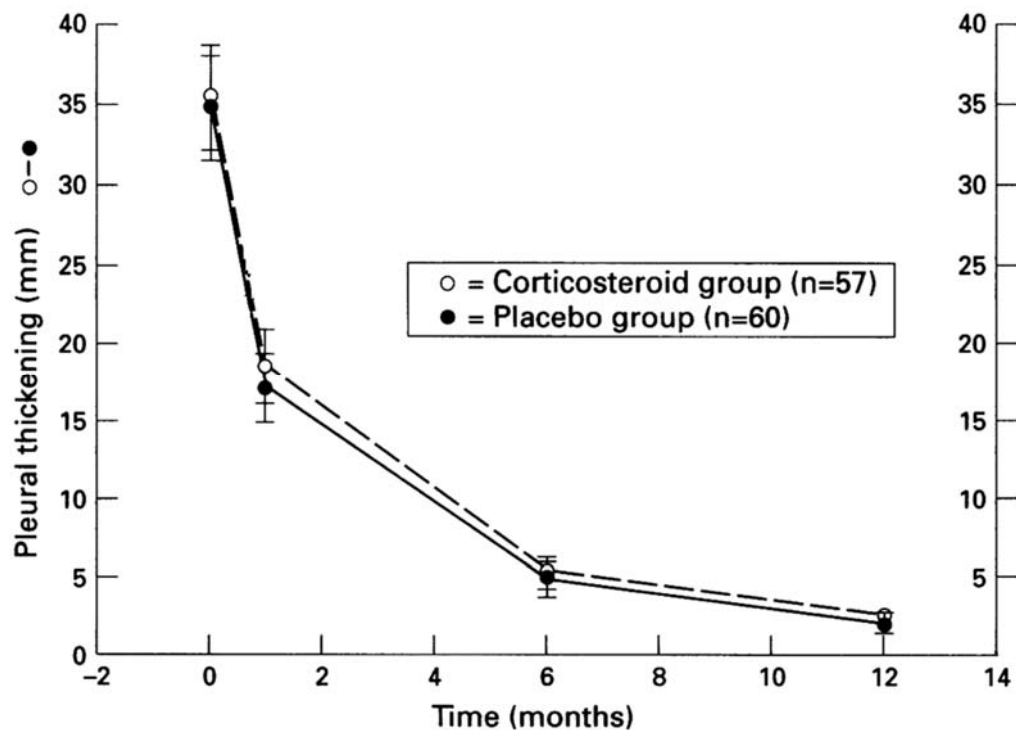
<b>Bibliographic reference</b>	Galarza I, Cañete C, Granados A et al (1995) Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. <i>Thorax</i> 50: 1305-7
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> double-blind</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although the details provided were limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p>

	<p>yes <i>Population studied is the same as the population of interest?</i></p> <p>yes <i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although patients received only 2 drugs, lacking ethambutol and pyrazinamide <i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no <i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>								
<b>Number of patients</b>	<p>Randomised = 117</p> <p>prednisolone group = 57</p> <p>placebo group = 60</p>								
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Pleural effusion of tuberculous aetiology</p> <p><i>Exclusion</i></p> <p>HIV infection</p> <p><i>Baseline</i></p> <p>Definite microbiological or pathological diagnosis was obtained in 63% of patients</p> <table border="1" data-bbox="618 1238 2078 1414"> <thead> <tr> <th data-bbox="618 1238 1357 1358"></th> <th data-bbox="1357 1238 1715 1358"><b>Prednisolone group</b> (n = 57)</th> <th data-bbox="1715 1238 2078 1358"><b>Placebo group</b> (n = 60)</th> </tr> </thead> <tbody> <tr> <td data-bbox="618 1358 1357 1414">Age (mean (range)), years</td> <td data-bbox="1357 1358 1715 1414">26 (11–53)</td> <td data-bbox="1715 1358 2078 1414">28 (14–53)</td> </tr> </tbody> </table>				<b>Prednisolone group</b> (n = 57)	<b>Placebo group</b> (n = 60)	Age (mean (range)), years	26 (11–53)	28 (14–53)
	<b>Prednisolone group</b> (n = 57)	<b>Placebo group</b> (n = 60)							
Age (mean (range)), years	26 (11–53)	28 (14–53)							



	Sex, male:female	33:27	30:31
	Side		
	right, n (%)	34	36
	left, n (%)	23	24
	Fever (mean (range)), days	3.32 (0–50)	4.15 (0–60)
	Thickening (mean (range)), mm	1.77 (0–40)	2.23 (0–15)
	FVC (mean (range)), % predicted	95 (65–130)	95 (63–140)
	Follow-up (mean (range)), months	46 (12–94)	46 (12–96)
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (30 days)</p> <p>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 0.1 mg/kg of body weight/day for the remaining days of the month</p> <p>Antituberculosis chemotherapy: 6HR</p> <p>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</p>		
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (30 days)</p> <p>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 0.1 mg/kg of body weight/day for the remaining days of the month</p> <p>Antituberculosis chemotherapy: 6HR</p>		

	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
<b>Length of follow up</b>	46 months
<b>Location</b>	Barcelona, Spain
<b>Outcomes measures and effect size</b>	<p><b>Changes in signs and symptoms – pleural thickening</b></p> <p>Number of patients to show pleural thickening at 12 months, as assessed using a chest x-ray</p> <p>prednisolone group = 1 of 57</p> <p>placebo group = 5 of 60</p> <p>OR<sup>2</sup> (95% CI) = 0.20 (0.02 to 1.74)</p> <p>i.e. not statistically significant</p> <p>Pleural thickening (mean (range), days) at 46 months, as assessed using a chest x-ray</p> <p>prednisolone group (n = 57) = 1.77 (0–40)</p> <p>placebo group (n = 60) = 2.23 (0–15)</p> <p>MD<sup>3</sup> = -0.46</p>



**Changes in signs and symptoms – pleural hemithorax reabsorption**

Index of reabsorption (mean±SE (range), %) at 12 months<sup>1</sup>

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

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

MD<sup>3</sup> (95% CI) = 4 (-18 to 26)

i.e. not statistically significant

	<p>The graph plots the Index of reabsorption (%) on the y-axis (ranging from 70 to 100) against Time (months) on the x-axis (ranging from -2 to 14). Two data series are shown: the Corticosteroid group (n=57) represented by open inverted triangles and a dotted line, and the Placebo group (n=60) represented by solid inverted triangles and a solid line. Both groups start at approximately 75% at 0 months. The Corticosteroid group rises to about 93% at 1 month, 95% at 6 months, and 97% at 12 months. The Placebo group rises to about 90% at 1 month, 95% at 6 months, and 96% at 12 months. Error bars representing standard error are included for each data point.</p> <table border="1"> <caption>Estimated data from the graph</caption> <thead> <tr> <th>Time (months)</th> <th>Corticosteroid group (n=57) (%)</th> <th>Placebo group (n=60) (%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>~75</td> <td>~77</td> </tr> <tr> <td>1</td> <td>~93</td> <td>~90</td> </tr> <tr> <td>6</td> <td>~95</td> <td>~95</td> </tr> <tr> <td>12</td> <td>~97</td> <td>~96</td> </tr> </tbody> </table>	Time (months)	Corticosteroid group (n=57) (%)	Placebo group (n=60) (%)	0	~75	~77	1	~93	~90	6	~95	~95	12	~97	~96
Time (months)	Corticosteroid group (n=57) (%)	Placebo group (n=60) (%)														
0	~75	~77														
1	~93	~90														
6	~95	~95														
12	~97	~96														
	<p><b>Changes in signs and symptoms – fever</b></p> <p>Duration of fever (mean (range), days) at 46 months</p> <p>prednisolone group (n = 57) = 3.32 (0–50)</p> <p>placebo group (n = 60) = 4.15 (0–60)</p> <p>MD<sup>3</sup> = -0.83</p>															
<b>Source of funding</b>	Fondo de Investigaciones de la Seguridad Social															
<b>Comments</b>																
<p><sup>1</sup> Standard error read of the graph by reviewer</p>																

<sup>2</sup> Odds ratio and 95% confidence intervals, where possible, calculated by reviewer

<sup>3</sup> 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**

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> unclear</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p>

	<p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although patients did not receive pyrazinamide</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>no</p>
<b>Number of patients</b>	<p>Randomised = 45</p> <p>Outcome data available for = 40</p> <p>prednisolone group = 21</p> <p>placebo group = 19</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>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</p> <p>Aged &lt;45 years</p> <p><i>Diagnostic criteria</i></p> <p>Diagnosis of tuberculous pleurisy was confirmed on the basis of pleural biopsy</p>

	<p><i>Exclusion</i></p> <p>Other diseases or pulmonary diseases</p> <p>Conditions that contraindicated the use of corticosteroids, such as diabetes, peptic ulcer or hypertension</p> <p><i>Baseline</i></p> <table border="1" data-bbox="618 424 2078 1070"> <thead> <tr> <th></th> <th>Prednisolone group (n = 21)</th> <th>Placebo group (n = 19)</th> </tr> </thead> <tbody> <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<sup>1</sup></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> </tbody> </table>		Prednisolone group (n = 21)	Placebo group (n = 19)	Sex			male, n	12	12	female, n	9	7	Age (mean (range)), years	28.4 (18–44)	28.9 (18–45)	Time from onset of symptoms to diagnosis (mean), days	20.6	15.4	Initial amount of pleural effusions <sup>1</sup>			small, n	9	5	moderate, n	9	9	large, n	3	5
	Prednisolone group (n = 21)	Placebo group (n = 19)																													
Sex																															
male, n	12	12																													
female, n	9	7																													
Age (mean (range)), years	28.4 (18–44)	28.9 (18–45)																													
Time from onset of symptoms to diagnosis (mean), days	20.6	15.4																													
Initial amount of pleural effusions <sup>1</sup>																															
small, n	9	5																													
moderate, n	9	9																													
large, n	3	5																													
<p><b>Intervention</b></p>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone</p> <p>administered in an oral dose of 0.75 mg/kg of body weight/day initially</p> <p>the dosage was tapered once the chest radiograph showed improvement</p> <p>the dosage was diminished by two-thirds if any of the following conditions existed: 1) the effusion was right-sided and</p>																														

	<p>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</p> <p>Antituberculosis chemotherapy: 3HRE/6-9HR</p> <p>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</p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo</p> <p>administered in an oral dose of 0.75 mg/kg of body weight/day initially</p> <p>the dosage was tapered once the chest radiograph showed improvement</p> <p>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</p> <p>Antituberculosis chemotherapy: 3HRE/6-9HR</p> <p>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</p>
<b>Length of follow up</b>	Exact period unclear, though at least 1 year
<b>Location</b>	Taipei, Taiwan
<b>Outcomes measures and effect size</b>	<p><b>Change in signs and symptoms – disappearance of clinical signs and symptoms</b></p> <p>Time (mean±SD<sup>2</sup> (range), days) to disappearance of clinical signs and symptoms (including fever, chest pain and dyspnea)</p> <p>prednisolone group (n = 21) = 2.4±1.6 (1–7)</p> <p>placebo group (n = 19) = 9.2±16.5 (1–75)</p> <p>p&lt;0.05</p>



	<p>MD<sup>3</sup> (95% CI) = -6.8 (-14.3 to 0.7) i.e. not statistically significant</p> <p><b>Change in signs and symptoms – pleural effusion</b></p> <p>Time (mean<sup>4</sup> (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)</p> <p>prednisolone group (n = 21) = 54.5 (6–365) placebo group (n = 19) = 123.2 (7–395)</p> <p><b>p&lt;0.01</b></p> <p><b>MD<sup>3</sup> = -68.7</b></p>
	<p><b>Change in signs and symptoms – pleural adhesions</b></p> <p>Number of patients to experience pleural adhesions</p> <p>prednisolone group = 1 of 21 placebo group = 3 of 19</p> <p>p = 0.27</p> <p>OR<sup>5</sup> (95% CI) = 0.27 (0.03 to 2.82) i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Small = less than one-third of one hemithorax; moderate = between one-third and two-thirds of one hemithorax; large = more than two-thirds of one hemithorax</p> <p><sup>2</sup> Standard deviation calculated from the individual patient data read off the graph by reviewer</p> <p><sup>3</sup> Mean difference and 95% confidence intervals, where possible, calculated by reviewer</p>	

<sup>4</sup> Standard deviation could not be calculated by reviewer as individual patient data could not be read off the graph

<sup>5</sup> 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

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> double-blind</p> <p><i>Groups comparable at baseline?</i> although not statistically significant (<math>p = 0.06</math>), more patients receiving placebo (44.4%) had pleuritis and pulmonary tuberculosis than amongst those receiving prednisolone (21.2)</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> follow-up not for the full treatment period</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p>

	<p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although patients did not receive ethambutol</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>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</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>no</p>
<b>Number of patients</b>	<p>Randomised = 74</p> <p>Outcome data available for = 70</p> <p>prednisolone group = 34</p> <p>placebo group = 36</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Exudative pleural effusions</p> <p>Biopsy specimen-proven tuberculous pleurisy</p> <p><i>Diagnostic criteria</i></p> <p>Diagnosis confirmed by the presence of caseating granulomas with or without acid-fast bacilli on histologic study and/or a positive <i>M. tuberculosis</i> culture</p>

	<i>Exclusion</i>		
	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		
	<i>Baseline</i>		
		<b>Prednisolone group</b> (n = 34)	<b>Placebo group</b> (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, %	2.9	0	
moderate, %	14.7	13.9	
large, %	82.4	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 <sup>1</sup>		
	type 1	9.0	5.7
	type 2	66.6	62.8
	type 3	30.4	31.5
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone</p> <p>administered in an oral dose of 0.75 mg/kg of body weight/day initially</p> <p>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</p> <p>Antituberculosis chemotherapy: 6HRZ</p> <p>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</p> <p>All patients received 25 mg/kg of body weight/day of pyridoxine</p>		
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo</p>		

	<p>administered in an oral dose of 0.75 mg/kg of body weight/day initially</p> <p>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</p> <p>Antituberculosis chemotherapy: 6HRZ</p> <p>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</p> <p>All patients received 25 mg/kg of body weight/day of pyridoxine</p>
<b>Length of follow up</b>	24 weeks
<b>Location</b>	Cape Town, South Africa
<b>Outcomes measures and effect size</b>	<p><b>Changes in signs and symptoms – ‘morbidity’</b></p> <p>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</p> <p>Morbidity score (median (range)) at 24 weeks</p> <p>prednisolone group (n = 34) = 0 (0–0)</p> <p>placebo group (n = 36) = 0 (0–0)</p> <p>Median difference<sup>2</sup> = 0</p> <p>i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – pleural thickening</b></p> <p>Number of people to with residual pleural thickening, as assessed using a chest x-ray</p> <p>prednisolone group = 17 of 34</p> <p>placebo group = 18 of 36</p> <p>OR<sup>3</sup> (95% CI) = 1.00 (0.39 to 2.55)</p>

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

	<p>prednisolone group = 4 of 34</p> <p>placebo group = 3 of 36</p> <p>OR<sup>3</sup> (95% CI) = 1.47 (0.30 to 7.10)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	<p><sup>1</sup> 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</p> <p><sup>2</sup> Median difference calculated by reviewer</p> <p><sup>3</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>4</sup> Mean difference and 95% confidence interval calculated by reviewer</p> <p><sup>5</sup> Changes in mean and 95% confidence interval calculated by reviewer</p> <p><sup>5</sup> Difference in the changes in mean calculated by reviewer</p> <p>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</p>

### 1.5.9 Singh & Yesikar, 1965

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



	<p><i>Allocation concealment used?</i></p> <p>no</p> <p><i>Blinding used?</i></p> <p>no</p> <p><i>Groups comparable at baseline?</i></p> <p>unclear</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>unclear</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although patients did not receive rifampicin, pyrazinamide and ethambutol but received streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>recurrence is a substitute for relapse</p> <p><i>Analysis followed the intent-to-treat principle?</i></p>
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	yes
<b>Number of patients</b>	Randomised = 50 dexamethasone group = 30 antituberculosis chemotherapy alone group = 20
<b>Patient characteristics</b>	<i>Inclusion</i> Pleural effusion with tuberculous aetiology Typical onset and course of disease Positive Mantoux test
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus dexamethasone</i> 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
<b>Comparison</b>	<i>Antituberculosis chemotherapy alone</i> 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

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

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

	<p>antituberculosis chemotherapy alone group (n = 20) = 41.8</p> <p>MD<sup>1</sup> = 1.6</p> <p>Change in mean weight (kg) from baseline to the end of follow-up</p> <p>dexamethasone group (n = 30) = 2.0</p> <p>antituberculosis chemotherapy alone group (n = 20) = 1.5</p> <p>MD<sup>1</sup> = 0.5</p>
	<p><b>Recurrence</b></p> <p>Number of patients to experience recurrence</p> <p>dexamethasone group = 0 of 30</p> <p>antituberculosis chemotherapy alone group = 4 of 20</p> <p>OR<sup>2</sup> (95% CI) = 0.06 (0.00 to 1.19)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Mean difference and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; MD, mean difference; OR, odds ratio; S, streptomycin</p>	

## TUBERCULOSIS WITH SEVERE BRONCHIAL OBSTRUCTION

### 1.5.10 Toppet et al, 1990

<b>Bibliographic reference</b>	Toppet M, Malfroot A, Derde MP et al (1990) Corticosteroids in primary tuberculosis with bronchial obstruction. Archives of Disease in Childhood 65: 1222-6
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> numbered envelopes</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> 'open' trial, although examination of bronchoscopy and radiographs blinded</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> 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</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack pyrazinamide</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> yes – need for multiple bronchoscopies is a surrogate for changes in signs and symptoms</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>
<b>Number of patients</b>	<p>Randomised = 29</p> <p>prednisolone group = 15</p> <p>antituberculosis chemotherapy alone group = 14</p> <p>Outcome data available for outcomes based on bronchoscopy = 29</p> <p>prednisolone group = 15</p> <p>antituberculosis chemotherapy alone group = 14</p> <p>Outcome data available for outcomes based on radiography = 23</p> <p>prednisolone group = 13</p> <p>antituberculosis chemotherapy alone group = 10</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Children</p>

	<p>Symptomatic tuberculosis with severe bronchial obstruction suspected by radiology and demonstrated by bronchoscopy</p> <p>A compression of at least 50% of a bronchus</p> <p>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 &gt;75% = 4; 50-75% = 2; &lt;50% = 1; no obstruction = 0</p> <p><i>Diagnostic criteria</i></p> <p>A combination of the following:</p> <p>recent tuberculin conversion with an induration of at least 10 mm after 48 or 72 hours</p> <p>clinical signs such as an unexpected course of pulmonary consolidation, long standing unexplained fever or cough</p> <p>family history of tuberculosis</p> <p>chest radiographs</p> <p>bronchoscopy</p> <p><i>Exclusion</i></p> <p>Patients who already had bronchial fistulisation were not included in this study as the aim was to verify whether fistulisation could be prevented</p> <p>Meningitis</p> <p>Miliary tuberculosis</p> <p>Patients without clinical and radiological abnormalities and negative bacteriology for <i>M. tuberculosis</i></p> <p><i>Baseline<sup>1</sup></i></p>		
		<p><b>Prednisolone</b> (n = 15)</p>	<p><b>Antituberculosis chemotherapy alone group</b></p>



			(n = 10)
	Age (mean±SD (range)), years	4.3±4.2 (0.3–12)	5.5±4.2 (0.5–15)
	Sex		
	males, n	11	8
	females, n	4	6
	<i>M. tuberculosis</i> culture		
	positive, n	9	9
	negative, n	6	5
	Score on radiology <sup>2</sup> (mean±SD (range))	4.8±2.2 (3–10)	3.9±1.4 (2–6)
	Score on bronchoscopy <sup>3</sup> (mean±SD (range))	15.4±6.9 (2–26)	11.8±5.7 (3–21)
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (3 to 3.5 months)</p> <p>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</p> <p>Antituberculosis chemotherapy: 2HRZE/10HR</p> <p>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</p> <p>isoniazid and rifampicin at the same doses for the following 10 months</p>		
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: 2HRZE/10HR</p>		

	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
<b>Length of follow up</b>	Full treatment period (12 months)
<b>Location</b>	Brussels, Belgium
<b>Outcomes measures and effect size</b>	<p><b>Changes in signs and symptoms – radiological status</b></p> <p>Number of patients whose radiological score normalised during treatment</p> <p>prednisolone group = 13 of 15</p> <p>antituberculosis chemotherapy alone group = 9 of 14</p> <p>OR<sup>4</sup> (95% CI) = 3.61 (0.57 to 22.90)</p> <p>i.e. not statistically significant</p> <p>Number of patients whose radiological score improved in <math>\leq 1</math> month</p> <p>prednisolone group = 7 of 15</p> <p>antituberculosis chemotherapy alone group = 0 of 14</p> <p><b>OR<sup>4</sup> (95% CI) = 25.59 (1.29 to 506.48)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of patients whose radiological score deteriorated during treatment</p> <p>prednisolone group = 2 of 15</p> <p>antituberculosis chemotherapy alone group = 5 of 14</p> <p>OR<sup>4</sup> (95% CI) = 0.28 (0.04 to 1.76)</p> <p>i.e. not statistically significant</p>

	<p><b>Changes in signs and symptoms – bronchial status</b></p> <p>Change (mean±SD) in bronchoscopy score<sup>3</sup> from baseline to 1 month post-treatment</p> <p>prednisolone group (n = 15) = 12.1±6.9</p> <p>antituberculosis chemotherapy alone group (n = 14) = 5.9±5.0</p> <p><b>MD<sup>5</sup> (95% CI) = 6.2 (1.83 to 10.57)</b></p> <p><b>i.e. statistically significant</b></p> <hr/> <p><b>Response to treatment – need for multiple bronchoscopies</b></p> <p>Number of patients to require &gt;2 bronchoscopies</p> <p>prednisolone group = 1 of 15</p> <p>antituberculosis chemotherapy alone group = 6 of 14</p> <p><b>OR<sup>4</sup> (95% CI) = 0.10 (0.01 to 0.94)</b></p> <p><b>i.e. statistically significant</b></p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Authors provided individual patient data; reviewer summarised for comparison of the 2 groups</p> <p><sup>2</sup> 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</p> <p><sup>3</sup> Bronchoscopy score:</p> <p>localisation: trachea = 4; main bronchus = 3; lobar bronchus = 2; segmental bronchus = 1</p> <p>importance of the obstruction: total or &gt;75% = 4; 50-75% = 2; &lt;50% = 1; no obstruction = 0</p> <p><sup>4</sup> Odds ratio and 95% confidence interval calculated by reviewer</p>	

<sup>5</sup> 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

<b>Bibliographic reference</b>	Chotmongkol V, Jitpimolmard S & Thavornpitak Y (1996) Corticosteroid in tuberculous meningitis. Journal of the Medical Association of Thailand 79(2): 83-90
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear – patients were randomised by a block size of 4 using coded treatment (A = placebo; B = prednisolone)</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> 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</p> <p><i>Groups comparable at baseline?</i> 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</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes – 12 months after treatment completion</p>

	<p><i>Groups comparable for treatment completion and availability of outcome data?</i>          yes – 100% in both groups</p> <p><i>Study used precise definitions and reliable measures of outcome?</i>          yes, although details provided are limited</p> <p><i>Population studied is the same as the population of interest?</i>          yes</p> <p><i>Intervention used is the same as the intervention of interest?</i>          antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack ethambutol and contain streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i>          yes – need for additional intervention (response to treatment) is a substitute for treatment success/failure</p> <p><i>Analysis followed the intent-to-treat principle?</i>          yes</p>
<p><b>Number of patients</b></p>	<p>Randomised = 59          prednisolone group = 29          placebo group = 30</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i>          Tuberculous meningitis          Aged more than 15 years          Negative serologic test for syphilis and HIV</p> <p><i>Diagnostic criteria</i></p>

	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				
<i>Severity of disease</i>				
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				
<i>Baseline</i>				
		<b>Prednisolone group</b> (n = 29)	<b>Placebo group</b> (n = 30)	<b>p value</b>
	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 (paraparesis, 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



	<p>CSF abnormalities</p> <p>high opening pressure (&gt;300 mmH<sub>2</sub>O), %</p> <p>white blood cell count (/mm<sup>3</sup>)</p> <p>mean</p> <p>range</p> <p>protein content (mg/dl)</p> <p>mean</p> <p>range</p>	<p>51.7</p> <p>403</p> <p>25–1202</p> <p>247.8</p> <p>57–9570</p>	<p>56.7</p> <p>388</p> <p>10–2000</p> <p>287</p> <p>76–8500</p>	<p>0.90</p> <p>0.80</p> <p>0.67</p>
	positive AFB stain, %	3.4	0.0	
	positive culture for <i>M. tuberculosis</i> , %	13.8	3.3	
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (5 weeks)</p> <p>60 mg/day taken orally with alum milk in 3 divided doses after meals during the first week</p> <p>the dose was reduced to 45, 30, 20 and 10 mg/day for the second, third, fourth and fifth weeks respectively, then discontinued</p> <p>Antituberculosis chemotherapy: 2HRZS/4HR</p> <p>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</p> <p>isoniazid and rifampicin at the same doses for the following 4 months</p>			
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (5 weeks)</p>			

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

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

	<p>placebo group = 4 of 30</p> <p>p = 0.67</p> <p>OR<sup>1</sup> (95% CI) = 0.48 (0.08 to 2.86)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience urinary retention newly developed during treatment</p> <p>prednisolone group = 1 of 29</p> <p>placebo group = 1 of 30</p> <p>OR<sup>1</sup> (95% CI) = 1.04 (0.06 to 17.38)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience arm weakness newly developed during treatment</p> <p>prednisolone group = 1 of 29</p> <p>placebo group = 0 of 30</p> <p>OR<sup>1</sup> (95% CI) = 3.21 (0.13 to 82.07)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience paraparesis newly developed during treatment</p> <p>prednisolone group = 0 of 29</p> <p>placebo group = 2 of 30</p> <p>OR<sup>1</sup> (95% CI) = 0.19 (0.01 to 4.20)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience hemiparesis newly developed during treatment</p> <p>prednisolone group = 0 of 29</p>
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	<p>placebo group = 1 of 30</p> <p>OR<sup>1</sup> (95% CI) = 0.33 (0.01 to 8.52)</p> <p>i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – neurological abnormalities after treatment</b></p> <p>Number of patients to experience neurological abnormalities after treatment</p> <p>prednisolone group = 4 of 29</p> <p>placebo group = 2 of 30</p> <p>p = 0.42</p> <p>OR<sup>1</sup> (95% CI) = 2.24 (0.38 to 13.30)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience decreased vision after treatment</p> <p>prednisolone group = 2 of 29</p> <p>placebo group = 1 of 30</p> <p>OR<sup>1</sup> (95% CI) = 2.15 (0.18 to 25.07)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience spastic paraparesis after treatment</p> <p>prednisolone group = 1 of 29</p> <p>placebo group = 1 of 30</p> <p>OR<sup>1</sup> (95% CI) = 1.04 (0.06 to 17.38)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience hemiparesis after treatment</p>

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

	<p>i.e. not statistically significant</p> <p><b>Adverse events - gastrointestinal bleeding</b></p> <p>Number of patients to experience gastrointestinal bleeding</p> <p>prednisolone group = 0 of 29</p> <p>placebo group = 0 of 30</p> <p>OR<sup>1</sup> (95% CI) = 1.03 (0.02 to 53.83)</p> <p>i.e. not statistically significant</p> <p><b>Adverse events - hyperglycaemia</b></p> <p>Number of patients to experience hyperglycaemia</p> <p>prednisolone group = 0 of 29</p> <p>placebo group = 0 of 30</p> <p>OR<sup>1</sup> (95% CI) = 1.03 (0.02 to 53.83)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Tablets of prednisolone and placebo were provided by Siam Pharmaceutical Co. Ltd.
<b>Comments</b>	<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Mean difference calculated by reviewer</p> <p>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</p>

## 1.5.12 Girgis et al, 1983

<b>Bibliographic reference</b>	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
<b>Study type</b>	Non-randomised controlled trial
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>no – allocation was not randomised, rather patients were alternately assigned to receive antituberculosis chemotherapy plus dexamethasone or antituberculosis chemotherapy alone</p> <p><i>Allocation concealment used?</i></p> <p>no</p> <p><i>Blinding used?</i></p> <p>unclear</p> <p><i>Groups comparable at baseline?</i></p> <p>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</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>unclear</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>unclear</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p>



	<p>yes, although details provided are limited</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin and pyrazinamide, but contain streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p>								
<p><b>Number of patients</b></p>	<p>Included = 136</p> <p>dexamethasone group = 66</p> <p>antituberculosis chemotherapy alone group = 70</p>								
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Tuberculous meningitis</p> <p><i>Diagnostic criteria</i></p> <p>Isolation of tubercle bacilli from the CSF, or a CSF findings consistent with tuberculous meningitis (increased protein, low glucose, and lymphocytotic pleocytosis)</p> <p><i>Baseline</i></p> <table border="1" data-bbox="618 1129 2074 1430"> <thead> <tr> <th data-bbox="618 1129 1357 1318"></th> <th data-bbox="1357 1129 1715 1318"> <b>Dexamethasone group</b> (n = 66)             </th> <th data-bbox="1715 1129 2074 1318"> <b>Antituberculosis chemotherapy alone group</b> (n = 70)             </th> </tr> </thead> <tbody> <tr> <td data-bbox="618 1318 1357 1430">                     Sex                          males, %                 </td> <td data-bbox="1357 1318 1715 1430">                     45.5                 </td> <td data-bbox="1715 1318 2074 1430">                     54.3                 </td> </tr> </tbody> </table>				<b>Dexamethasone group</b> (n = 66)	<b>Antituberculosis chemotherapy alone group</b> (n = 70)	Sex males, %	45.5	54.3
	<b>Dexamethasone group</b> (n = 66)	<b>Antituberculosis chemotherapy alone group</b> (n = 70)							
Sex males, %	45.5	54.3							

	<table border="1"> <tbody> <tr> <td>females, %</td> <td>54.5</td> <td>45.7</td> </tr> <tr> <td>Age (mean (range)), years</td> <td>14.6 (0.5 – 52)</td> <td>13.6 (0.6 – 42)</td> </tr> <tr> <td>CSF positive for tubercle bacilli, %</td> <td>45.5</td> <td>48.6</td> </tr> <tr> <td>Duration of symptoms prior to admission (mean (range)), days</td> <td>27.8 (6 – 120)</td> <td>25.5 (5 – 105)</td> </tr> <tr> <td>Clinical condition on admission</td> <td></td> <td></td> </tr> <tr> <td>    alert, %</td> <td>3.0</td> <td>7.1</td> </tr> <tr> <td>    drowsy, %</td> <td>34.8</td> <td>47.1</td> </tr> <tr> <td>    comatose, %</td> <td>62.1</td> <td>45.7</td> </tr> </tbody> </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
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comatose, %	62.1	45.7																							
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus dexamethasone</i></p> <p>Dexamethasone (3 weeks)</p> <p>8 to 12 mg/day</p> <p>Antituberculosis chemotherapy: 1.5HSE/22.5HE</p> <p>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</p> <p>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</p>																								
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: 1.5HSE/22.5HE</p> <p>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</p> <p>10 mg/kg of body weight/day isoniazid and 25 mg/kg of body weight/ day ethambutol for the remainder of the 2-year</p>																								

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

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

<sup>1</sup> 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

<b>Bibliographic reference</b>	Girgis NI, Farid Z, Kilpatrick ME (1991) Dexamethasone adjunctive treatment for tuberculous meningitis. <i>Pediatric Infectious Disease Journal</i> 10(3): 179-83
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> yes – number randomisation chart</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> unclear</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> 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)</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i> yes, although details provided are limited</p> <p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin and pyrazinamide, but contain streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> no</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>
<b>Number of patients</b>	<p>Included = 280</p> <p>dexamethasone group = 145</p> <p>antituberculosis chemotherapy alone group = 135</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Tuberculous meningitis</p> <p><i>Diagnostic criteria</i></p> <p>Clinical history</p> <p>Signs and symptoms compatible with tuberculous meningitis:</p> <p>low grade fever</p> <p>severe progressive headache</p>

	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				
	<i>Baseline</i>				
			<b>Dexamethasone group</b> (n = 145)		<b>Antituberculosis chemotherapy alone group</b> (n = 135)
		<b>CSF culture-positive</b> (n = 75)	<b>CSF culture-negative</b> (n = 70)	<b>CSF culture-positive</b> (n = 85)	<b>CSF culture-negative</b> (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
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus dexamethasone</i>				



	<p>Dexamethasone (3 weeks)</p> <p>12 mg/day in adults, and 8 mg/day in children weighing less than 25 kg</p> <p>Antituberculosis chemotherapy: 1.5HSE/22.5HE</p> <p>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</p> <p>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</p> <p>In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed</p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: 1.5HSE/22.5HE</p> <p>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</p> <p>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</p> <p>In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed</p>
<b>Length of follow up</b>	Full treatment period
<b>Location</b>	Cairo, Egypt
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>dexamethasone group = 72 of 145</p> <p>antituberculosis chemotherapy alone group = 79 of 135</p> <p>OR<sup>1</sup> (95% CI) = 0.70 (0.44 to 1.12)</p> <p>i.e. not statistically significant</p>

	<p>CSF positive for tubercle bacilli</p> <p>dexamethasone group = 32 of 75</p> <p>antituberculosis chemotherapy alone group = 50 of 85</p> <p><b>OR<sup>1</sup> (95% CI) = 0.52 (0.28 to 0.98)</b></p> <p><b>i.e. statistically significant</b></p> <p>CSF negative for tubercle bacilli</p> <p>dexamethasone group = 40 of 70</p> <p>antituberculosis chemotherapy alone group = 29 of 50</p> <p>OR<sup>1</sup> (95% CI) = 0.97 (0.46 to 2.01)</p> <p>i.e. not statistically significant</p> <p>Alert on admission</p> <p>dexamethasone group = 0 of 6</p> <p>antituberculosis chemotherapy alone group = 2 of 5</p> <p>OR<sup>1</sup> (95% CI) = 0.11 (0.00 to 2.93)</p> <p>i.e. not statistically significant</p> <p>Drowsy on admission</p> <p>dexamethasone group = 10 of 42</p> <p>antituberculosis chemotherapy alone group = 18 of 45</p> <p>OR<sup>1</sup> (95% CI) = 0.47 (0.19 to 1.18)</p> <p>i.e. not statistically significant</p> <p>Comatose admission</p>
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	<p>dexamethasone group = 62 of 97</p> <p>antituberculosis chemotherapy alone group = 59 of 85</p> <p>OR<sup>1</sup> (95% CI) = 0.78 (0.42 to 1.45)</p> <p>i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – neurologic abnormalities (developed during treatment)</b></p> <p>Number of patients to develop neurologic abnormalities (fundus, hemiparesis or hydrocephalus) during treatment</p> <p>dexamethasone group = 8 of 145</p> <p>antituberculosis chemotherapy alone group = 15 of 135</p> <p>OR<sup>1</sup> (95% CI) = 0.47 (0.19 to 1.14)</p> <p>i.e. not statistically significant</p> <p>CSF positive for tubercle bacilli</p> <p>dexamethasone group = 4 of 75</p> <p>antituberculosis chemotherapy alone group = 10 of 85</p> <p>OR<sup>1</sup> (95% CI) = 0.42 (0.13 to 1.41)</p> <p>i.e. not statistically significant</p> <p>CSF negative for tubercle bacilli</p> <p>dexamethasone group = 4 of 70</p> <p>antituberculosis chemotherapy alone group = 5 of 50</p> <p>OR<sup>1</sup> (95% CI) = 0.67 (0.17 to 2.60)</p> <p>i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – neurologic abnormalities (permanent residual sequelae)</b></p>

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

	<p>i.e. not statistically significant</p> <p><b>Changes in signs and symptoms – responsiveness</b></p> <p>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)</p> <p>dexamethasone group (n = 75) = 35±33</p> <p>antituberculosis chemotherapy alone group (n = 85) = 31±23</p> <p>MD<sup>2</sup> (95% CI) = 4 (-4.9 to 12.9)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Supported by the United States Navy Department, the Department of Defence, the United States Government and the Egyptian Ministry of Health
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Mean difference and 95% confidence interval calculated by reviewer</p> <p>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</p>	

**1.5.14 Malhotra et al, 2009**

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

	<p>unclear</p> <p><i>Blinding used?</i></p> <p>no</p> <p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes, although some patients received streptomycin instead of ethambutol during the initial phase of treatment</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
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<p><b>Number of patients</b></p>	<p>Randomised = 97</p> <p>dexamethasone group = 32</p> <p>methylprednisolone group = 33</p> <p>antituberculosis chemotherapy alone group = 32</p> <p>Outcome data available for = 91</p> <p>dexamethasone group = 31</p> <p>methylprednisolone group = 30</p> <p>antituberculosis chemotherapy alone group = 30</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Tuberculous meningitis</p> <p>Aged &gt;14 years</p> <p><i>Diagnostic criteria</i></p> <p>Based on the results of clinical and radiological examination, the evaluation of cell types and numbers, and protein and glucose concentrations in the CSF</p> <p>The essential clinical indicator was the presence of a meningitic syndrome, as defined by the presence of headache vomiting and fever</p> <p>In the CSF samples, a predominantly lymphocytotic pleocytosis and an elevated protein concentration were taken as further evidence tuberculous meningitis</p> <p>‘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</p> <p>‘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</p> <p>‘Possible’ meningitis = at least 4 of the following:</p>

	<p>history of tuberculosis</p> <p>predominance of lymphocytes in the CSF</p> <p>illness lasting &gt;5 days</p> <p>a ratio of CSF glucose concentration:plasma glucose concentration of &lt;0.5</p> <p>altered consciousness</p> <p>yellow CSF</p> <p>focal neurological signs</p> <p>Drug susceptibility was not tested</p> <p><i>Severity of disease</i></p> <p>Classified according to the system of the British Medical Research Council:</p> <p>stage 1: no definite neurological symptoms; scoring 15 on the Glasgow coma scale</p> <p>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</p> <p>stage 3: severe clouding of sensorium, convulsions, focal neurological deficit and involuntary movements; scoring <math>\leq 10</math> on the Glasgow coma scale</p> <p><i>Exclusion</i></p> <p>HIV infection</p> <p>Contraindication of corticosteroids</p> <p>Previous use of antituberculosis chemotherapy and/or corticosteroids</p> <p>Evidence of a brain abscess or tumour – e.g. an intracranial space-occupying lesion visible by CT</p> <p><i>Baseline</i></p>			
		<b>Dexamethasone</b>	<b>Methylprednisolone</b>	<b>Antituberculosis</b>



				<b>chemotherapy alone</b>
Sex				
male, n	15	14	14	14
female, n	16	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	7
stage 2, n	18	17	18	18
stage 3, n	6	6	5	5
History of tuberculosis, n	4	6	7	7
Fever, n	27	29	27	27
Headache, n	27	27	25	25
Vomiting, n	22	17	17	17
Seizures, n	7	11	7	7
Visual symptoms, n	15	14	16	16
Altered sensorium, n	12	15	12	12
Cranial nerve palsies, n	12	11	9	9
Focal deficits, n	5	4	4	4

	Visual impairment, n	11	9	8
	Miliary shadow on chest x-ray, n	2	5	3
	Parenchymal shadow on chest x-ray, n	1	0	3
	Pleural effusion on chest x-ray, n	0	2	1
	Basal exudates on CT scan of brain, n	13	11	10
	Hydrocephalus on CT scan of brain, n	10	3	7
	Infarction on CT scan of brain, n	5	4	3
	Culture-positive for <i>M. tuberculosis</i> , n	1	1	1
	PCR-positive for <i>M. tuberculosis</i> , n	5	8	3
<b>Intervention 1</b>	<p><i>Antituberculosis chemotherapy plus dexamethasone</i></p> <p>Dexamethasone (4 weeks)</p> <p>0.4, 0.3, 0.2 and 0.1 mg/kg of bodyweight/day during weeks 1, 2, 3 and 4, respectively</p> <p>Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR</p> <p>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</p> <p>10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months</p> <p>Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required</p>			
<b>Intervention 2</b>	<p><i>Antituberculosis chemotherapy plus methylprednisolone</i></p> <p>Methylprednisolone (5 days)</p>			

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

	<p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.52 (0.21 to 1.27)</p> <p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.56 (0.15 to 2.02)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.48 (0.14 to 1.68)</p> <p>i.e. not statistically significant</p> <p>Stage 1</p> <p>dexamethasone group = 0 of 7</p> <p>methylprednisolone group = 0 of 7</p> <p>antituberculosis chemotherapy alone group = 1 of 7</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.15 (0.01 to 4.18)</p> <p>i.e. not statistically significant</p> <p>Stage 2</p> <p>dexamethasone group = 5 of 18</p> <p>methylprednisolone group = 6 of 17</p> <p>antituberculosis chemotherapy alone group = 8 of 18</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p>
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	<p>OR (95% CI) = 0.57 (0.18 to 1.85)  i.e. not statistically significant</p> <p>Stage 3</p> <p>dexamethasone group = 3 of 6  methylprednisolone group = 3 of 6  antituberculosis chemotherapy alone group = 4 of 5</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.25 (0.02 to 2.94)  i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – disability</b></p> <p>Assessed using a modified Rankin scale:</p> <p>score of 0 = no symptoms at all</p> <p>score of 1 = no significant disability despite the presence of symptoms, with the subject able to carry out all their usual duties and activities</p> <p>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</p> <p>score of 3 = moderate disability, with the subject requiring help but able to walk without assistance</p> <p>score of 4 = moderately severe disability, with the subject unable to walk without assistance and unable to attend to own bodily needs without assistance</p> <p>score of 5 = severe disability, with the subject bedridden, incontinent and requiring constant nursing care and attention</p> <p>Final scores:</p> <p>0 = good outcome</p>

	<p>1–2 = intermediate disability</p> <p>3–5 = severe disability</p> <p>Number of patients to experience severe disability after 6 months of treatment</p> <p>dexamethasone group = 5 of 32</p> <p>methylprednisolone group = 6 of 33</p> <p>antituberculosis chemotherapy alone group = 5 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 1.10 (0.35 to 3.49)</p> <p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 1.30 (0.22 to 7.55)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.96 (0.21 to 4.47)</p> <p>i.e. not statistically significant</p> <p>Severe disability among patients defined as stage 1 at baseline</p> <p>dexamethasone group = 1 of 7</p> <p>methylprednisolone group = 1 of 7</p> <p>antituberculosis chemotherapy alone group = 1 of 7</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 1.00 (0.07 to 13.37)</p>
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	<p>i.e. not statistically significant</p> <p>Severe disability among patients defined as stage 2 at baseline</p> <p>dexamethasone group = 3 of 18</p> <p>methylprednisolone group = 3 of 17</p> <p>antituberculosis chemotherapy alone group = 3 of 18</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 1.03 (0.23 to 4.73)</p> <p>i.e. not statistically significant</p> <p>Severe disability among patients defined as stage 3 at baseline</p> <p>dexamethasone group = 1 of 6</p> <p>methylprednisolone group = 2 of 6</p> <p>antituberculosis chemotherapy alone group = 1 of 5</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 1.22 (0.10 to 17.10)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience intermediate disability after 6 months of treatment</p> <p>dexamethasone group = 3 of 32</p> <p>methylprednisolone group = 0 of 33</p> <p>antituberculosis chemotherapy alone group = 4 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.34 (0.07 to 1.62)</p>
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	<p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone</i><sup>2</sup></p> <p>OR (95% CI) = 0.72 (0.11 to 4.84)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone</i><sup>2</sup></p> <p>OR (95% CI) = 0.09 (0.00 to 1.92)</p> <p>i.e. not statistically significant</p> <p>Number of patients with a good outcome after 6 months of treatment</p> <p>dexamethasone group = 15 of 32</p> <p>methylprednisolone group = 15 of 33</p> <p>antituberculosis chemotherapy alone group = 8 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone</i><sup>1</sup></p> <p><b>OR (95% CI) = 2.57 (1.01 to 6.56)</b></p> <p><b>i.e. statistically significant</b></p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone</i><sup>2</sup></p> <p>OR (95% CI) = 2.65 (0.70 to 9.99)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone</i><sup>2</sup></p> <p>OR (95% CI) = 2.50 (0.67 to 9.39)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events - hepatic</b></p>



	<p>Number of patients to experience clinical or subclinical hepatitis</p> <p>dexamethasone group = 5 of 32</p> <p>methylprednisolone group = 7 of 33</p> <p>antituberculosis chemotherapy alone group = 8 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.68 (0.25 to 1.88)</p> <p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.56 (0.13 to 2.44)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.81 (0.20 to 3.30)</p> <p>i.e. not statistically significant</p> <p>Number of patients to experience clinical hepatitis</p> <p>dexamethasone group = 1 of 32</p> <p>methylprednisolone group = 2 of 33</p> <p>antituberculosis chemotherapy alone group = 2 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.73 (0.12 to 4.58)</p> <p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone<sup>2</sup></i></p>
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	<p>OR (95% CI) = 0.48 (0.03 to 8.28)  i.e. not statistically significant  <i>Methylprednisolone vs antituberculosis chemotherapy alone</i><sup>2</sup>  OR (95% CI) = 0.97 (0.08 to 11.54)  i.e. not statistically significant</p>
	<p><b>Adverse events – gastrointestinal bleeding</b>  Number of patients to experience gastrointestinal bleeding  dexamethasone group = 4 of 32  methylprednisolone group = 2 of 33  antituberculosis chemotherapy alone group = 1 of 32  <i>Any corticosteroid vs antituberculosis chemotherapy alone</i><sup>1</sup>  OR (95% CI) = 3.15 (0.36 to 27.37)  i.e. not statistically significant  <i>Dexamethasone vs antituberculosis chemotherapy alone</i><sup>2</sup>  OR (95% CI) = 5.21 (0.26 to 103.00)  i.e. not statistically significant  <i>Methylprednisolone vs antituberculosis chemotherapy alone</i><sup>2</sup>  OR (95% CI) = 0.97 (0.08 to 11.54)  i.e. not statistically significant</p>
	<p><b>Adverse events – paradoxical tuberculoma</b>  Number of patients to experience paradoxical tuberculoma</p>

	<p>dexamethasone group = 2 of 32</p> <p>methylprednisolone group = 1 of 33</p> <p>antituberculosis chemotherapy alone group = 5 of 32</p> <p><i>Any corticosteroid vs antituberculosis chemotherapy alone<sup>1</sup></i></p> <p>OR (95% CI) = 0.26 (0.06 to 1.17)</p> <p>i.e. not statistically significant</p> <p><i>Dexamethasone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.47 (0.06 to 3.66)</p> <p>i.e. not statistically significant</p> <p><i>Methylprednisolone vs antituberculosis chemotherapy alone<sup>2</sup></i></p> <p>OR (95% CI) = 0.14 (0.01 to 1.42)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	<p><sup>1</sup> Pooled odds ratio, combining the data for the dexamethasone and methylprednisolone arms into a single ‘corticosteroid’ arm, and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> 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 <i>versus</i> antituberculosis chemotherapy alone and methylprednisolone plus antituberculosis chemotherapy <i>versus</i> antituberculosis chemotherapy alone</p> <p><sup>3</sup> Pooled mean difference, combining the data for the dexamethasone and methylprednisolone arms into a single ‘corticosteroid’ arm, calculated by reviewer</p> <p><sup>4</sup> 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 <i>versus</i> antituberculosis chemotherapy alone and</p>

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

<b>Bibliographic reference</b>	O'Toole RD, Thornton GF, Mukherjee MK et al (1969) Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. <i>Annals of Internal Medicine</i> 70(1): 39-48
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> yes – block randomisation using coded medication</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> double-blind</p> <p><i>Groups comparable at baseline?</i> yes, although details provided are limited</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> unclear</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> unclear</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin, pyrazinamide and ethambutol, but contain streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>unclear</p>
<p><b>Number of patients</b></p>	<p>Outcome data available for = 23</p> <p>dexamethasone group = 11</p> <p>placebo group = 12</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>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)</p> <p>Moderately advanced or severe disease</p> <p><i>Severity of disease</i></p> <p>Classified according to the system of the British Medical Research Council:</p> <p>stage 1: mild cases; without altered consciousness or focal neurologic signs</p>

	<p>stage 2: moderately advanced cases; altered consciousness; not comatose; moderate neurologic deficits, such as single cranial nerve palsies, paraparesis and hemiparesis</p> <p>stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia</p> <p><i>Baseline</i></p> <table border="1" data-bbox="732 400 1960 1077"> <thead> <tr> <th data-bbox="732 400 1301 552"></th> <th data-bbox="1301 400 1630 552"><b>Dexamethasone group</b> (n = 11)</th> <th data-bbox="1630 400 1960 552"><b>Placebo group</b> (n = 12)</th> </tr> </thead> <tbody> <tr> <td data-bbox="732 552 1301 783">Age, years</td> <td data-bbox="1301 552 1630 783"></td> <td data-bbox="1630 552 1960 783"></td> </tr> <tr> <td data-bbox="732 632 1301 671">&lt;2, n</td> <td data-bbox="1301 632 1630 671">2</td> <td data-bbox="1630 632 1960 671">3</td> </tr> <tr> <td data-bbox="732 695 1301 735">2 to 45, n</td> <td data-bbox="1301 695 1630 735">8</td> <td data-bbox="1630 695 1960 735">9</td> </tr> <tr> <td data-bbox="732 759 1301 783">&gt;45, n</td> <td data-bbox="1301 759 1630 783">1</td> <td data-bbox="1630 759 1960 783">0</td> </tr> <tr> <td data-bbox="732 783 1301 1015">Severity of disease</td> <td data-bbox="1301 783 1630 1015"></td> <td data-bbox="1630 783 1960 1015"></td> </tr> <tr> <td data-bbox="732 871 1301 911">stage 1, n</td> <td data-bbox="1301 871 1630 911">1</td> <td data-bbox="1630 871 1960 911">0</td> </tr> <tr> <td data-bbox="732 935 1301 975">stage 2, n</td> <td data-bbox="1301 935 1630 975">6</td> <td data-bbox="1630 935 1960 975">8</td> </tr> <tr> <td data-bbox="732 999 1301 1038">stage 3, n</td> <td data-bbox="1301 999 1630 1038">4</td> <td data-bbox="1630 999 1960 1038">4</td> </tr> <tr> <td data-bbox="732 1038 1301 1077">Culture-positive CSF, n</td> <td data-bbox="1301 1038 1630 1077">8</td> <td data-bbox="1630 1038 1960 1077">6</td> </tr> </tbody> </table>		<b>Dexamethasone group</b> (n = 11)	<b>Placebo group</b> (n = 12)	Age, years			<2, n	2	3	2 to 45, n	8	9	>45, n	1	0	Severity of disease			stage 1, n	1	0	stage 2, n	6	8	stage 3, n	4	4	Culture-positive CSF, n	8	6
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<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus dexamethasone</i></p> <p>Dexamethasone (4 weeks)</p> <p>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 the second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week</p> <p>paediatric dosage was derived from a standard table based on surface area</p>																														

	<p>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</p> <p>All patients received high doses of vitamin B<sub>6</sub></p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (4 weeks)</p> <p>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 the second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week</p> <p>paediatric dosage was derived from a standard table based on surface area</p> <p>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</p> <p>All patients received high doses of vitamin B<sub>6</sub></p>
<b>Length of follow up</b>	Unclear
<b>Location</b>	Calcutta, India
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>dexamethasone group = 6 of 11</p> <p>placebo group = 9 of 12</p> <p>OR<sup>1</sup> (95% CI) = 0.40 (0.07 to 2.34)</p> <p>i.e. not statistically significant</p> <p>Number of deaths amongst those &lt;2 years of age</p> <p>dexamethasone group = 2 of 2</p>

	<p>placebo group = 3 of 3</p> <p>OR<sup>1</sup> (95% CI) = 0.71 (0.01 to 49.71)</p> <p>i.e. not statistically significant</p> <p>Number of deaths amongst those classed as stage 2 on admission</p> <p>dexamethasone group = 3 of 6</p> <p>placebo group = 5 of 8</p> <p>OR<sup>1</sup> (95% CI) = 0.60 (0.07 to 5.14)</p> <p>i.e. not statistically significant</p> <p>Number of deaths amongst those classed as stage 3 on admission</p> <p>dexamethasone group = 3 of 4</p> <p>placebo group = 4 of 4</p> <p>OR<sup>1</sup> (95% CI) = 0.26 (0.01 to 8.52)</p> <p>i.e. not statistically significant</p> <p>(Mean) survival time (days)</p> <p>dexamethasone group = 14</p> <p>placebo group = 14</p> <p>MD<sup>2</sup> = 0</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Mean difference calculated by reviewer</p>	



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

### 1.5.16 Kumarvelu et al, 1994

<b>Bibliographic reference</b>	Kumarvelu S, Prasad K, Khosla A et al (1994) Randomised controlled trial of dexamethasone in tuberculous meningitis. <i>Tubercle and Lung Disease</i> 75(3): 203-7
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> yes – random numbers table</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> unclear</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> follow-up was equal in both groups although was only for 3 months after treatment initiation (i.e. not for the full treatment period)</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p>

	<p>'full/partial recovery' and 'unchanged' status not defined</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>antituberculosis chemotherapeutic regimens lacked ethambutol</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>yes – used composites of outcomes of interest: 'poor' and 'good' outcome were composites of mortality and changes in signs and symptoms</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>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</p>
<p><b>Number of patients</b></p>	<p>Randomised = 47</p> <p>dexamethasone group = 24</p> <p>antituberculosis chemotherapy alone group = 23</p> <p>Outcome data available at 3 months = 41</p> <p>dexamethasone group = 20</p> <p>antituberculosis chemotherapy alone group = 21</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Probable tuberculous meningitis</p> <p><i>Diagnostic criteria</i></p> <p>Diagnosis of probable tuberculous meningitis was made if at least 3 of the following criteria were present:</p>

	<p>clinical: fever &gt;38°C, headache, neck stiffness with or without seizures or altered sensorium for at least 2 weeks</p> <p>characteristic CSF findings: leukocytes &gt;20 /mm<sup>3</sup> with lymphocytotic predominance, proteins &gt;1 g/l, sugar &lt;2/3 of corresponding blood sugar, cultures negative for pyrogenic organisms and fungi, and negative cytology for malignant cells</p> <p>contrast-enhanced CT scan of the head: basal exudates or hydrocephalus with or without infarcts and tuberculoma</p> <p>clinical, radiological or histological evidence of extracranial tuberculosis</p> <p><i>Severity of disease</i></p> <p>Analysed on admission using the following scoring system:</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Weightage (points)</th> </tr> </thead> <tbody> <tr> <td>Sensorium</td> <td></td> </tr> <tr> <td>    normal</td> <td>1</td> </tr> <tr> <td>    delirium</td> <td>2</td> </tr> <tr> <td>    drowsy</td> <td>3</td> </tr> <tr> <td>    semi-coma</td> <td>4</td> </tr> <tr> <td>    coma</td> <td>5</td> </tr> <tr> <td>Associated pulmonary tuberculosis</td> <td>0.5</td> </tr> <tr> <td>Associated extensive tuberculous or non-tuberculous disease</td> <td>0.5</td> </tr> <tr> <td>Age &lt;10 years or &gt;50 years</td> <td>0.5</td> </tr> <tr> <td>CSF protein &gt;3 g/l</td> <td>0.5</td> </tr> <tr> <td>CT scan evidence</td> <td></td> </tr> <tr> <td>    exudates</td> <td></td> </tr> </tbody> </table>	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	
Parameter	Weightage (points)																										
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	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										
<p>'Severe' disease = a score of 8 or more</p> <p>'Mild-to-moderate' disease = a score of less than 8</p> <p><i>Exclusion</i></p> <p>Aged &lt;10 years</p> <p>Previous antituberculosis chemotherapy for &gt;4 weeks</p> <p>Previous glucocorticoid use</p> <p><i>Baseline</i></p> <table border="1" data-bbox="734 1182 1962 1390"> <thead> <tr> <th></th> <th>Dexamethasone group</th> <th>Antituberculosis chemotherapy alone</th> </tr> </thead> <tbody> <tr> <td>Clinical features</td> <td></td> <td></td> </tr> <tr> <td>  hypotension, %</td> <td>29</td> <td>13</td> </tr> </tbody> </table>					Dexamethasone group	Antituberculosis chemotherapy alone	Clinical features			hypotension, %	29	13
	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	
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus dexamethasone</i> 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				

	<p>off over the next 14 days</p> <p>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</p> <p>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</p> <p>Pyridoxine supplements were given routinely</p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>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</p> <p>Pyridoxine supplements were given routinely</p>
<b>Length of follow up</b>	3 months after treatment initiation
<b>Location</b>	New Delhi, India
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>dexamethasone group = 9 of 24</p> <p>antituberculosis chemotherapy alone group = 9 of 23</p> <p>OR<sup>1</sup> (95% CI) = 0.93 (0.29 to 3.03)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – full/partial recovery</b></p> <p>Definition not provided</p> <p>Number of patients to achieve a full or partial recovery</p>

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

	<p>i.e. not statistically significant</p> <p>Number of patients who were defined as ‘severe’ on admission and to survive whose status was unchanged</p> <p>dexamethasone group = 0 of 4</p> <p>antituberculosis chemotherapy alone group = 1 of 2</p> <p>OR<sup>1</sup> (95% CI) = 0.11 (0.00 to 4.48)</p> <p>i.e. not statistically significant</p> <p>Number of patients who were defined as ‘mild-to-moderate’ on admission and to survive whose status was unchanged</p> <p>dexamethasone group = 0 of 11</p> <p>antituberculosis chemotherapy alone group = 0 of 12</p> <p>OR<sup>1</sup> (95% CI) = 1.09 (0.02 to 59.40)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – ‘poor’ outcome</b></p> <p>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)</p> <p>Number of patients to experience a poor outcome</p> <p>dexamethasone group = 5 of 24</p> <p>antituberculosis chemotherapy alone group = 8 of 23</p> <p>OR<sup>1</sup> (95% CI) = 0.49 (0.13 to 1.82)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – ‘good’ outcome</b></p> <p>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</p>



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

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

	<p>Time (mean, days) to recovery of headache amongst patients who were defined as ‘mild-to-moderate’ on admission and who survived</p> <p>dexamethasone group (n = 11) = 18</p> <p>antituberculosis chemotherapy alone group (n = 12) = 11</p> <p>MD<sup>3</sup> = 7</p>
	<p><b>Changes in signs and symptoms – cognitive status</b></p> <p>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’)</p> <p>Time (mean, days) to improvement in mini-mental score amongst patients who survived</p> <p>dexamethasone group (n = 15)<sup>2</sup> = 8.3</p> <p>antituberculosis chemotherapy alone group (n = 14)<sup>2</sup> = 4.9</p> <p>MD<sup>3</sup> = 3.4</p> <p>Time (mean, days) to improvement in mini-mental score amongst patients who were defined as ‘severe’ on admission and who survived</p> <p>dexamethasone group (n = 4) = 9</p> <p>antituberculosis chemotherapy alone group (n = 2) = 10</p> <p>MD<sup>3</sup> = -1</p> <p>Time (mean, days) to improvement in mini-mental score amongst patients who were defined as ‘mild-to-moderate’ on admission and who survived</p> <p>dexamethasone group (n = 11) = 8</p> <p>antituberculosis chemotherapy alone group (n = 12) = 4</p> <p>MD<sup>3</sup> = 4</p>
	<p><b>Changes in signs and symptoms – activity of daily living</b></p>

	<p>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)</p> <p>Time (mean, days) to improvement in Barthel score amongst patients who survived</p> <p>dexamethasone group (n = 15)<sup>2</sup> = 7.6</p> <p>antituberculosis chemotherapy alone group (n = 14)<sup>2</sup> = 2.3</p> <p>MD<sup>3</sup> = 5.3</p> <p>Time (mean, days) to improvement in Barthel score amongst patients who were defined as ‘severe’ on admission and who survived</p> <p>dexamethasone group (n = 4) = 12</p> <p>antituberculosis chemotherapy alone group (n = 2) = 4</p> <p>MD<sup>3</sup> = 8</p> <p>Time (mean, days) to improvement in Barthel score amongst patients who were defined as ‘mild-to-moderate’ on admission and who survived</p> <p>dexamethasone group (n = 11) = 6</p> <p>antituberculosis chemotherapy alone group (n = 12) = 2</p> <p>MD<sup>3</sup> = 4</p>
<b>Source of funding</b>	No details provided
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> 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</p> <p><sup>3</sup> Mean difference calculated by reviewer</p>	

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

<b>Bibliographic reference</b>	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. <i>Pediatrics</i> 99(2): 226-31
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> 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</p> <p><i>Groups comparable at baseline?</i> yes, although details provided are limited</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> yes</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> yes</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>
<p><b>Number of patients</b></p>	<p>Randomised = 141</p> <p>prednisolone group = 70</p> <p>antituberculosis chemotherapy alone group = 71</p> <p>Outcome data available for incidence of mortality and the incidence of tuberculoma = 141</p> <p>prednisolone group = 70</p> <p>antituberculosis chemotherapy alone group = 71</p> <p>Outcome data available for IQ = 119</p> <p>prednisolone group = 65</p> <p>antituberculosis chemotherapy alone group = 54</p> <p>Outcome data available for motor function = 126</p> <p>prednisolone group = 66</p>

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

	<p>stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia</p> <p>Only patients with stage 2 or 3 were included</p> <p><i>Baseline</i></p> <table border="1" data-bbox="734 363 1960 852"> <thead> <tr> <th></th> <th>Prednisolone group</th> <th>Placebo group</th> </tr> </thead> <tbody> <tr> <td>Severity of disease</td> <td></td> <td></td> </tr> <tr> <td>    stage 2, n</td> <td>37</td> <td>36</td> </tr> <tr> <td>    stage 3, n</td> <td>33</td> <td>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> </tbody> </table>		Prednisolone group	Placebo group	Severity of disease			stage 2, n	37	36	stage 3, n	33	35	Baseline pressure (mean±SD), mm Hg	28.5±12.7	26.0±11.8	Pulse pressure (mean±SD), mm Hg	6.1±5.5	5.6±5.8	Ventricular size (mean±SD), ratio of biventricular diameter to biparietal diameter	0.26±0.08	0.25±0.08
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<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (1 month)</p> <p>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<sup>2</sup></p> <p>Antituberculosis chemotherapy: 6HRZE</p> <p>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</p> <p>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</p> <p>All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery</p>																					



<b>Comparison</b>	<p><i>Antituberculosis chemotherapy alone</i></p> <p>Antituberculosis chemotherapy: 6HRZE</p> <p>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</p> <p>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</p> <p>All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery</p>
<b>Length of follow up</b>	6 months from treatment initiation (i.e. full treatment period)
<b>Location</b>	South Africa
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>prednisolone group = 4 of 70</p> <p>antituberculosis chemotherapy alone group = 13 of 71</p> <p><b>OR<sup>1</sup> (95% CI) = 0.28 (0.09 to 0.90)</b></p> <p><b>i.e. statistically significant</b></p> <p>Number of deaths among those classified as stage 2 on admission</p> <p>prednisolone group = 1 of 37</p> <p>antituberculosis chemotherapy alone group = 1 of 36</p> <p>OR<sup>1</sup> (95% CI) = 0.97 (0.06 to 16.16)</p> <p>i.e. not statistically significant</p> <p>Number of deaths among those classified as stage 3 on admission</p> <p>prednisolone group = 3 of 33</p>

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

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

	<p>i.e. not statistically significant</p> <p><b>Changes in signs and symptoms - hearing</b></p> <p>Number of patients with deterioration in their hearing (decreased hearing, though not deaf) at 6 months</p> <p>prednisolone group = 3 of 70</p> <p>antituberculosis chemotherapy alone group = 6 of 71</p> <p>OR<sup>1</sup> (95% CI) = 0.49 (0.12 to 2.02)</p> <p>i.e. not statistically significant</p> <p>Number of patients to be deaf at 6 months</p> <p>prednisolone group = 0 of 70</p> <p>antituberculosis chemotherapy alone group = 0 of 71</p> <p>OR<sup>1</sup> (95% CI) = 1.01 (0.02 to 51.82)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	South Africa Medical Research Council
<b>Comments</b>	<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> 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%</p> <p>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</p>

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

<b>Study type</b>	RCT
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<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>yes – computer-generated sequence of random numbers was used to allocate treatment in blocks of 30</p> <p><i>Allocation concealment used?</i></p> <p>yes</p> <p><i>Blinding used?</i></p> <p>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</p> <p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes</p>
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	<p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
<b>Number of patients</b>	<p>Randomised = 545</p> <p>dexamethasone group = 274</p> <p>placebo group = 271</p> <p>Lost to follow-up (last observation carried forward) = 62</p> <p>dexamethasone group = 35</p> <p>placebo group = 27</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Clinical evidence of meningitis</p> <p>Over 14 years of age</p> <p><i>Diagnostic criteria</i></p> <p>Combination of nuchal rigidity and CSF abnormalities</p> <p>‘Definite’ tuberculosis = acid-fast bacilli were seen in the CSF</p> <p>‘Probable tuberculosis = patients with one or more of the following:</p> <p>suspected active pulmonary tuberculosis on chest radiography</p> <p>acid-fast bacilli found in any specimen other than the CSF</p> <p>clinical evidence of other extrapulmonary tuberculosis</p> <p>‘Possible’ tuberculosis = patients with at least four of the following:</p>

	<p>a history of tuberculosis, predominance of lymphocytes in the CSF</p> <p>a duration of illness of more than five days</p> <p>a ratio of CSF glucose to plasma glucose of less than 0.5</p> <p>altered consciousness</p> <p>yellow cerebrospinal fluid</p> <p>focal neurologic signs</p> <p><i>Severity of disease</i></p> <p>Patients were stratified on entry according to the British Medical Research Council criteria, modified as follows:</p> <p>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</p> <p>stage 2 = a score on the Glasgow coma scale of either 11 to 14, or of 15 with focal neurologic signs</p> <p>stage 3 = a score on the Glasgow coma score of 10 or less</p> <p><i>Exclusion</i></p> <p>Corticosteroids contraindicated</p> <p>&gt;1 dose of any corticosteroid</p> <p>&gt;30 days of antituberculosis chemotherapy immediately before study entry</p> <p><i>Baseline</i></p>		
		<b>Dexamethasone</b> (n = 274)	<b>Placebo</b> (n = 271)
Age			
median, years	36.0	35.0	

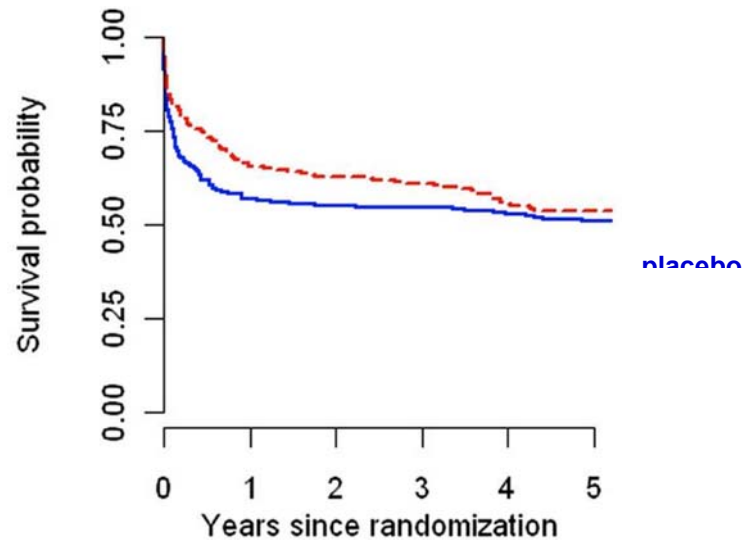
	range, years	15–88	15–84
	Sex		
	male, n (%)	168 (61.3)	163 (60.1)
	Diagnosis		
	definite	98 (35.8)	89 (32.8)
	probable	130 (47.4)	131 (48.3)
	possible	44 (16.1)	47 (17.3)
	not tuberculous meningitis	2 (0.7)	4 (1.5)
	Weight		
	median, kg	45.0	45.0
	range, kg	25–75	30–70
	Score on the Glasgow coma scale		
	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, /mm <sup>3</sup>	64	66
		range, /mm <sup>3</sup>	14–694	7–359
		CD8		
		median, /mm <sup>3</sup>	606	386
		range, /mm <sup>3</sup>	134–998	28–1001
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus dexamethasone</i></p> <p>Dexamethasone sodium phosphate (8 weeks)</p> <p>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)</p> <p>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</p> <p>Antituberculosis chemotherapy:</p> <p>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</p>			

	<p>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</p> <p>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</p> <p>None of the patients received antiretroviral drugs</p>
<p><b>Comparison</b></p>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (8 weeks)</p> <p>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)</p> <p>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</p> <p>Antituberculosis chemotherapy:</p> <p>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</p> <p>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</p> <p>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</p> <p>None of the patients received antiretroviral drugs</p>

<b>Location</b>	Ho Chi Minh City, Vietnam					
<b>Bibliographic reference</b>	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					
<b>Length of follow up</b>	5 years after randomisation					
<b>Outcomes measures and effect size</b>	<b>Mortality</b>					
	<b>Years after treatment initiation</b>	<b>Dexamethasone</b> (n = 274)		<b>Placebo</b> (n = 271)		<b>Difference in survival rate (95% CI); p-value</b>
		Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
	<b>0</b>	274	-	271	-	-
	<b>1</b>	160	0.65 (0.60 to 0.71)	131	0.57 (0.51 to 0.63)	0.09 (0.00 to 0.17); p = 0.04
	<b>2</b>	152	0.63 (0.57 to 0.69)	125	0.55 (0.49 to 0.69)	0.08 (0.00 to 0.16); p = 0.07
	<b>3</b>	147	0.61 (0.55 to 0.67)	124	0.55 (0.49 to 0.61)	0.06 (-0.02 to 0.15); p = 0.15
	<b>4</b>	130	0.55 (0.50 to 0.62)	117	0.53 (0.47 to 0.59)	0.03 (-0.06 to 0.11); p = 0.56
<b>5</b>	82	0.54 (0.48 to 0.60)	64	0.51 (0.45 to 0.57)	0.03 (-0.06 to 0.12); p = 0.51	



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

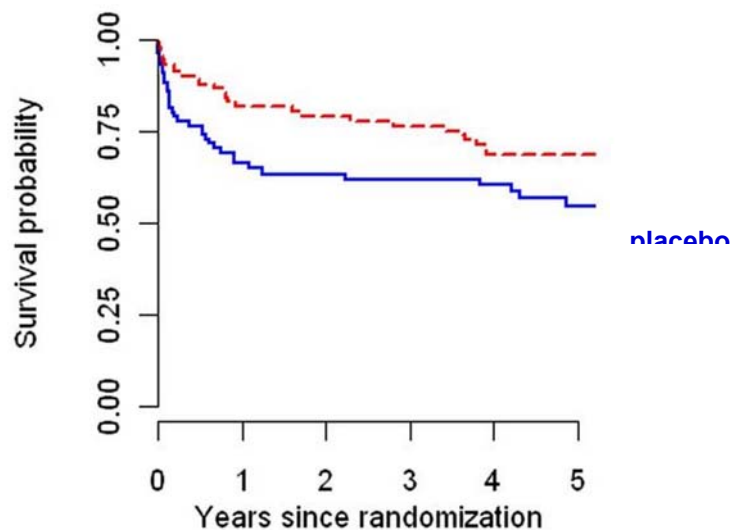
placebo group = 128 of 271

OR<sup>1</sup> (95% CI) = 0.88 (0.63 to 1.24)

i.e. not statistically significant

Stage 1 disease:

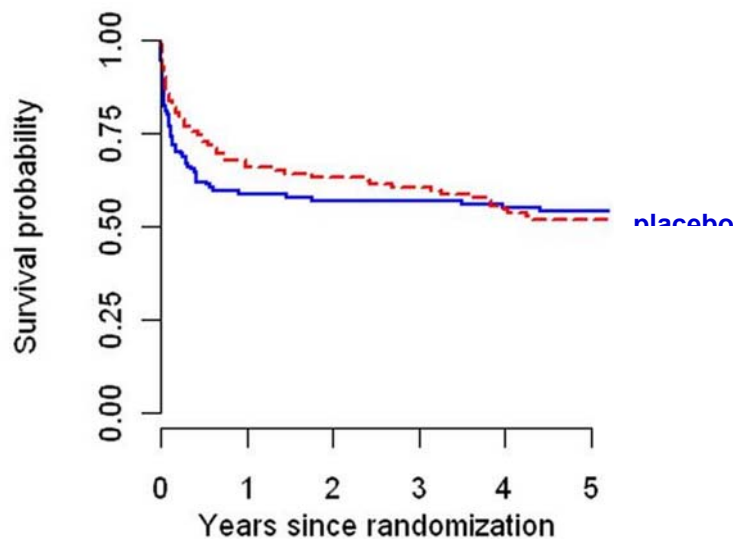
Years after treatment initiation	Dexamethasone (n = 90)		Placebo (n = 86)		Difference in survival rate (95% CI); p-value
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
<b>0</b>	90	-	86	-	-
<b>1</b>	65	0.82 (0.74 to 0.90)	46	0.66 (0.57 to 0.77)	0.15 (0.02 to 0.29); p = 0.02
<b>2</b>	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
<b>3</b>	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
<b>4</b>	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
<b>5</b>	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 0.64)	60	0.55 (0.47 to 0.63)	0.00 (-0.18 to 0.17); p = 1.00

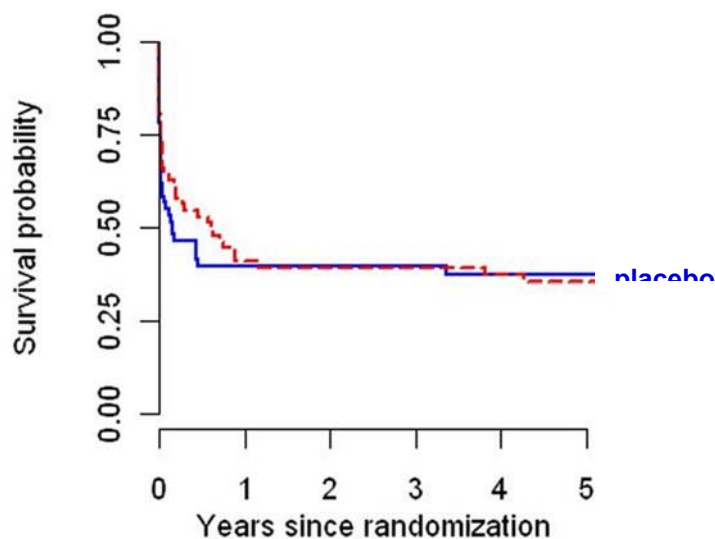
		0.65)		0.65)	0.98
<b>5</b>	34	0.52 (0.43 to 0.62)	33	0.54 (0.46 to 0.64)	-0.02 (-0.15 to 0.11); p = 0.73



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)	
<b>0</b>	62	-	60	-	-
<b>1</b>	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
<b>2</b>	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

<b>3</b>	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
<b>4</b>	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
<b>5</b>	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<sup>1</sup> (95% CI) = 1.14 (0.77 to 1.69)

i.e. not statistically significant



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

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

	<p>i.e. not statistically significant</p> <p>Number of patients without paraparesis at baseline to be experiencing paraparesis after 9 months of treatment</p> <p>dexamethasone group = 11 of 246</p> <p>placebo group = 11 of 260</p> <p>OR<sup>1</sup> (95% CI) = 1.06 (0.45 to 2.49)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>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</p> <p>Number of patients to experience relapse</p> <p>dexamethasone group = 41 of 274</p> <p>placebo group = 48 of 271</p> <p>OR<sup>1</sup> (95% CI) = 0.82 (0.52 to 1.29)</p> <p>i.e. not statistically significant</p> <p>Time to relapse (median, days)</p> <p>dexamethasone group = 41</p> <p>placebo group = 38</p> <p>p = 0.12</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – ‘severe’ events</b></p> <p>Defined as any event causing or threatening to cause prolonged hospital stay, disability, or death</p>

	<p>Number of patients to experience a severe event</p> <p>dexamethasone group = 26 of 274</p> <p>placebo group = 45 of 271</p> <p><b>OR<sup>1</sup> (95% CI) = 0.53 (0.31 to 0.88)</b></p> <p><b>i.e. statistically significant</b></p>
<b>Bibliographic reference</b>	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. <i>Lancet Neurology</i> 6(3): 230-6
<b>Length of follow up</b>	9 months after treatment initiation
<b>Outcomes measures and effect size</b>	<p><b>Changes in signs and symptoms – tuberculoma</b></p> <p>Number of patients to experience a tuberculoma</p> <p>dexamethasone group = 9 of 274</p> <p>placebo group = 5 of 271</p> <p>OR<sup>1</sup> (95% CI) = 1.81 (0.60 to 5.46)</p> <p>i.e. not statistically significant</p>
	<p><b>Changes in signs and symptoms – hydrocephalus</b></p> <p>Number of patients to experience hydrocephalus</p> <p>dexamethasone group = 10 of 274</p> <p>placebo group = 7 of 271</p> <p>OR<sup>1</sup> (95% CI) = 1.43 (0.54 to 3.81)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Wellcome Trust

<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>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</p>	

## BONE & JOINT, INCLUDING SPINAL, TUBERCULOSIS

### 1.5.19 Cathro, 1958

<b>Bibliographic reference</b>	Cathro AJM (1958) A clinical trial of prednisolone in bone and joint tuberculosis. East African Medical Journal 35(1): 31-5
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> unclear</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> unclear</p> <p><i>Groups comparable at baseline?</i> 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</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> no – not for the full treatment period</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes, although follow-up not for the full treatment period and therefore completion of antituberculosis chemotherapy could not be assessed</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes, although details provided are limited</p> <p><i>Intervention used is the same as the intervention of interest?</i> antituberculosis chemotherapeutic regimens lacked rifampicin, pyrazinamide and ethambutol</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> yes - response to treatment</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>								
<b>Number of patients</b>	<p>Randomised = 16</p> <p>prednisolone group = 10</p> <p>antituberculosis chemotherapy alone group = 6</p>								
<b>Patient characteristics</b>	<p><i>Inclusion</i> Active tuberculosis of bone and joint</p> <p><i>Baseline</i> Ages ranged from 4 to 47, with an average of 16 years</p> <table border="1" data-bbox="732 1179 1960 1388"> <thead> <tr> <th data-bbox="732 1179 1299 1275"></th> <th data-bbox="1299 1179 1628 1275"><b>Prednisolone</b></th> <th data-bbox="1628 1179 1960 1275"><b>Antituberculosis chemotherapy alone</b></th> </tr> </thead> <tbody> <tr> <td data-bbox="732 1275 1299 1388">Site of disease spinal, n (%)</td> <td data-bbox="1299 1275 1628 1388">7 (70)</td> <td data-bbox="1628 1275 1960 1388">0 (0)</td> </tr> </tbody> </table>				<b>Prednisolone</b>	<b>Antituberculosis chemotherapy alone</b>	Site of disease spinal, n (%)	7 (70)	0 (0)
	<b>Prednisolone</b>	<b>Antituberculosis chemotherapy alone</b>							
Site of disease spinal, n (%)	7 (70)	0 (0)							

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



	i.e. not statistically significant
	<p><b>Changes in signs and symptoms – weight</b></p> <p>Number of patients that failed to gain weight</p> <p>prednisolone group = 1 of 10</p> <p>antituberculosis chemotherapy alone group = 1 of 6</p> <p>OR<sup>1</sup> (95% CI) = 0.56 (0.03 to 10.93)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Prednisolone supplied by Pfizer Ltd.
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin</p>	

## PERICARDIAL TUBERCULOSIS

### 1.5.20 Hakim et al, 2000

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i> yes – use of a computer generated randomisation list</p> <p><i>Allocation concealment used?</i> unclear</p> <p><i>Blinding used?</i> 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</p> <p><i>Groups comparable at baseline?</i> yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i> yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> unclear</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p>

	<p>yes <i>Population studied is the same as the population of interest?</i></p> <p>yes <i>Intervention used is the same as the intervention of interest?</i></p> <p>yes <i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>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</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>unclear</p>
<b>Number of patients</b>	<p>Randomised = 58</p> <p>prednisolone group = 29</p> <p>antituberculosis chemotherapy alone group = 29</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Age 18–55 years</p> <p>Residence in Harare city to ensure good follow up</p> <p>HIV seropositive</p> <p>No diagnosis of tuberculosis within the past two years</p> <p>Large pericardial effusion on echocardiography (&gt;1 cm anteriorly and &gt;1 cm posteriorly)</p> <p>Pericardial aspirate with &gt;50% lymphocytes</p> <p>Protein content &gt;30 g/l</p>

	<i>Diagnostic criteria</i>	
	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	
	<i>Exclusion</i>	
	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		
<i>Baseline</i>		
	<b>Prednisolone</b> (n = 29)	<b>Antituberculosis chemotherapy alone</b> (n = 29)
Age (mean (range)), years	33 (19–53)	29 (21–41)

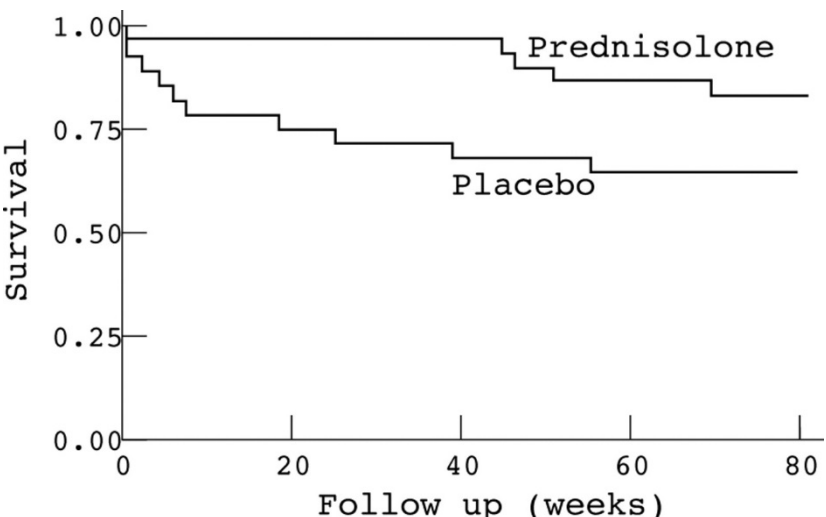
	Sex, male:female	22:7	18:11
	Duration of illness		
	unknown	1	1
	<2 weeks, n	4	3
	2–8 weeks, n	20	15
	>8 weeks, n	4	10
	Symptoms		
	cough, n	27	28
	sputum production, n	22	22
	haemoptysis, n	6	3
	dyspnea		
	nil, n	3	5
	on exertion, n	16	18
	at rest, n	10	6
	chest pain, n	26	23
	Past medical history		
	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

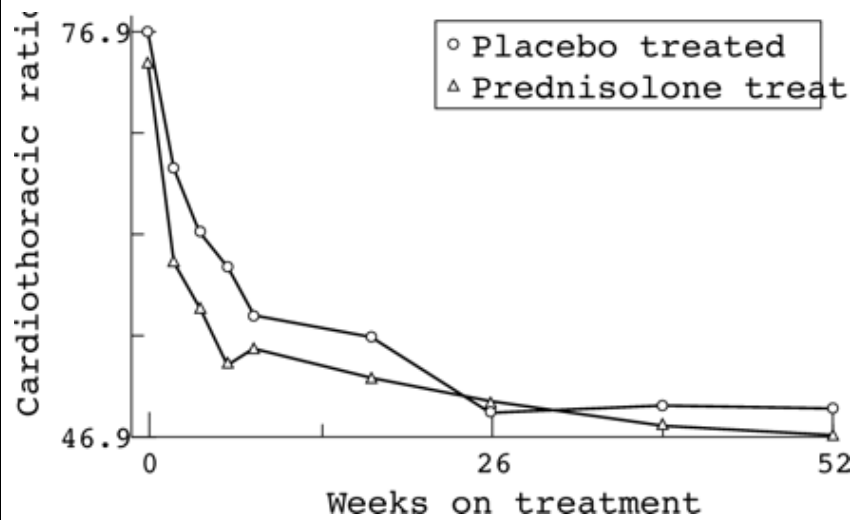
	Hepatomegaly		
	≤4 cm, n	7	6
	5–8 cm, n	16	16
	>8 cm, n	4	3
	Patients' perception of wellbeing		
	completely well, n	0	0
	well, but not perfect, n	12	11
	unwell, n	17	17
	Level of physical activity		
	unrestricted, n	11	11
	out and about, but restricted, n	11	12
	restricted to home or hospital, n	6	5
	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 aspartate transaminase alkaline phosphatase albumin	11 (10–180) 35 (5–520) 178 (145–361) 16	11 (10–27) 32 (6–127) 237 (100–610) 12
	Cardiothoracic ratio (chest x-ray)		
	<55% 55–75% >75%	0 9 5	0 6 8
	Low voltage ECG	4	5
	Pericardial effusion size (mean±SD)		
	anterior, cm posterior, cm subcostal,cm	2.5±2.1 2.6±1.0 2.7±1.0	2.2±1.3 2.8±1.3 2.7±1.0
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus prednisolone</i> 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		
<b>Comparison</b>	<i>Antituberculosis chemotherapy plus placebo</i> Placebo (6 weeks)		

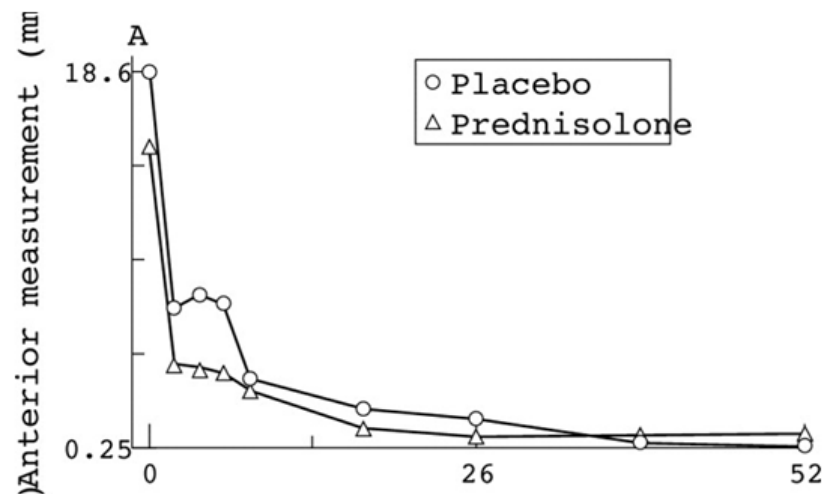


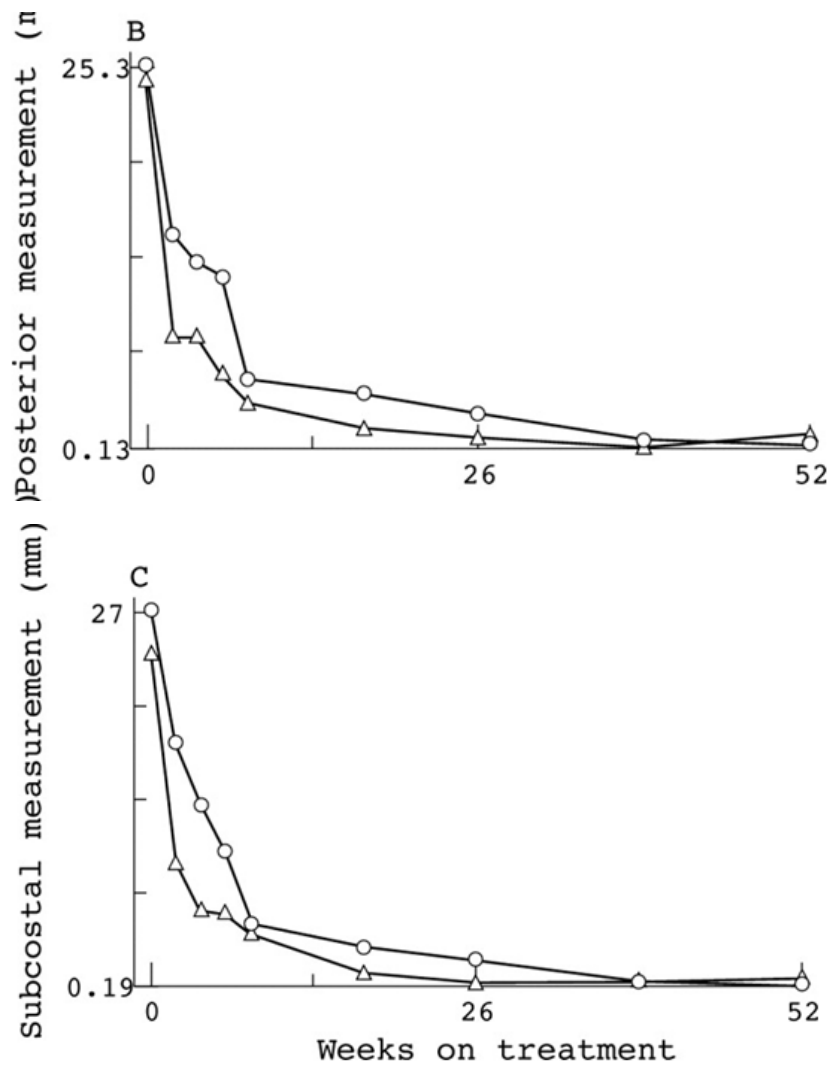
	<p>starting at a dose of 60 mg (12 tablets) and tapering by 10 mg per week until completion at the end of the sixth week</p> <p>Antituberculosis chemotherapy: 2HRZE/4HR</p> <p>doses not provided</p>
<b>Length of follow up</b>	18 months after treatment initiation
<b>Location</b>	Harare, Zimbabwe
<b>Outcomes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

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



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)<sup>2</sup>





**Adherence**

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

	<p>prednisolone group = 169 of 230</p> <p>antituberculosis chemotherapy alone group = 119 of 182</p> <p>p = 0.008</p> <p>i.e. statistically significant</p> <p>OR<sup>1</sup> (95% CI) = 1.47 (0.96 to 2.24)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	CAPS(Pvt) Ltd. provided the prednisolone and placebo tablets and financial support
<b>Comments</b>	
<p><sup>1</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>2</sup> Authors do not specify the statistic used (mean vs median etc)</p> <p>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</p>	

**1.5.21 Reuter et al, 2006**

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>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</p> <p><i>Allocation concealment used?</i></p> <p>yes – randomisation schedule provided to the treating physician with the assigned treatment by a non-clinical administrator</p>

	<p><i>Blinding used?</i></p> <p>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</p> <p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>yes</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>no</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
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<b>Number of patients</b>	<p>Randomised = 57</p> <p>prednisolone group = 16</p> <p>triamcinolone group = 17</p> <p>placebo group = 24</p>			
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Large pericardial effusion on echocardiography (epi-pericardial distance &gt; 10 mm)</p> <p>Pericardial aspirate with protein content &gt; 30 g/l; (4) pericardial fluid adenosine deaminase (ADA) activity &gt; 35 U/l</p> <p>Aged 13 to 75 years</p> <p><i>Exclusion</i></p> <p>CD4 counts &lt;200 cells/<math>\mu</math>l were excluded due to uncertainty as to the effects of corticosteroids on immunocompromised patients with TB with regard to risk for disseminated disease</p> <p>Patients presenting with signs of constrictive pericarditis or requiring pericardial surgery within the first 5 days of admission</p> <p><i>Baseline</i></p> <p>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</p>			
		<b>Prednisolone group</b> (n= 16)	<b>Triamcinolone group</b> (n= 17)	<b>Placebo group</b> (n= 24)
	Sex			
	female, n	7	4	12
	male, n	9	13	12
	HIV-seropositive	9	6	6

	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)



<b>Intervention 1</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (injection plus 11 weeks)</p> <p>oral prednisone plus intrapericardial placebo (5 ml 0.9% saline solution)</p> <p>intrapericardial placebo: 5 ml 0.9% saline solution</p> <p>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</p> <p>Antituberculosis chemotherapy: 2HRZE/4HR</p> <p>doses not provided</p> <p>Patients were discharged on antituberculous therapy and pyridoxine with adjunctive prednisone</p>
<b>Intervention 2</b>	<p><i>Antituberculosis chemotherapy plus triamcinolone</i></p> <p>Triamcinolone (injection)</p> <p>200 mg (5 ml) intrapericardial triamcinolone hexacetonide</p> <p>due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone</p> <p>Antituberculosis chemotherapy: 2HRZE/4HR</p> <p>doses not provided</p> <p>Patients were discharged on antituberculous therapy and pyridoxine</p>
<b>Comparison</b>	<p><i>Antituberculosis chemotherapy plus placebo</i></p> <p>Placebo (injection)</p> <p>200 mg (5 ml) intrapericardial placebo</p> <p>due to limited resources, an oral placebo was not used in conjunction with the intrapericardial placebo</p>

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

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

	<p>OR<sup>2</sup> (95% CI) = 1.07 (0.08 to 13.90) i.e. not statistically significant</p> <p><i>Prednisolone<sup>3</sup> vs placebo</i></p> <p>OR<sup>2</sup> (95% CI) = 1.00 (0.09 to 11.24) i.e. not statistically significant</p>
<b>Source of funding</b>	Crossley Fund and the South African Medical Research Council
<b>Comments</b>	<p><sup>1</sup> Data for the 2 corticosteroid groups pooled by reviewer</p> <p><sup>2</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p><sup>3</sup> Data for prednisolone arm split in 2 to allow 2 pairwise comparisons of prednisolone vs triamcinolone and prednisolone vs placebo</p> <p>Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide</p>

### 1.5.22 Strang et al, 1987/2004

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

	<p><i>Groups comparable at baseline?</i></p> <p>yes</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i></p> <p>yes</p> <p><i>Population studied is the same as the population of interest?</i></p> <p>yes</p> <p><i>Intervention used is the same as the intervention of interest?</i></p> <p>antituberculosis chemotherapeutic regimens lacked ethambutol and contained streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i></p> <p>yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence</p> <p><i>Analysis followed the intent-to-treat principle?</i></p> <p>yes</p>
<b>Number of patients</b>	<p>Randomised = 143</p> <p>prednisolone group = 70</p>

	<p>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</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i>  Active tuberculous constrictive pericarditis  Normal, or only moderately enlarged, cardiac shadow on x-ray  5 years and older  <i>Diagnostic criteria</i>  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  <i>Exclusion</i></p>

Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year		
<i>Baseline</i>		
	<b>Prednisolone group</b>	<b>Placebo group</b>
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)
	<b>Ascites<sup>1</sup></b>		
	0–1, n (%)	16 (30)	14 (23)
	2, n (%)	27 (51)	40 (66)
	3, n (%)	10 (19)	7 (11)
	<b>Oedema<sup>2</sup></b>		
	0–1, n (%)	33 (62)	25 (41)
	2, n (%)	6 (11)	10 (16)
	3, n (%)	14 (26)	26 (43)
	<b>Activity<sup>3</sup></b>		
	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)
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus prednisolone</i>		



	<b>Prednisolone (11 weeks)</b>				
	Age, years	<b>3x daily for</b>			<b>1x daily for week 11</b> (total daily dose, mg)
		<b>weeks 1 to 4</b> (total daily dose, mg)	<b>weeks 5 to 8</b> (total daily dose, mg)	<b>weeks 9 to 10</b> (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
	<b>Antituberculosis chemotherapy: 3HRZS/HR</b>				
	Weight, kg	<b>1x daily</b>			
		<b>Streptomycin</b> (total daily dose, mg)	<b>Isoniazid</b> (total daily dose, mg)	<b>Rifampicin</b> (total daily dose, mg)	<b>Pyrazinamide</b> (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					
<b>Comparison</b>	<i>Antituberculosis chemotherapy plus placebo</i>				
	Placebo (11 weeks)				
Age, years	<b>3x daily for</b>			<b>1x daily for week 11</b> (total daily dose, mg)	
	<b>weeks 1 to 4</b>	<b>weeks 5 to 8</b>	<b>weeks 9 to 10</b>		

		(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					
		<b>1x daily</b>			
	Weight, kg	<b>Streptomycin</b> (total daily dose, mg)	<b>Isoniazid</b> (total daily dose, mg)	<b>Rifampicin</b> (total daily dose, mg)	<b>Pyrazinamide</b> (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					
<b>Location</b>	Transkei				
<b>Bibliographic reference</b>	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				
<b>Length of follow up</b>	10 years				
<b>Outcomes measures and effect size</b>	<b>Mortality</b> Number of deaths during 10 years of follow-up prednisolone group = 16 of 70				

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

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

	i.e. not statistically significant
<b>Source of funding</b>	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
<b>Comments</b>	<p><sup>1</sup> Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen</p> <p><sup>2</sup> Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum</p> <p><sup>3</sup> 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</p> <p><sup>4</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis</p>

**1.5.23 Strang et al, 1988/2004**

<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>quasi-randomised: randomised in blocks of by entering names consecutively into a register</p> <p><i>Allocation concealment used?</i></p> <p>yes</p> <p><i>Blinding used?</i></p> <p>double-blind; all the clinical, radiographic, bacteriological, echocardiogram and histological data reviewed blind by an independent assessor</p> <p><i>Groups comparable at baseline?</i></p> <p>unclear</p>

	<p><i>Groups received the same care apart from the intervention(s) studied?</i> yes, although details provided are limited</p> <p><i>Groups followed up for an equal and appropriate length of time?</i> yes</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i> yes</p> <p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> antituberculosis chemotherapeutic regimens lacked ethambutol and contained streptomycin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence</p> <p><i>Analysis followed the intent-to-treat principle?</i> no</p>
<p><b>Number of patients</b></p>	<p>Randomised = 240</p> <p>prednisolone group = 117</p> <p>placebo group = 123</p> <p>Outcome data available at 24 months = 198</p>

	<p>prednisolone group = 97</p> <p>placebo group = 101</p> <p>Outcome data available at 10 years = 228</p> <p>prednisolone group = 112</p> <p>placebo group = 116</p>																														
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Active tuberculous pericardial effusion confirmed by pericardiocentesis (diagnosis considered definitely or probably correct in 238 of 240 patients)</p> <p>5 years and older</p> <p><i>Exclusion</i></p> <p>Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year</p>																														
<b>Intervention</b>	<p><i>Antituberculosis chemotherapy plus prednisolone</i></p> <p>Prednisolone (11 weeks)</p> <table border="1"> <thead> <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> </thead> <tbody> <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> </tbody> </table> <p>Antituberculosis chemotherapy: 3HRZS/HR</p> <table border="1"> <thead> <tr> <th>Weight, kg</th> <th>1x daily</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>				Age, years	3x daily for			1x daily for week 11 (total daily dose, mg)	weeks 1 to 4 (total daily dose, mg)	weeks 5 to 8 (total daily dose, mg)	weeks 9 to 10 (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	Weight, kg	1x daily		
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≥15	60	30	15	5																											
Weight, kg	1x daily																														

		<b>Streptomycin</b>	<b>Isoniazid</b>	<b>Rifampicin</b>	<b>Pyrazinamide</b>
		(total daily dose, mg)	(total daily dose, mg)	(total daily dose, mg)	(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					
Patients that gave their consent were also randomised to receive complete open surgical drainage or pericardiocentesis					
<b>Comparison</b>	<i>Antituberculosis chemotherapy plus placebo</i>				
	Placebo (11 weeks)				
	Age, years	<b>3x daily for</b>			<b>1x daily for week 11</b>
		<b>weeks 1 to 4</b>	<b>weeks 5 to 8</b>	<b>weeks 9 to 10</b>	
		(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	<b>1x daily</b>				
	<b>Streptomycin</b>	<b>Isoniazid</b>	<b>Rifampicin</b>	<b>Pyrazinamide</b>	



		(total daily dose, mg)	(total daily dose, mg)	(total daily dose, mg)	(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				
	Patients that gave their consent were also randomised to receive complete open surgical drainage or pericardiocentesis				
<b>Location</b>	Transkei				
<b>Bibliographic reference</b>	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				
<b>Length of follow up</b>	10 years				
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths during 10 years of follow-up</p> <p>prednisolone group = 26 of 117</p> <p>placebo group = 33 of 123</p> <p>OR<sup>4</sup> (95% CI) = 0.78 (0.43 to 1.41)</p> <p>i.e. not statistically significant</p> <p>Survival analysis</p>				

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<sup>4</sup> (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

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

	<p>ascites and oedema classified as nil or just detectable</p> <p>physical activity unrestricted</p> <p>cardiothoracic ration of <math>\leq 55\%</math></p> <p>echocardiogram voltage of <math>\geq 6</math> mm in V6 or <math>\geq 4</math> mm along the frontal axis</p> <p>Number of patients to be considered in a favourable status after 24 months of follow-up</p> <p>prednisolone group = 91 of 117</p> <p>placebo group = 88 of 123</p> <p>OR<sup>4</sup> (95% CI) = 1.39 (0.77 to 2.50)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	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
<b>Comments</b>	<p><sup>1</sup> Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen</p> <p><sup>2</sup> Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum</p> <p><sup>3</sup> 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</p> <p><sup>4</sup> Odds ratio and 95% confidence interval calculated by reviewer</p> <p>Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis</p>

## IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

### 1.5.24 Meintjes et al, 2010

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p><i>Appropriate method of randomisation used?</i></p> <p>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</p> <p><i>Allocation concealment used?</i></p> <p>unclear</p> <p><i>Blinding used?</i></p> <p>double-blind</p> <p><i>Groups comparable at baseline?</i></p> <p>there was a longer period (<math>p = 0.02</math>) between taking antituberculosis chemotherapy and initiating ART amongst patients in the prednisolone arm (66 days) than the placebo arm (43.5 days)</p> <p><i>Groups received the same care apart from the intervention(s) studied?</i></p> <p>yes</p> <p><i>Groups followed up for an equal and appropriate length of time?</i></p> <p>study period only 12 weeks</p> <p><i>Groups comparable for treatment completion and availability of outcome data?</i></p> <p>yes</p>

	<p><i>Study used precise definitions and reliable measures of outcome?</i> yes</p> <p><i>Population studied is the same as the population of interest?</i> yes</p> <p><i>Intervention used is the same as the intervention of interest?</i> yes, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin</p> <p><i>Have substitute outcomes been used instead of the patient-important outcomes of interest?</i> no</p> <p><i>Analysis followed the intent-to-treat principle?</i> yes</p>
<p><b>Number of patients</b></p>	<p>Randomised = 110</p> <p>prednisolone group = 55</p> <p>antituberculosis chemotherapy alone group = 55</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>New or recurrent tuberculosis symptoms and <math>\geq 1</math> of the following TB-IRIS manifestations were enrolled:</p> <ul style="list-style-type: none"> <li>infiltrate on chest radiograph</li> <li>enlarging lymph node/s</li> <li>serous effusion</li> <li>cold abscess</li> </ul> <p><i>Exclusion</i></p> <p>Age &lt; 18 years</p>

	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 pO <sub>2</sub> < 8 kPa, altered level of consciousness, new focal neurological sign/s, or compression of a vital structure		
	<i>Baseline</i>		
		<b>Prednisolone</b> (n = 55)	<b>Placebo</b> (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/ $\mu$ l	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/ $\mu$ l	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)
<b>Intervention</b>	<i>Antituberculosis chemotherapy plus prednisolone</i> Prednisolone (4 weeks)		



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

	<p>OR<sup>1</sup> (95% CI) = 1.53 (0.25 to 9.53) i.e. not statistically significant</p>
	<p><b>Change in signs and symptoms – improvement/deterioration</b></p> <p>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’</p> <p>Number of patients in whom symptoms improved or were resolved after 4 weeks prednisolone group = 44 of 55 antituberculosis chemotherapy alone = 31 of 55</p> <p>OR<sup>1</sup> (95% CI) = 1.81 (0.72 to 4.50) i.e. not statistically significant</p> <p>Number of patients in whom symptoms deteriorated after 4 weeks prednisolone group = 7 of 55 antituberculosis chemotherapy alone = 9 of 55</p> <p>OR<sup>1</sup> (95% CI) = 0.75 (0.26 to 2.17) i.e. not statistically significant</p>
	<p><b>Change in signs and symptoms – chest radiograph</b></p> <p>Utilized a 3-point scale (deteriorated, no change, or improved/resolved)</p> <p>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</p> <p><b>OR<sup>1</sup> (95% CI) = 3.20 (1.44 to 7.09)</b></p>

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

<sup>1</sup> 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

<b>Bibliographic reference</b>	Doğanay M, Çalangu S, Turgut H et al (1995) Treatment of tuberculous meningitis in Turkey. Scandinavian Journal of Infectious Diseases 27: 135-8
<b>Study type</b>	Non-randomised controlled trial / prospective cohort (unclear from the report)
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest: different combinations used in each arm</p> <p>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</p> <p>No randomisation or allocation concealment, and blinding is unclear</p> <p>Allocation was based upon which centre a patient attended – potential for differences in the way care is delivered?</p> <p>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</p> <p>Groups received different regimens of corticosteroids</p> <p>Unclear if groups were comparable at the baseline</p> <p>Unclear if the groups were comparable for treatment completion</p> <p>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</p> <p>Relapse follow-up varied widely in both groups</p> <p>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</p>
<b>Number of patients</b>	n = 72

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

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



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

	<p>i.e. not statistically significant</p> <p><b>Adverse effects – any</b></p> <p>Number of patients to experience side effects</p> <p>8 months = 6 of 37</p> <p>12–16 months = 8 of 35</p> <p>OR<sup>1</sup> (95% CI) = 0.65 (0.20 to 2.12)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details given
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>different combinations used in each arm</p> <p>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</p> <p>Allocation was based upon which centre a patient attended – potential for differences in the way care is delivered?</p> <p>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</p> <p>Groups received different regimens of corticosteroids</p>
<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; IQR, interquartile range; OR, odds ratio; R, rifampicin; S, streptomycin; Z, pyrazinamide</p>	

### 1.6.2 Jacobs et al, 1992

<b>Bibliographic reference</b>	Jacobs RF, Sunakorn P, Chotpitayasunonah T et al (1992) Intensive short course chemotherapy for tuberculous meningitis. <i>Pediatric Infectious Disease Journal</i> 11: 194-8
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<b>Study type</b>	Non-randomised controlled trial / prospective cohort (unclear from the report)
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>the interventions did not differ by treatment duration alone – 6-month regimen contains pyrazinamide in the initial phase, 9-month regimen does not</p> <p>a 12-month arm contained a regimen that did not use rifampicin; this arm was therefore not extracted</p> <p>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</p> <p>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</p> <p>No randomisation, allocation concealment or blinding</p> <p>Unclear how patients were allocated to each regimen, or if attempts were made to balance potential confounding factors</p> <p>Unclear if groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Unclear if groups were followed up for the same length of time</p> <p>The 9 month group had a sample of just 4</p>
<b>Number of patients</b>	<p>n = 49</p> <p>6-month group = 45</p> <p>9-month group = 4</p>
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Children</p>

	<p>Tuberculous meningitis</p> <p><i>Diagnostic criteria</i></p> <p>Characteristic cerebrospinal fluid findings of pleocytosis with mononuclear predominance, and</p> <p>Decrease in glucose content initially or during the course of the disease, and</p> <p>Elevated protein content, and</p> <p>Two or more of the following:</p> <p>positive tuberculin skin test, <math>\geq 10</math> mm induration</p> <p>radiographic evidence of pulmonary tuberculosis that included parenchymal or hilar lymph node involvement</p> <p>history of contact with a known tuberculosis patient</p> <p>presence of <i>M. tuberculosis</i> in the cerebrospinal fluid</p> <p><i>Severity of disease</i></p> <p>Stage I: clinical presentation of fever with meningeal signs; the only diagnostic clue was the cerebrospinal fluid</p> <p>Stage II: findings in stage I associated with signs of increased intracranial pressure, paresis of extremities or cranial nerve palsy</p> <p>Stage III: findings in stages I and II associated with severe impairment in consciousness and/or decerebrate posturing</p> <p><i>Baseline characteristics</i></p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: left;">Treatment group</th> <th style="text-align: left;">Number of patients</th> </tr> </thead> <tbody> <tr> <td>6-month group (n = 45)</td> <td></td> </tr> <tr> <td style="padding-left: 20px;">stage I</td> <td style="text-align: center;">8</td> </tr> <tr> <td style="padding-left: 20px;">stage II</td> <td style="text-align: center;">25</td> </tr> <tr> <td style="padding-left: 20px;">stage III</td> <td style="text-align: center;">12</td> </tr> </tbody> </table>	Treatment group	Number of patients	6-month group (n = 45)		stage I	8	stage II	25	stage III	12
Treatment group	Number of patients										
6-month group (n = 45)											
stage I	8										
stage II	25										
stage III	12										

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

	<p>isoniazid: 15 mg/kg of body weight/day</p> <p>rifampicin: 20 mg/kg of body weight/day</p> <p>Corticosteroids:</p> <p>dexamethasone (all patients): 0.3 to 0.5 mg/kg of body weight/day in the first week of treatment</p> <p>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</p> <p>Standard neurosurgical techniques and supportive and critical care were provided to all patients</p>
<b>Length of follow up</b>	<p>At least the full treatment period</p> <p>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</p> <p>9-month group: no information given</p>
<b>Location</b>	Thailand
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths</p> <p>6-month group = 7 of 45</p> <p>9-month group = 2 of 4</p> <p>OR<sup>1</sup> (95% CI) = 0.18 (0.02 to 1.53)</p> <p>i.e. not statistically significant</p> <p><b>Change in symptoms – neurological sequelae</b></p> <p>Number of patients to experience neurological sequelae (hydrocephalus, cerebral palsy with mental retardation, hemiparesis, long-term seizures, or behavioural changes)</p> <p>6-month group = 11 of 45</p>

	<p>9-month group = 2 of 4</p> <p>OR<sup>1</sup> (95% CI) = 0.32 (0.04 to 2.58)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	No details given
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>the interventions did not differ by treatment duration alone – each regimen contained a different, though similar, combination of drugs</p> <p>the 12-month arm contained a regimen that did not use rifampicin; this arm was therefore not extracted</p> <p>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</p> <p>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</p>
<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; S, streptomycin; Z, pyrazinamide</p>	

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

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

	<p>6 of the 43 patients tested had single or combined drug resistance</p> <p>Appropriate method of randomisation used: numbered series of sealed envelopes containing the allocated regimen</p> <p>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</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups not followed up for the same length of time</p> <p>Groups were comparable for treatment completion and availability of outcome data</p> <p>Favourable status at the end of treatment is a composite of cure and change in signs and symptoms; it is a substitute outcome</p>
<p><b>Number of patients</b></p>	<p>n = 60</p> <p>6-month group = 31</p> <p>9-month group = 29</p> <p>Analysed over 36-month follow-up = 51</p> <p>6-month group = 25</p> <p>9-month group = 26</p> <p>Analysed over 60-month follow-up = 50</p> <p>6-month group = 24</p> <p>9-month group = 26</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>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</p>



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

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

	<i>quiescent</i>	0	1
<b>Intervention</b>	<p><i>6-month regimen</i></p> <p>6H<sub>7</sub>R<sub>7</sub>S<sub>2</sub> + surgery</p> <p>Dosing:</p> <p>isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg</p> <p>rifampicin: 15 mg/kg of body weight/day up to a maximum of 600 mg</p> <p>streptomycin: 20 mg/kg of body weight/day up to a maximum of 1 g intramuscularly</p> <p>Triple drug regimens were used because of the high levels of pretreatment drug resistance known to exist in Hong Kong</p> <p>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</p> <p>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</p>		
<b>Comparator</b>	<p><i>9-month regimen</i></p> <p>9H<sub>7</sub>R<sub>7</sub>S<sub>2</sub> + surgery</p> <p>Dosing:</p> <p>isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg</p> <p>rifampicin: 15 mg/kg of body weight/day up to a maximum of 600 mg</p> <p>streptomycin: 20 mg/kg of body weight/day up to a maximum of 1 g intramuscularly</p> <p>Triple drug regimens were used because of the high levels of pretreatment drug resistance known to exist in Hong Kong</p>		

	<p>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</p> <p>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</p>
<b>Location</b>	Hong Kong
<b>Bibliographic reference</b>	Griffiths DLI 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
<b>Length of follow up</b>	36 months (after treatment initiation?)
<b>Outcomes measures and effect size</b>	<p><b>Change in signs and symptoms – sinuses</b></p> <p>Number of patients with sinus and/or clinically evident abscesses on admission which had resolved without additional intervention<sup>2</sup></p> <p>6-month group = 4 of 5</p> <p>9-month group = 2 of 2</p> <p>OR<sup>1</sup> (95% CI) = 0.60 (0.02 to 20.98)</p> <p>i.e. not statistically significant</p> <p>Number of patients in whom new sinuses and/or clinically evident abscesses formed and resolved without additional intervention<sup>2,3</sup></p> <p>6-month group = 1 of 1</p> <p>9-month group = 2 of 3</p> <p>OR<sup>1</sup> (95% CI) = 1.80 (0.04 to 79.43)</p> <p>i.e. not statistically significant</p>
	<b>Change in signs and symptoms – nervous system involvement</b>

	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 <sup>1</sup> (95% CI) = 0.60 (0.01 to 49.45) i.e. not statistically significant				
	<p><b>Change in signs and symptoms – bony fusion</b></p> Number of patients with complete bony fusion at 36 months 6-month group = 25 of 25 9-month group = 26 of 26 OR <sup>1</sup> (95% CI) = 0.96 (0.02 to 50.35) i.e. not statistically significant Cumulative occurrence of complete bony fusion over time <sup>4</sup>				
	<b>survival time</b> (months after treatment initiation)	<b>6-month group (n = 25)</b>		<b>9-month group (n = 26)</b>	
		number with complete bony fusion	survival probability	number with complete bony fusion	survival probability
	<b>3</b>	4	0.84	0	1
	<b>6</b>	9	0.64	11	0.58
	<b>9</b>	11	0.56	20	0.23
	<b>12</b>	14	0.44	21	0.19

		<b>18</b>	17	0.32	23	0.12	
		<b>24</b>	23	0.08	25	0.04	
		<b>30</b>	24	0.04	26	0	
		<b>36</b>	25	0	26	0	
	<p><b>Adverse events – events requiring interruption and modification of the allocated regimen</b></p> <p>Number of patients to experience adverse events that led to an interruption of treatment and subsequent modification of the allocated regimen</p> <p>6-month group = 2 of 31</p> <p>9-month group = 0 of 29</p> <p>OR<sup>1</sup> (95% CI) = 5.00 (0.23 to 108.68)</p> <p>i.e. not statistically significant</p>						
<b>Bibliographic reference</b>	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						
<b>Length of follow up</b>	60 months after the initiation of treatment						
<b>Outcomes measures and effect size</b>	<p><b>Mortality</b></p> <p>Number of deaths associated with spinal tuberculosis</p> <p>6-month group = 0 of 24</p> <p>9-month group = 0 of 26</p> <p>OR<sup>1</sup> (95% CI) = 1.08 (0.02 to 56.64)</p>						

	i.e. not statistically significant
	<p><b>Response to treatment – favourable</b></p> <p>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</p> <p>Number of patients whose response to treatment was classified as favourable at 60 months</p> <p>6-month group = 23 of 24</p> <p>9-month group = 25 of 26</p> <p>OR<sup>1</sup> (95% CI) = 0.92 (0.05 to 15.58)</p> <p>i.e. not statistically significant</p>
	<p><b>Response to treatment – unfavourable response requiring additional chemotherapy and/or surgery</b></p> <p>Number of patients who had an unfavourable response to treatment that required additional chemotherapy and/or during the 60-month follow-up</p> <p>6-month group = 1 of 24</p> <p>9-month group = 1 of 26</p> <p>OR<sup>1</sup> (95% CI) = 1.09 (0.06 to 18.40)</p> <p>i.e. not statistically significant</p>
	<p><b>Change in signs and symptoms – vertebral loss</b></p> <p>Mean vertebral loss from 36 months to 60 months</p> <p>6-month group (n = 24) = 0.05</p> <p>9-month group (n = 25) = 0.15</p> <p>MD<sup>6</sup> = -0.10</p> <p>Mean vertebral loss from treatment initiation to 60 months<sup>8</sup></p>

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



	<p>6-month group (n = 14) = 12.5°</p> <p>9-month group (n = 14) = -1.6°</p> <p>MD<sup>6</sup> = 14.1°</p> <p>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<sup>6</sup> was 10.9°</p> <p>% of patients with improvement in their angle of kyphosis (reduction of 11° or more) from baseline to 60 months</p> <p>6-month group (n = 14) = 0</p> <p>9-month group (n = 14) = 1</p> <p>OR<sup>1</sup> (95% CI) = 0.31 (0.01 to 8.29)</p> <p>i.e. not statistically significant</p> <p>% of patients with no change in their angle of kyphosis (within ±10°) from baseline to 60 months</p> <p>6-month group (n = 14) = 5</p> <p>9-month group (n = 14) = 11</p> <p><b>OR<sup>1</sup> (95% CI) = 0.15 (0.03 to 0.81)</b></p> <p><b>i.e. statistically significant</b></p> <p>% of patients with deterioration in their angle of kyphosis (increase of 11° or more) from baseline to 60 months</p> <p>6-month group (n = 14) = 9</p> <p>9-month group (n = 14) = 2</p> <p><b>OR<sup>1</sup> (95% CI) = 10.80 (1.69 to 68.94)</b></p> <p><b>i.e. statistically significant</b></p>
<b>Source of funding</b>	No details provided

<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest: both arms received surgery in addition to antituberculosis chemotherapy</p> <p>Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance</p>
<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>2</sup> Follow-up unclear; all events occurred within the treatment period, though follow-up may have been for the full 36 months</p> <p><sup>3</sup> 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</p> <p><sup>4</sup> Reviewer used the reported data on the cumulative occurrence of complete bony fusion to produce the survival probabilities and a Kaplan-Meier curve</p> <p><sup>5</sup> Hazard ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>6</sup> Mean difference not provided by authors; calculated by reviewer</p> <p><sup>7</sup> Mean change from baseline to 36 months not provided by authors; change in mean calculated by author</p> <p><sup>8</sup> 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)</p> <p>Abbreviations: CI, confidence interval; H, isoniazid; HR, hazard ratio; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin</p>	

#### 1.6.4 Upadhyay et al, 1995

<b>Bibliographic reference</b>	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
<b>Study type</b>	RCT
<b>Study quality</b>	<p>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</p>

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

	<p>The extent of disease at entry was similar in both groups</p> <table border="1" data-bbox="864 248 1827 879"> <thead> <tr> <th data-bbox="864 248 1301 368"></th> <th colspan="2" data-bbox="1301 248 1827 312"><b>% patients</b></th> </tr> <tr> <th data-bbox="864 312 1301 368"></th> <th data-bbox="1301 312 1565 368"><b>6-month</b></th> <th data-bbox="1565 312 1827 368"><b>9-month</b></th> </tr> </thead> <tbody> <tr> <td data-bbox="864 368 1301 552"><i>Age (mean years ± SD)</i></td> <td data-bbox="1301 368 1565 552"></td> <td data-bbox="1565 368 1827 552"></td> </tr> <tr> <td data-bbox="864 448 1301 496"><i>at surgery</i></td> <td data-bbox="1301 448 1565 496">32.6±18.3</td> <td data-bbox="1565 448 1827 496">28.5±19.6</td> </tr> <tr> <td data-bbox="864 496 1301 552"><i>at final follow-up</i></td> <td data-bbox="1301 496 1565 552">42.8±18.4</td> <td data-bbox="1565 496 1827 552">38.6±20.0</td> </tr> <tr> <td data-bbox="864 552 1301 783"><i>Site of lesion</i></td> <td data-bbox="1301 552 1565 783"></td> <td data-bbox="1565 552 1827 783"></td> </tr> <tr> <td data-bbox="864 632 1301 679"><i>thoracic</i></td> <td data-bbox="1301 632 1565 679">9</td> <td data-bbox="1565 632 1827 679">8</td> </tr> <tr> <td data-bbox="864 679 1301 727"><i>thoracolumbar</i></td> <td data-bbox="1301 679 1565 727">12</td> <td data-bbox="1565 679 1827 727">10</td> </tr> <tr> <td data-bbox="864 727 1301 783"><i>lumbar</i></td> <td data-bbox="1301 727 1565 783">4</td> <td data-bbox="1565 727 1827 783">8</td> </tr> <tr> <td data-bbox="864 783 1301 879"><i>Incidence of pulmonary tuberculosis</i></td> <td data-bbox="1301 783 1565 879">5/25 (20%)</td> <td data-bbox="1565 783 1827 879">13/26 (50%)</td> </tr> </tbody> </table>		<b>% patients</b>			<b>6-month</b>	<b>9-month</b>	<i>Age (mean years ± SD)</i>			<i>at surgery</i>	32.6±18.3	28.5±19.6	<i>at final follow-up</i>	42.8±18.4	38.6±20.0	<i>Site of lesion</i>			<i>thoracic</i>	9	8	<i>thoracolumbar</i>	12	10	<i>lumbar</i>	4	8	<i>Incidence of pulmonary tuberculosis</i>	5/25 (20%)	13/26 (50%)
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<i>Incidence of pulmonary tuberculosis</i>	5/25 (20%)	13/26 (50%)																													
<b>Intervention</b>	<p><i>6-month regimen</i></p> <p>3HRS/3HR + surgery</p> <p>Dosing:</p> <p>isoniazid: 6 mg/kg of body weight/day up to a maximum of 300 mg</p> <p>rifampicin: up to 20 mg/kg of body weight/day up to a maximum of 600 mg</p> <p>streptomycin: 20 mg/kg of body weight/day up to a maximum of 1.0 g</p> <p>Radical surgery (Hong Kong radical resection of the tuberculous focus and subsequent reconstruction using bone grafting) was performed on all patients</p>																														
<b>Comparison</b>	<i>9-month regimen</i>																														

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

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

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

	<p><b>Change in signs and symptoms – kyphosis at final follow-up</b></p> <p>Changes in the mean angle of deformity (mean ± SD) at final follow-up from 6-month post-operative evaluation</p> <p>6-month group (n = 25) = 3.5±7.9</p> <p>9-month group (n = 26) = 4.2±8.8</p> <p>MD (95% CI)<sup>3</sup> = -0.7 (-5.31 to 3.91)</p> <p>i.e. not statistically significant</p> <hr/> <p><b>Relapse</b></p> <p>Number of patients to experience recurrence or reactivation of tuberculosis during follow-up</p> <p>6-month group = 0 of 25</p> <p>9-month group = 0 of 26</p> <p>OR<sup>4</sup> (95% CI) = 1.04 (0.02 to 54.38)</p> <p>i.e. not statistically significant</p> <hr/> <p><b>Adverse events</b></p> <p>Number of patients to experience adverse events during treatment</p> <p>6-month group = 6 of 25</p> <p>9-month group = 5 of 26</p> <p>OR<sup>4</sup> (95% CI) = 1.33 (0.35 to 5.06)</p> <p>i.e. not statistically significant</p> <p>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</p>
<b>Source of funding</b>	No details given



<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>the interventions did not differ by treatment duration alone – 18-month regimen contained PAS, the 6- and 9-month regimens contained rifampicin</p> <p>does not contain the 4 drugs of the standard recommended regimen – regimens contain streptomycin but lack ethambutol and pyrazinamide</p> <p>18-month regimen contained PAS - not licensed in the UK; data for this arm was not extracted</p> <p>all patients had surgery</p> <p>Population does not exactly match the population of interest:</p> <p>some patients also had respiratory TB</p>
	<p><sup>1</sup> note: data for arm containing PAS (3SPH/15PH = 63) was not extracted</p> <p><sup>2</sup> Calculated by the reviewer</p> <p><sup>3</sup> 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>4</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>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</p>

***BONE & JOINT TUBERCULOSIS***

*No papers found*

***PERICARDIAL TUBERCULOSIS***

*No papers found*

***LYMPH NODE TUBERCULOSIS***

**1.6.5 Al-Aska et al, 1992**

<b>Bibliographic</b>	Al-Aska A, Al-Majed S, Al-Mofleh I et al (1992) Short-course chemotherapy for cervical lymph node tuberculosis. Saudi
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<b>reference</b>	Medical Journal 13(2): 129-3								
<b>Study type</b>	RCT								
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>the interventions did not differ by treatment duration alone: 9-month regimens have an additional drug (pyrazinamide) during the initial phase</p> <p>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</p> <p>Method of randomisation, and allocation concealment and blinding were unclear</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for availability of outcome data and treatment completion</p> <p>‘Favourable’ response to treatment not explicitly defined, but appears to be a substitute outcome</p>								
<b>Number of patients</b>	<p>Randomised = 77</p> <p>9-month group = 34</p> <p>18-month group = 33</p>								
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Cervical tuberculous lymphadenitis microbiologically or histologically proven in lymph nodes obtained through aspiration or biopsy</p> <p><i>Exclusion</i></p> <p>Active pulmonary tuberculosis</p> <p>Pregnancy</p> <table border="1" data-bbox="851 1316 1836 1436"> <thead> <tr> <th></th> <th><b>9-month</b></th> <th><b>12-month</b></th> </tr> </thead> <tbody> <tr> <td><i>Male : female ratio</i></td> <td>1.4:1</td> <td>1.2:1</td> </tr> </tbody> </table>				<b>9-month</b>	<b>12-month</b>	<i>Male : female ratio</i>	1.4:1	1.2:1
	<b>9-month</b>	<b>12-month</b>							
<i>Male : female ratio</i>	1.4:1	1.2:1							

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

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

	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
<sup>1</sup>	Data for the two 9-month regimens not reported separately
<sup>2</sup>	Data for the two 12-month regimens not reported separately
<sup>3</sup>	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

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

	<p>18-month group = 57</p> <p>Analysed at 5 years = 73</p> <p>9-month group = 34</p> <p>18-month group = 39</p>																																					
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Tuberculosis of the cervical, axillary or inguinal lymph nodes</p> <p>Aged 15 to 80</p> <p><i>Exclusion</i></p> <p>Previous chemotherapy for tuberculosis</p> <p>Active pulmonary tuberculosis</p> <p>Pregnancy</p> <p>Important impairment of visual, hepatic or renal function</p> <p><i>Baseline characteristics</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>9-month</i></th> <th colspan="2"><i>18-month</i></th> </tr> <tr> <th><i>Number of patients</i></th> <th><i>Mean age (years)</i></th> <th><i>Number of patients</i></th> <th><i>Mean age (years)</i></th> </tr> </thead> <tbody> <tr> <td><i>Asian</i></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td style="padding-left: 20px;"><i>male</i></td> <td style="text-align: center;">22</td> <td style="text-align: center;">30</td> <td style="text-align: center;">15</td> <td style="text-align: center;">30</td> </tr> <tr> <td style="padding-left: 20px;"><i>female</i></td> <td style="text-align: center;">23</td> <td style="text-align: center;">40</td> <td style="text-align: center;">24</td> <td style="text-align: center;">38</td> </tr> <tr> <td><i>Non-Asian</i></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td style="padding-left: 20px;"><i>male</i></td> <td style="text-align: center;">2</td> <td style="text-align: center;">65</td> <td style="text-align: center;">5</td> <td style="text-align: center;">41</td> </tr> </tbody> </table>					<i>9-month</i>		<i>18-month</i>		<i>Number of patients</i>	<i>Mean age (years)</i>	<i>Number of patients</i>	<i>Mean age (years)</i>	<i>Asian</i>					<i>male</i>	22	30	15	30	<i>female</i>	23	40	24	38	<i>Non-Asian</i>					<i>male</i>	2	65	5	41
	<i>9-month</i>		<i>18-month</i>																																			
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	<i>female</i>	9	47	13	42
	<i>Surgical removal of all affected nodes</i>	18	35	14	48
	<i>Biopsy or needle aspiration of nodes for diagnostic purposes</i>	30	37	32	37
	<i>Initial diagnosis had been clinically supported by a positive tuberculin skin test</i>	8	32	11	30
<b>Intervention</b>	<p><i>9-month regimen</i>            2HRE<sub>7</sub>/7HR<sub>7</sub>            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</p>				
<b>Comparison</b>	<p><i>18-month regimen</i>            2HRE<sub>7</sub>/16HR<sub>7</sub>            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</p>				
<b>Location</b>	UK				
<b>Bibliographic</b>	Campbell IA et al (1985) Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. British				

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



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

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

	i.e. not statistically significant
<b>Bibliographic reference</b>	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
<b>Length of follow up</b>	5 years
<b>Outcomes measures and effect size</b>	<p><b>Relapse</b></p> <p>Number of patients to experience clinical or microbiological relapse</p> <p>9-month group = 0 of 34</p> <p>18-month group = 0 of 39</p> <p>OR<sup>1</sup> (95% CI) = 1.14 (0.02 to 59.26)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Supported by grants from Ciba Geigy Pharmaceuticals and Merrel Dow Pharmaceuticals
<b>Comments</b>	Intervention does not exactly match the intervention of interest: does not contain the 4 drugs of the standard recommended regimen – regimens lack pyrazinamide
<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial</p>	

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

<b>Bibliographic reference</b>	Campbell IA et al (1993) Six months <i>versus</i> nine months chemotherapy for tuberculosis of the lymph nodes: final results. British Thoracic Society Research Committee. Respiratory medicine 87:621-3
<b>Study type</b>	RCT
<b>Study quality</b>	<p>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 4<sup>th</sup> drug, 6-month regimen lack ethambutol</p> <p>Method of randomisation and blinding were unclear, though there appeared to be adequate allocation concealment</p>

	<p>It is unclear if the groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were comparable for availability of outcome data and treatment completion</p> <p>Did not follow the intent-to-treat principle</p>
<p><b>Number of patients</b></p>	<p>Randomised = 199</p> <p>6-month group = 66</p> <p>9-month groups = 133<sup>1</sup></p> <p>Followed up to 30 months = 165</p> <p>6-month group = 58</p> <p>9-month groups = 107<sup>2</sup></p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Tuberculosis of the cervical, axillary or chest wall lymph nodes</p> <p>Aged 16 to 80</p> <p><i>Exclusion</i></p> <p>Previous chemotherapy for tuberculosis</p> <p>Active pulmonary parenchymal tuberculosis (but not isolated mediastinal lymphadenopathy)</p> <p>Pregnancy</p> <p>Significant impairment of visual, hepatic or renal function</p>
<p><b>Intervention</b></p>	<p><i>6-month regimen</i></p> <p>2HRZ<sub>7</sub>/4HR<sub>7</sub></p> <p>Dosing:</p>

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

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

	<p>Number of patients to experience clinical relapse by 30 months</p> <p>6-month group = 3 of 58</p> <p>9-month groups<sup>3</sup> = 6 of 107</p> <p>OR<sup>4</sup> (95% CI) = 0.92 (0.22 to 3.82)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Supported by a grant from Merrel Dow Pharmaceuticals
<b>Comments</b>	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 4 <sup>th</sup> drug, 6-month regimen lack ethambutol
	<p><sup>1</sup> 2HRE/7HR = 63; 2HRZ/7HR = 70</p> <p><sup>2</sup> 2HRE/7HR = 49; 2HRZ/7HR = 58</p> <p><sup>3</sup> Pooled by reviewer</p> <p><sup>4</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>Abbreviations: CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide</p>

### 1.6.8 Yuen et al, 1997

<b>Bibliographic reference</b>	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. <i>Otolaryngology Head and Neck Surgery</i> 116: 189-92
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>does not contain the 4 drugs of the standard recommended regimen – regimens lack ethambutol but contain streptomycin</p> <p>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</p>

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



	<p>Mantoux test</p> <p>Chest x-ray</p> <p>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</p> <p><i>Baseline characteristics</i></p> <table border="1" data-bbox="719 491 1973 1217"> <thead> <tr> <th></th> <th><b>6-month</b></th> <th><b>9-month</b></th> <th><i>Statistical significance</i></th> </tr> </thead> <tbody> <tr> <td><i>Female : male ratio</i></td> <td>1.4</td> <td>1.7</td> <td><math>p = 0.67^1</math></td> </tr> <tr> <td><i>Mean age (years) ± SD</i></td> <td>32±14</td> <td>28±10</td> <td><math>p = 0.08^2</math></td> </tr> <tr> <td><i>Neck lymph node</i></td> <td></td> <td></td> <td></td> </tr> <tr> <td>    <i>left side</i></td> <td>14</td> <td>7</td> <td rowspan="3"><math>p = 0.125^1</math></td> </tr> <tr> <td>    <i>right side</i></td> <td>20</td> <td>29</td> </tr> <tr> <td>    <i>bilateral</i></td> <td>9</td> <td>12</td> </tr> <tr> <td><i>Mean number of lymph nodes ± SD</i></td> <td>3±2.4</td> <td>3±2.5</td> <td><math>p = 0.995^2</math></td> </tr> <tr> <td><i>Largest node size (mm) ± SD</i></td> <td>19±14</td> <td>23±15</td> <td><math>p = 0.181^2</math></td> </tr> <tr> <td><i>Abscess</i></td> <td>4/43 (9%)</td> <td>1/48 (2%)</td> <td><math>p = 0.185^3</math></td> </tr> <tr> <td><i>Discharging sinus</i></td> <td>2/43 (5%)</td> <td>1/48 (2%)</td> <td><math>p = 0.600^3</math></td> </tr> </tbody> </table>		<b>6-month</b>	<b>9-month</b>	<i>Statistical significance</i>	<i>Female : male ratio</i>	1.4	1.7	$p = 0.67^1$	<i>Mean age (years) ± SD</i>	32±14	28±10	$p = 0.08^2$	<i>Neck lymph node</i>				<i>left side</i>	14	7	$p = 0.125^1$	<i>right side</i>	20	29	<i>bilateral</i>	9	12	<i>Mean number of lymph nodes ± SD</i>	3±2.4	3±2.5	$p = 0.995^2$	<i>Largest node size (mm) ± SD</i>	19±14	23±15	$p = 0.181^2$	<i>Abscess</i>	4/43 (9%)	1/48 (2%)	$p = 0.185^3$	<i>Discharging sinus</i>	2/43 (5%)	1/48 (2%)	$p = 0.600^3$
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	<p>Dosing:</p> <p>isoniazid: 15 mg/kg of body weight/day</p> <p>rifampicin: 600 mg/day</p> <p>pyrazinamide: 2.5 g for patients weighing 50 kg or more, and 2.0 g for patients weighing 50 kg or less</p> <p>streptomycin: 1 g/day</p> <p>Treatment was fully supervised in the chest outpatient clinic</p> <p>Abscesses were drained surgically before the commencement of treatment</p>
<b>Comparison</b>	<p><i>9-month regimen</i></p> <p>4SHRZ<sub>3</sub>/5HR<sub>3</sub> + surgery</p> <p>Dosing:</p> <p>isoniazid: 15 mg/kg of body weight/day</p> <p>rifampicin: 600 mg/day</p> <p>pyrazinamide: 2.5 g for patients weighing 50 kg or more, and 2.0 g for patients weighing 50 kg or less</p> <p>streptomycin: 1 g/day</p> <p>Treatment was fully supervised in the chest outpatient clinic</p> <p>Abscesses were drained surgically before the commencement of treatment</p>
<b>Length of follow up</b>	Median follow-up of 21 months, longest follow-up of 66 months
<b>Location</b>	Hong Kong
<b>Outcomes measures and effect size</b>	<p><b>Treatment success</b></p> <p>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)</p>

	<p>Number of patients to experience relapse during follow-up</p> <p>6-month group = 39 of 43</p> <p>9-month group = 47 of 48</p> <p>OR<sup>4</sup> (95% CI) = 0.21 (0.02 to 1.93)</p> <p>i.e. not statistically significant</p>
	<p><b>Treatment failure</b></p> <p>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</p> <p>Number of patients to experience relapse during follow-up</p> <p>6-month group = 2 of 43</p> <p>9-month group = 1 of 48</p> <p>OR<sup>4</sup> (95% CI) = 2.29 (0.20 to 26.22)</p> <p>i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>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</p> <p>Number of patients to have experienced relapse by 5 years of follow-up<sup>5</sup></p> <p>6-month group (n = 41) = 11%</p> <p>9-month group (n = 48) = 10%</p> <p>OR<sup>4</sup> (95% CI) = 1.11 (0.45 to 2.75)</p> <p>i.e. not statistically significant</p>
	<p><b>Adverse events – requiring modification of treatment</b></p>

	<p>Number of patients to experience drug reactions requiring modification of treatment</p> <p>6-month group = 4 of 49</p> <p>9-month group = 13 of 64</p> <p>OR<sup>4</sup> (95% CI) = 0.35 (0.11 to 1.15)</p> <p>i.e. not statistically significant</p> <p>note: drug reactions included drug-induced hepatitis, gastrointestinal upset, skin rash, tinnitus and thrombocytopenia</p>
	<p><b>Adherence – treatment default</b></p> <p>Number of patients to default treatment</p> <p>6-month group = 2 of 49</p> <p>9-month group = 3 of 64</p> <p>OR<sup>4</sup> (95% CI) = 0.87 (0.14 to 5.39)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Supported by a research grant from the University of Hong Kong
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>does not contain the 4 drugs of the standard recommended regimen – regimens lack ethambutol but contain streptomycin</p> <p>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</p> <p>any abscesses were drained before treatment initiation</p>
<p><sup>1</sup> Chi-square test</p> <p><sup>2</sup> t-test</p> <p><sup>3</sup> Fisher's exact test</p>	

<sup>4</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

<sup>5</sup> 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**

<b>Bibliographic reference</b>	Kim SG, Kim JS, Jung HC et al (2003) Is a 9-month treatment sufficient in tuberculosis enterocolitis? A prospective, randomised, single-centre study. <i>Alimentary Pharmacology &amp; Therapeutics</i> 18: 85-91
<b>Study type</b>	RCT
<b>Study quality</b>	<p>Population does not exactly match the population of interest: some patients also had respiratory TB</p> <p>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</p> <p>Appropriate method of randomisation: computer-generated</p> <p>Investigators were blinded, but the use of allocation concealment and blinding of participants and individuals administering care were unclear</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were not followed up for the same length of time</p> <p>Groups were comparable for availability of outcome data and treatment completion</p>

	'Complete response' to treatment is a composite outcome that includes both cure and change in signs and symptoms; it is a substitute outcome																							
<b>Number of patients</b>	n = 40 9-month group = 22 15-month group = 18																							
<b>Patient characteristics</b>	<p><i>Inclusion</i></p> <p>Intestinal tuberculosis</p> <p><i>Exclusion</i></p> <p>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</p> <p><i>Diagnostic criteria</i></p> <p>At least one of the following criteria:</p> <p>demonstration of acid-fast bacilli, either by stain or culture of a histological specimen</p> <p>confirmation of caseating granuloma on a histological specimen</p> <p>clinical, radiological and endoscopic abnormalities strongly suggestive of intestinal tuberculosis and a response to antituberculosis chemotherapy</p> <p><i>Baseline characteristics</i></p> <table border="1"> <thead> <tr> <th></th> <th><b>9-month</b></th> <th><b>15-month</b></th> <th><i>p-value</i></th> </tr> </thead> <tbody> <tr> <td><i>Male : female ratio</i></td> <td>11:11</td> <td>5:13</td> <td>0.15</td> </tr> <tr> <td><i>Mean age (years) ± SD</i></td> <td>40±16</td> <td>38±17</td> <td>0.93</td> </tr> <tr> <td><i>Symptom presentation</i></td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>abdominal pain</i></td> <td>21/22</td> <td>14/18</td> <td>0.16</td> </tr> </tbody> </table>					<b>9-month</b>	<b>15-month</b>	<i>p-value</i>	<i>Male : female ratio</i>	11:11	5:13	0.15	<i>Mean age (years) ± SD</i>	40±16	38±17	0.93	<i>Symptom presentation</i>				<i>abdominal pain</i>	21/22	14/18	0.16
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		<i>weight loss</i>	13/22	12/18	0.62
		<i>diarrhea</i>	7/22	8/18	0.41
		<i>Pulmonary tuberculosis</i>	5/22	7/18	0.27
<b>Intervention</b>	<p><i>9-month regimen</i></p> <p>9HREZ</p> <p>Dosing:</p> <p>isoniazid: 400 mg/day</p> <p>rifampicin: 450 mg/day</p> <p>ethambutol: 800 mg/day</p> <p>pyrazinamide: 500 mg 3 times daily</p>				
<b>Comparison</b>	<p><i>15-month regimen</i></p> <p>15HREZ</p> <p>Dosing:</p> <p>isoniazid: 400 mg/day</p> <p>rifampicin: 450 mg/day</p> <p>ethambutol: 800 mg/day</p> <p>pyrazinamide: 500 mg 3 times daily</p>				
<b>Length of follow up</b>	<p>Mean (months) ± SD</p> <p>9-month group = 23±12</p> <p>15-month group = 34±19</p>				

	MD <sup>1</sup> (95% CI) = -11 (-21.1 to -0.9) i.e. statistically significant
<b>Location</b>	South Korea
<b>Outcomes measures and effect size</b>	<p><b>Response to treatment – complete response</b></p> <p>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</p> <p>Number to achieve complete response during follow-up period</p> <p>9-month group = 22 of 22 15-month group = 18 of 18</p> <p>OR<sup>2</sup> (95% CI) = 1.22 (0.02 to 64.31) i.e. not statistically significant</p> <p>Mean interval (months ± SD) to complete response</p> <p>9-month group (n = 22) = 3.9±2.5 15-month group (n = 18) = 4.8±2.9</p> <p>MD<sup>1</sup> (95% CI) = -0.9 (-2.6 to 0.80) i.e. not statistically significant</p>
	<p><b>Relapse</b></p> <p>Defined as the recurrence of the abdominal symptoms present at entry, and/or endoscopic documentation of active intestinal tuberculosis</p>



	<p>Number to experience recurrence during follow-up period</p> <p>9-month group = 0 of 22</p> <p>15-month group = 0 of 18</p> <p>OR<sup>2</sup> (95% CI) = 0.82 (0.02 to 43.48)</p> <p>i.e. not statistically significant</p>
<b>Source of funding</b>	Details not provided
<b>Comments</b>	<p>Population does not exactly match the population of interest: some patients also had respiratory TB</p> <p>Intervention does not exactly match the intervention of interest: 4 drugs used throughout, therefore more intensive the standard recommended regimen</p> <p>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</p>
<p><sup>1</sup> Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>2</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>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</p>	

**1.6.10 Park et al, 2009**

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

	<p>standard recommended regimen</p> <p>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</p> <p>Appropriate method of randomisation: computer-generated</p> <p>Use of allocation concealment is unclear</p> <p>Open (unblinded) trial</p> <p>Groups were comparable at the baseline</p> <p>Groups received the same care apart from the interventions studied</p> <p>Groups were followed up for the same length of time, and were comparable for availability of outcome data and treatment completion</p> <p>Response to treatment is a substitute for outcome</p>
<p><b>Number of patients</b></p>	<p>n = 90</p> <p>6-month group = 45</p> <p>9-month group = 45</p>
<p><b>Patient characteristics</b></p>	<p><i>Inclusion</i></p> <p>Intestinal tuberculosis</p> <p><i>Exclusion</i></p> <p>Patients aged under 18 years or over 75 years</p> <p>Extrapulmonary TB other than intestinal TB</p> <p>Histories of antituberculosis chemotherapy within the past 5 years</p> <p>Immunosuppressive disorders, or chronic liver disease</p> <p>Pregnancy</p>

	Patients in whom poor compliance was anticipated				
	<i>Diagnostic criteria</i>				
	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 <i>M. tuberculosis</i> 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				
	<i>Baseline characteristics</i>				
			<b>6-month</b>	<b>9-month</b>	<i>p-value</i>
		<i>Male : female ratio</i>	18:27	22:23	0.53
		<i>Median age (years) (range)</i>	36 (18 – 71)	42 (20 – 71)	0.12
		<i>Symptom presentation</i>			
		<i>abdominal pain</i>	37/45	35/45	0.79
		<i>weight loss</i>	24/45	31/45	0.19
	<i>fever</i>	6/45	10/45	0.41	
	<i>diarrhea</i>	22/45	18/45	0.53	
	<i>Laboratory findings</i>				
	<i>anemia</i>	21/45	28/45	0.20	
	<i>leukocytosis</i>	4/45	5/45	1.00	
	<i>thrombocytosis</i>	15/45	21/45	0.28	

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

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

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

	i.e. not statistically significant
<b>Source of funding</b>	No details provided
<b>Comments</b>	<p>Intervention does not exactly match the intervention of interest:</p> <p>continuation phase contains 3 drugs and is therefore more intensive than the 2-drug continuation phase of the standard recommended regimen</p> <p>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</p>
<p><sup>1</sup> Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p><sup>2</sup> Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer</p> <p>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</p>	

**GENITOURINARY TUBERCULOSIS**

*No papers found*

**DISSEMINATED (INCLUDING MILIARY) TUBERCULOSIS**

No papers found

