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A.1 RQ B

A.1.1 Approaches to sample collection in children unable to expectorate spontaneously

Nasogastric aspiration/lavage vs induced sputum

			Quality ass	essment			No of p	atients	E	ffect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration / lavage	Induced sputum	Relative (95% Cl)	Absolute	Quality
Culture p	ositivity by s	pecimen (assesse	ed with: number posit	tive/total number o	f specimens obtair	ned)					
4 ^{1,2,3,4}	cross- sectional	very serious ^{5,6,7,8,9}	no serious inconsistency	no serious indirectness	no serious imprecision	none	286/3086 (9.3%)	224/2747 (8.2%)	OR 1.13 (0.94 to 1.36) ^{10,16}	1 more per 100 (from 0 fewer to 3 more)	⊙OOO VERY LOW
Cumulati	ve culture po	sitivity: 2 specim	ens (assessed with:	number of particip	ants with 1 or more	e positive culture)					
2 ^{3,11}	cross- sectional	very serious ^{5,7,8,12}	no serious inconsistency	no serious indirectness	serious ¹³	none	142/420 (33.8%)	78/420 (18.6%)	OR 2.24 (1.63 to 3.09) ^{10,17}	15 more per 100 (from 9 more to 23 more)	⊙OOO VERY LOW
Cumulati	ve culture po	sitivity: 3 specim	ens (assessed with:	number of particip	ants with 1 or more	e positive culture)					
2 ^{4,11}	cross- sectional	very serious ^{5,7,8,12}	no serious inconsistency	no serious indirectness	serious ¹³	none	46/267 (17.2%)	58/267 (21.7%)	OR 0.74 (0.48 to 1.15) ^{10,18}	5 fewer per 100 (from 10 fewer to 2 more)	⊙OOO VERY LOW
Smear po	ositivity by sp	ecimen (assessed	d with: number positi	ve/total number of	specimens obtaine	ed)					
3 ^{1,3,4}	cross- sectional	very serious ^{5,6,7,8,9}	no serious inconsistency	no serious indirectness	serious ¹³	none	53/1217 (4.4%)	42/869 (4.8%)	OR 0.99 (0.65 to 1.5) ^{10,19}	0 fewer per 100 (from 2 fewer to 2 more)	©OOO VERY LOW
Cumulati	ve smear pos	itivity: 2 specime	ns (assessed with: r	number of participa	ints with 1 or more	positive smear)					
1 ³	cross- sectional	serious ^{5,7,8}	no serious inconsistency	no serious indirectness	serious ¹³	none	42/403 (10.4%)	23/403 (5.7%)	OR 1.92 (1.13 to 3.26) ¹⁰	5 more per 100 (from 1 more to 11 more)	⊙OOO VERY LOW
Cumulati	ve smear pos	itivity: 3 specime	ens (assessed with: r	number of participa	ants with 1 or more	positive smear)					
2 ^{4,11}	cross- sectional	very serious ^{5,7,8,12}	no serious inconsistency	no serious indirectness	serious ¹³	none	18/267 (6.7%)	27/267 (10.1%)	OR 0.64 (0.34 to 1.2) ^{10,20}	3 fewer per 100 (from 6 fewer to 2 more)	⊙OOO VERY LOW

			Quality ass	essment			No of p	atients	E	ffect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration / lavage	Induced sputum	Relative (95% CI)	Absolute	Quality
			s (assessed with: nu								
11	cross- sectional	very serious ^{5,7,8,12}	no serious inconsistency	no serious indirectness	very serious ^{13,14}	none	2/17 (11.8%)	3/17 (17.6%)	OR 0.62 (0.09 to 4.29) ¹⁰	6 fewer per 100 (from 16 fewer to 30 more)	⊙OOC VERY LOW
ulture p	ositivity by s	pecimen (subgro	up: <5 years) (asses	ssed with: number	positive/total number	er of specimens obta	ined)				
22,4	cross- sectional	serious ^{5,7,8}	no serious inconsistency	serious ¹⁵	no serious imprecision	none	146/2119 (6.9%)	145/2119 (6.8%)	OR 1.01 (0.79 to 1.28) ^{10,21}	0 more per 100 (from 1 fewer to 2 more)	⊙OOC VERY LOW
umulativ	/e culture po	sitivity: 3 specime	ens (subgroup: <5 ye	ars) (assessed wit	h: number of partici	pants with 1 or more	positive culture)				
14	cross- sectional	serious ^{5,7,8}	no serious inconsistency	no serious indirectness	serious ¹³	none	38/250 (15.2%)	51/250 (20.4%)	OR 0.70 (0.44 to 1.11) ¹⁰	5 fewer per 100 (from 10 fewer to 2 more)	⊙OOO VERY LOW
mear po	sitivity by sp	ecimen (subgrou	ip: <5 years) (asses	sed with: number p	ositive/total numbe	r of specimens obtain	ned)				
4	cross- sectional	serious ^{5,7,8}	no serious inconsistency	no serious indirectness	serious ¹³	none	8/250 (3.2%)	19/250 (7.6%)	OR 0.40 (0.17 to 0.94) ¹⁰	4 fewer per 100 (from 0 fewer to 6 fewer)	⊙OOO VERY LOW
Cumulativ	/e smear pos	sitivity: 3 specime	ens (subgroup: <5 y	ears) (assessed w	ith: number of parti	cipants with 1 or mor	e positive smear)				
4	cross- sectional	serious ^{5,7,8}	no serious inconsistency	no serious indirectness	serious ¹³	none	17/250 (6.8%)	25/250 (10%)	OR 0.66 (0.35 to 1.25) ¹⁰	3 fewer per 100 (from 6 fewer to 2 more)	⊙OOO VERY LOW
 Study dia Blinding intervent Precise a Unclear i Calculat Jiménez Inapprop GRADE Wide co 	2009 ee, 2013 5 f a random or d not obtain se of individuals ions criteria for pos f there was ar ed by reviewe c, 2013 oriate exclusio rule of thumb nfidence inter	administering care sitivity is not stated n appropriate inter er ons - excluded par o: <300 events rval	luded participants (A e (all studies) and inv	estigators uncléar llection techniques non-tuberculous m	(Al-Aghbari, 2009) ycobacteria (Jiméno	ez, 2013)	005); blinding of pa	rticipants not s	tated, but unli	kely given the n	ature of ti

			Quality ass	essment			No of pa	tients	E	ffect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration / lavage	Induced sputum	Relative (95% Cl)	Absolute	Quality
¹⁶ Forest p	olot (culture po	sitivity by specime	n):								
¹⁷ Forest p	olot (cumulative	e culture positivity:	2 specimens):								
¹⁸ Forest p	olot (cumulative	e culture positivity:	3 specimens):								
¹⁹ Forest p	olot (smear pos	sitivity by specimer	ו):								
²⁰ Forest p	olot (cumulative	e smear positivity:	3 specimens):								
²¹ Forest p	olot (culture po	sitivity by specime	n; subgroup: <5 yea	rs)							

Nasogastric aspiration/lavage vs induced or spontaneously produced sputum

			Quality asse	essment			No of	patients	Ef	ffect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration / lavage	Induced or spontaneously produced sputum	Relative (95% Cl)	Absolute	Quality
Culture p	ositivity (asse	essed with: numbe	r of participants to be	e considered cultu	re-positive)						
1 ¹	cross- sectional	serious ^{2,3,4}	no serious inconsistency	serious ⁵	serious ⁶	none	5/67 (7.5%)	7/67 (10.4%)	OR 0.69 (0.21 to 2.3) ⁷	3 fewer per 100 (from 8 fewer to 11 more)	⊙OOO VERY LOW
³ Use of b ⁴ Precise of ⁵ Compara	if a random or linding uncleai criteria for posi	itivity is not stated pontaneously prod	le was used luced sputum (not th	e comparator of in	terest)						

⁶ Calculated by reviewer

Nasopharyngeal aspiration vs induced sputum

			Quality asse	essment			No of patie	ents	Effe	ect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Induced sputum	Relative (95% CI)	Absolute	Quality
Culture po	sitivity by sp	ecimen (assesse	d with: number posit	ive/total number o	f specimens obtain	ed)					
3 ^{1,2,3}	cross- sectional	very serious ^{4,5,6,7,8}	no serious inconsistency	no serious indirectness	serious ⁹	none	96/823 (11.7%)	134/839 (16%)	OR 0.69 (0.52 to 0.91) ^{10,12}	4 fewer per 100 (from 1 fewer to 7 fewer)	⊙OOO VERY LOW
Smear pos	sitivity by spe	ecimen (assessed	with: number positiv	ve/total number of	specimens obtaine	ed)					
3 ^{1,2,3}	cross- sectional	very serious ^{4,5,6,7,8}	no serious inconsistency	no serious indirectness	serious ⁹	none	75/829 (9%)	86/845 (10.2%)	OR 0.86 (0.62 to 1.19) ^{10,13}	1 fewer per 100 (from 4 fewer to 2 more)	⊙OOO VERY LOW
Culture po	sitivity by sp	ecimen (subgrou	u p: <5 years) (asses	sed with: number	positive/total numb	er of specimens obtai	ned)				
1 ³	cross- sectional	serious ^{4,6,7}	no serious inconsistency	serious ¹¹	serious ⁹	none	61/535 (11.4%)	84/535 (15.7%)	OR 0.69 (0.49 to 0.98) ¹⁰	4 fewer per 100 (from 0 fewer to 7 fewer)	⊙OOO VERY LOW

			Quality ass	essment			No of patie	ents	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Induced sputum	Relative (95% Cl)	Absolute	Quality
Smear po	sitivity by sp	ecimen (subgrou	p: <5 years) (asses	sed with: number p	positive/total numb	er of specimens obtair	ned)				
1 ³	cross- sectional	serious ^{4,6,7}	no serious inconsistency	serious ¹¹	serious ⁹	none	57/535 (10.7%)	69/535 (12.9%)	OR 0.81 (0.55 to 1.17) ¹⁰	2 fewer per 100 (from 5 fewer to 2 more)	©000 VERY LOW
 ⁵ Study dic ⁶ Blinding of ⁷ Precise of ⁸ Unclear i ⁹ GRADE of ¹⁰ Calculat ¹¹ Populati 	2007 f a random or I not obtain sa of individuals d rriteria for pos f there was ar "ule of thumb: ed by reviewe on is mostly b	administering care itivity is not stated appropriate interv <300 events r	luded participants (A (all studies) and inv val between the 2 cc ne, but some over 5s	estigators (Owens	s (Al-Aghbari, 2009	unclear; blinding of pa 9)	articipants not stated,	but unlikely	given the natu	re of the interv	entions

¹³ Forest plot (smear positivity by specimen):

Nasopharyngeal aspiration vs nasogastric aspiration/lavage

			Quality asses	sment			No of	patients	Eff	iect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Nasogastric aspiration/lavage	Relative (95% CI)	Absolute	Quality
Culture pos	sitivity by sp	ecimen (assess	ed with: number pos	itive/total number	of specimens obt	ained)					
3 ^{1,2,3}	cross- sectional	very serious ^{4.5,6,7,8}	no serious inconsistency	no serious indirectness	serious ⁹	none	34/729 (4.7%)	82/1101 (7.4%)	OR 0.68 (0.45 to 1.04) ^{10,11}	2 fewer per 100 (from 4 fewer to 0 more)	©OOO VERY LOW
Smear pos	itivity by spe	cimen (assesse	d with: number posit	ive/total number o	f specimens obta	ined)					
2 ^{1,2}	cross- sectional	very serious ^{4.5,6,7,8}	no serious inconsistency	no serious indirectness	serious ⁹	none	14/514 (2.7%)	25/885 (2.8%)	OR 1.12 (0.58 to 2.18) ^{10,12}	0 more per 100 (from 1 fewer to 3 more)	©OOO VERY LOW
PCR positi	vity by speci	men (assessed	with: number positive	e/total number of s	pecimens obtain	ed)					
1 ³	cross- sectional	serious ^{4,6,7}	no serious inconsistency	no serious indirectness	serious ⁹	none	26/218 (11.9%)	35/217 (16.1%)	OR 0.70 (0.41 to	4 fewer per 100	⊙OOO VERY

			Quality asse	essment			No of	patients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Nasogastric aspiration/lavage	Relative (95% Cl)	Absolute	Quality
									1.22) ¹⁰	(from 9 fewer to 3 more)	LOW
 ⁵ Study dia ⁶ Blinding of intervent. ⁷ Precise of ⁸ Unclear i. ⁹ GRADE i 	f a random or I not obtain sa of individuals a ions criteria for posi	administering car itivity is not stated appropriate inte <300 events	icluded participants re (all studies) and i	nvestigators (Ober	helman, 2006; Ol		nclear; blinding of part	licipants not stated, bu	t unlikely giv	en the nature	of the
		sitivity by specim	nen):								

Nasogastric aspiration/lavage vs bronchoalveolar lavage

			Quality asses	ssment			No of p	atients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Bronchoalveolar lavage	Relative (95% Cl)	Absolute	Quality
Culture pos	sitivity (asse		er of participants wit	h 1 or more positiv	e culture (cumula	ative yield for 3 GA s	pecimens vs 1 BAL sp	pecimen))			
3 ^{1,2,3}	cross- sectional	serious ^{4,5,6,7}	no serious inconsistency	no serious indirectness	serious ⁸	none	76/273 (27.8%)	59/273 (21.6%)	OR 1.41 (0.95 to 2.1) ^{9,12}	6 more per 100 (from 1 fewer to 15 more)	⊙OOO VERY LOW
Smear pos	sitivity (asses	sed with: numbe	r of participants with	a positive smear	(1 GA specimen v	/s 1 BAL specimen))					
1 ¹⁰	cross- sectional	serious ^{4,6,7}	no serious inconsistency	no serious indirectness	serious ⁸	none	6/52 (11.5%)	16/52 (30.8%)	OR 0.29 (0.1 to 0.83) ⁹	19 fewer per 100 (from 4 fewer to 27 fewer)	⊙OOO VERY LOW
Smear pos	sitivity (subg	roup: <5 years)	(assessed with: num	ber of participants	with a positive s	mear (cumulative yie	eld for 3 GA specimen	s vs 1 BAL specimer	1))		
1 ¹⁰	cross- sectional	serious ^{4,6,7}	no serious inconsistency	no serious indirectness	serious ⁸	none	0/20 (0%)	0/20 (0%)	OR 1.00 (0.02 to 52.85) ⁹	-	©OOO VERY LOW
Volume of	specimen (s	ubgroup: <5 ye	ars) (measured with	: mean volume of	specimens obtain	ed; better indicated l	by higher values)				
1 ¹⁰	cross- sectional	serious ^{4,6,7}	no serious inconsistency	no serious indirectness	serious ¹¹	none	20 mean (range) = 35 (20–55) ml	20 mean (range) = 56.5 (45 to 80)	-	MD 21.5 higher ⁹	⊙OOO VERY LOW

Need for anaesthesia (subgroup: <5 years) (assessed with: number of participants that required topical anaesthesia)

			Quality asse	essment			No of p	atients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Bronchoalveolar lavage	Relative (95% CI)	Absolute	Quality
1 ¹⁰	cross- sectional	serious ^{4,6,7}	no serious inconsistency	no serious indirectness	serious ⁸	none	0/20 (0%)	2/20 (10%)	OR 0.18 (0.01 to 4.01) ⁹	8 fewer per 100 (from 10 fewer to 21 more)	⊙OOO VERY LOW
 ⁵ Unclear i ⁶ Blinding of ⁷ Precise of ⁸ GRADE of ⁹ Calculate ¹⁰ Abadco, ¹¹ Insufficie 	94 f studies mad f if there was of individuals criteria for pos rule of thumb: ad by reviewer 1992	administering cai itivity is not state <300 events r able to appraise i	nterval between spe re and investigators d				given the nature of the	interventions			

Nasopharyngeal aspiration vs bronchoalveolar lavage

			Quality asses	sment			No of p	atients	Eff	ect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Bronchoalveolar lavage	Relative (95% CI)	Absolute	Quality
Culture pos	sitivity (asse	ssed with: numb	er of participants with	n a positive culture	e)						
11	cross- sectional	serious ^{2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	none	16/50 (32%)	6/50 (12%)	OR 3.45 (1.22 to 9.76) ⁶	20 more per 100 (from 2 more to 45 more)	⊙OOO VERY LOW

¹ Somu, 1995

² Unclear if studies made inappropriate exclusions
 ³ Blinding of individuals administering care and investigators unclear; blinding of participants not stated, but unlikely given the nature of the interventions
 ⁴ Precise criteria for positivity is not stated
 ⁵ CELESE is a time to exclusion

⁵ GRADE rule of thumb: <300 events

⁶ Calculated by reviewer

Nasogastric aspiration/lavage vs laryngeal swab

			Quality asses	ssment			No of p	atients	Effect		
No of						Other	Nasogastric		Relative		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	aspiration/lavage	Laryngeal swab	(95% CI)	Absolute	Quality
Cumulativ	umulative culture positivity: 3 specimens (assessed with: number of participants with 1 or more positive culture)										
2 ^{1,2}	cross-	serious3,4,5,6	no serious	no serious	serious ⁷	none	20/90	42/90	OR 0.29	26 fewer	0000

			Quality asse	essment			No of p	oatients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Laryngeal swab	Relative (95% CI)	Absolute	Quality
	sectional		inconsistency	indirectness			(22.2%)	(46.7%)	(0.14 to 0.57) ^{8,10}	per 100 (from 13 fewer to 36 fewer)	VERY LOW
	-					nore positive smear)					
1 ¹	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁷	none	4/30 (13.3%)	6/30 (20%)	OR 0.58 (0.14 to 2.50) ⁸	7 fewer per 100 (from 17 fewer to 18 more)	⊙OOC VERY LOW
							or more positive culture				
2 ^{1,2}	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	serious ⁹	serious ⁷	none	20/77 (26%)	41/77 (53.2%)	OR 0.29 (0.15 to 0.59) ^{8,11}	28 fewer per 100 (from 13 fewer to 39 fewer)	⊙OOO VERY LOW
Cumulativ	ve smear pos		iens (<5 years) (as	sessed with: numb	per of participants	s with 1 or more posit	tive smear)				
1 ¹	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁷	none	3/17 (17.6%)	4/17 (23.5%)	OR 0.70 (0.13 to 3.72) ⁸	6 fewer per 100 (from 20 fewer to 30 more)	⊙OOO VERY LOW
	ve culture pos	sitivity: 3 specir	nens (subgroup: >	5 years) (assesse	ed with: number of	of participants with 1	or more positive culture	e)			
1 ¹	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁷	none	0/13 (0%)	1/13 (7.7%)	OR 0.31 (0.01 to 8.30) ⁸	5 fewer per 100 (from 8 fewer to 33 more)	⊙OOO VERY LOW
				years) (assessed		f participants with 1 o	r more positive smear)				
1 ¹	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁷	none	1/13 (7.7%)	2/13 (15.4%)	OR 0.46 (0.04 to 5.79) ⁸	8 fewer per 100 (from 15 fewer to 36 more)	⊙OOO VERY LOW
 ⁴ Blinding ⁵ Precise of ⁶ Unclear ⁷ GRADE 	968 if a random or of individuals criteria for pos	itivity is not state ere appropriate <300 events	re and investigators	unclear; blinding o	of participants no	t stated, but unlikely	given the nature of the	interventions			

⁸ Calculated by reviewer
 ⁹ Population of Lloyd (1968) is >6 years of age as opposed to 5
 ¹⁰ Forest plot (cumulative culture positivity: 3 specimens):

¹¹ Forest plot (cumulative culture positivity: 3 specimens; subgroup: <5 years):

			Quality asses	ssment			No of p	atients	Eff	fect	
No of						Other	Nasogastric		Relative		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	aspiration/lavage	Laryngeal swab	(95% CI)	Absolute	Quality

Nasogastric aspiration/lavage vs lung puncture aspiration

			Quality asse	ssment			No of	patients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Lung puncture aspiration	Relative (95% CI)	Absolute	Quality
Cumulativ	ve culture pos	sitivity: 3 specin	nens (assessed with	n: number of parti	cipants with 1 or	more positive culture)				
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	3/30 (10%)	16/30 (53.3%)	OR 0.10 (0.02 to 0.39) ⁷	43 fewer per 100 (from 23 fewer to 51 fewer)	⊙OOO VERY LOW
		itivity: 3 specim				nore positive smear)					
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	4/30 (13.3%)	5/30 (16.7%)	OR 0.77 (0.19 to 3.20) ⁷	3 fewer per 100 (from 13 fewer to 22 more)	⊙OOO VERY LOW
	ve culture pos					of participants with 1 of	or more positive cultur	,			
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	3/17 (17.6%)	10/17 (58.8%)	OR 0.15 (0.03 to 0.73) ⁷	41 fewer per 100 (from 8 fewer to 55 fewer)	⊙OOO VERY LOW
Cumulativ	ve smear pos	itivity: 3 specim	ens (subgroup: <5	years) (assessed	d with: number of	f participants with 1 of	r more positive smear)			
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	3/17 (17.6%)	4/17 (23.5%)	OR 0.70 (0.13 to 3.72) ⁷	6 fewer per 100 (from 20 fewer to 30 more)	⊙OOO VERY LOW
	ve culture pos		· • ·	5 years) (assesse			or more positive cultur	,			
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	0/13 (0%)	6/13 (46.2%)	OR 0.04 (0.00 to 0.87) ⁷	43 fewer per 100 (from 3 fewer to 46 fewer)	⊙OOO VERY LOW
	-			2 / `		f participants with 1 of	r more positive smear				
1 ¹	cross- sectional	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	1/13 (7.7%)	1/13 (7.7%)	OR 1.00 (0.06 to 17.90) ⁷	0 fewer per 100 (from 7 fewer to 52 more)	⊙OOO VERY LOW
¹ Bhandari	i, 1976										

			Quality asses	sment			No of p	atients	Eff	fect	
No of studies	ies Design Risk of bias Inconsistency Indirectness Imprecision						Nasogastric aspiration/lavage	Lung puncture	Relative	Absolute	Quality
	a random or o	consecutive sam		muneetness	Imprecision	considerations	aspiration/lavage	aspiration		Absolute	Quanty

³ Blinding of individuals administering care and investigators unclear; blinding of participants not stated, but unlikely given the nature of the interventions

⁴ Precise criteria for positivity is not stated
 ⁵ Unclear if exclusions were appropriate

⁶ GRADE rule of thumb: <300 events

⁷ Calculated by reviewer

Suctioned vs coughed induced sputum

			Quality asses	ssment			No of j	oatients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Suctioned induced sputum	Coughed induced sputum	Relative (95% CI)	Absolute	Qualit
			d with: number pos	Indirectness			induced sputum	muuceu sputum	(95% 01)	Absolute	Qualit
1 ¹	observational	very serious ^{2,3,4}	serious⁵	no serious indirectness	serious ⁶	none	129/993 (13%)	62/264 (23.5%)	OR 0.49 (0.35 to 0.68) ⁷	10 fewer per 100 (from 6 fewer to 14 fewer)	©OO0 VERY LOW
	· ·	sessed with: n	umber of procedure	es completed with		nts)					
1 ¹	observational	very serious ^{2,3,4}	serious⁵	no serious indirectness	no serious imprecision	none	744/993 (74.9%)	259/264 (98.1%)	OR 0.06 (0.02 to 0.14) ⁷	22 fewer per 100 (from 10 fewer to 47 fewer)	⊙OOC VERY LOW
Adverse e	events - nose ble	ed (assessed	with: number of pro	ocedures in which	n nose bleed occ	urred)					
1 ¹	observational	very serious ^{2,3,4}	serious⁵	no serious indirectness	no serious imprecision	none	239/993 (24.1%)	4/264 (1.5%)	OR 20.60 (7.59 to 55.90) ⁷	23 more per 100 (from 9 more to 45 more)	⊙OOC VERY LOW
Adverse e	events - wheeze	(assessed with	: number of procee	dures that led to v	wheezing)						
1 ¹	observational	very serious ^{2,3,4}	serious⁵	no serious indirectness	no serious imprecision	none	11/993 (1.1%)	3/264 (1.1%)	OR 0.97 (0.27 to 3.52) ⁷	0 fewer per 100 (from 1 fewer to 3 more)	⊙OOC VERY LOW
Adverse e	events – exacerb	ation of cougl	h (assessed with: r	number of proced	ures that led to e	xacerbation of cough	1)				
1 ¹	observational	very serious ^{2,3,4}	serious⁵	no serious indirectness	no serious imprecision	none	3/993 (0.0%)	1/264 (0.0%)	OR 0.80 (0.08 to 7.69) ⁷	0 fewer per 100 (from 0 fewer to 2 more)	⊙OOC VERY LOW

¹ Planting, 2014

² Allocation connected to a potentially confounding factor - based on child's ability to spontaneously produce sputum
 ³ Blinding of individuals administering care and investigators unclear; blinding of participants not stated, but unlikely given the nature of the interventions

			Quality asses	ssment			No of p	oatients	Ef	fect	
No of		Risk of				Other	Suctioned	Coughed	Relative		
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	induced sputum	induced sputum	(95% CI)	Absolute	Quality
⁴ Precise c	riteria for positivi	ty is not stated									
⁵ Unclear if	groups were co	mparable at bas	seline								
⁶ GRADE r	ule of thumb: <3	00 events									
7 Calculate	d by reviewer										

Nasogastric aspiration/lavage with nebulisation vs nasogastric aspiration/lavage alone

			Quality asses	sment			No of p	atients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage with nebulisation	Nasogastric aspiration/lavage alone	Relative (95% CI)	Absolute	Quality
Culture pos	sitivity (assesse	d with: number	of participants wit	h a positive cultur	e)						
1 ¹	randomised trial	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	none	9/36 (25%)	24/68 (35.3%)	OR 1.29 (0.49 to 3.35) ⁷	6 more per 100 (from 14 fewer to 29 more)	⊙OOO VERY LOW
Volume of	specimen (meas	sured with: mea	an volume of speci	mens obtained; b	etter indicated by	/ higher values)					
1 ¹	randomised trial	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁸	none	36 mean = 25 ml	68 mean = 10 ml	-	MD 15 higher ⁷	⊙OOO VERY LOW
¹ Maciel 20	10										

² Unclear if a random or consecutive sample was used
 ³ Blinding of individuals administering care and investigators unclear; blinding of participants not stated, but unlikely given the nature of the interventions

⁴ Precise criteria for positivity is not stated
 ⁵ Unclear if exclusions were appropriate
 ⁶ GRADE rule of thumb: <300 events

⁷ Calculated by reviewer
 ⁸ Insufficient data available to appraise imprecision

Nasogastric aspiration/lavage with sedation vs nasogastric aspiration/lavage with placebo

			Quality asses	sment			No of p	atients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Induced sputum	Relative (95% Cl)	Absolute	Quality
	ity of the proced ated by higher so		s – usefulness of	the sedation (as	sessed with: sco	re derived from quest	tionnaire, answered us	sing a visual analogu	e scale ('0' fo	or worst, '10'	for best);
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 5 (3–7)	-	Difference in medians = 5^4	0000 LOW
	ity of the proced ated by higher so		s – impact on chil	l d's outlook (ass	essed with: score	e derived from question	onnaire, answered usi	ng a visual analogue	scale ('0' for	worst, '10' fo	or best);
1 ¹	randomised	serious ²	no serious	no serious	serious ³	none	Median (range) =	Median (range) =	-	Difference	$\odot \odot \odot \odot$

			Quality asse	ssment			No of p	oatients	Ef	ffect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Induced sputum	Relative (95% Cl)	Absolute	Quality
	trial		inconsistency	indirectness			8.9 (7–10)	5.8 (5–7)		in medians = 3.1 ⁴	LOW
•	ility of the proce cated by higher s	•	nts – impact on pa	rents' outlook (a	ssessed with: so	ore derived from que	estionnaire, answered u	sing a visual analogu	ie scale ('0'	for worst, '10'	for best);
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 9.1 (8–10)	Median (range) = 4.9 (3–7)	-	Difference in medians = 4.2 ⁴	©⊙OO LOW
	ility of the proce er indicated by hi		nts – child's tolera	nce of procedure	es (assessed with	h: score derived from	n questionnaire, answer	red using a visual and	alogue scale	e ('0' for worst	, '10' for
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 8.7 (7–10)	Median (range) = 8.5 (7–10)	-	Difference in medians = 0.2 ⁴	©©OO LOW
	ility of the proce			mend to other pa	arents (assessed	d with: score derived	from questionnaire, and	swered using a visua	I analogue s	scale ('0' for w	/orst, '10'
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 9.3 (9–10)	Median (range) = 4 (3–6)	-	Difference in medians = 5.3 ⁴	©©OO LOW
			nts – would like to); better indicated by		l atomizer devic	e used routinely (a	ssessed with: score der	rived from questionna	aire, answere	ed using a vis	ual
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 9.8 (9–10)	Median (range) = 4 (3–6)	-	Difference in medians = 5.8 ⁴	⊙⊙OO LOW
	ility of the proce er indicated by hi		ians – usefulness	of the sedation	(assessed with: s	score derived from qu	uestionnaire, answered	using a visual analog	gue scale ('C)' for worst, '1	0' for
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 3 (2–4)	-	Difference in medians = 7 ⁴	⊙⊙OO LOW
			ians – impact on c	hild's outlook (a	assessed with: so	core derived from que	estionnaire, answered ι	using a visual analogi	ue scale ('0'	for worst, '10	' for best);
1 ¹	cated by higher s randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 8 (7–9)	Median (range) = 3 (2–4)	-	Difference in medians = 5^4	©⊙OO LOW
	ility of the proce er indicated by hi		ians – impact on c	linician's outloc	k (assessed with	n: score derived from	questionnaire, answer	ed using a visual ana	alogue scale	('0' for worst,	'10' for
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 9.5 (9–10)	Median (range) = 4 (3–5)	-	Difference in medians = 5.5^4	⊙⊙OO LOW

			Quality asse	ssment			No of j	oatients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Induced sputum	Relative (95% Cl)	Absolute	Quality
•	ility of the proce er indicated by hi		cians – child's tole	rance of proced	u res (assessed v	vith: score derived fro	om questionnaire, ansv	vered using a visual a	inalogue sca	ale ('0' for wor	rst, '10' fo
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 8.2 (7–9)	Median (range) = 8 (7–9)	-	Difference in medians =	⊙⊙⊖0 LOW
	ility of the proce st); better indicate			mmend to other	clinicians (asse	ssed with: score der	ived from questionnaire	e, answered using a v	isual analog	ue scale ('0'	for worst
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 9.4 (9–10)	Median (range) = 3 (1–5)	-	Difference in medians = 6.4^4	⊙⊙OC LOW
			cians – would like f		sal atomizer dev	vice used routinely	(assessed with: score of	derived from question	naire, answe	ered using a	/isual
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 3 (1–5)	-	Difference in medians = 7 ⁴	⊙⊙OC LOW
	ility of the proce st); better indicate			rocedure more a	cceptable (asse	essed with: score der	ived from questionnair	e, answered using a v	risual analog	jue scale ('0'	for worst
1 ¹	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 3 (1–5)	-	Difference in medians = 7 ⁴	©©O0 LOW

⁴ Calculated by reviewer

A.2 RQ C

A.2.1 Diagnosis of active pulmonary tuberculosis in adults who are HIV-negative

Commercial nucleic acid amplification techniques compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-negative

	Number of	Quality a	ssessment				Number of	Summary of		
Test	Test evaluation			Inconsisten Indirectnes		Other	patients/		Overlite	
details	S	Design	Risk of bias	су	S	Imprecision	considerations	specimens	findings	Quality
Sensitivity	y ¹									

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Xpert MTB/RIF only	18	cross- sectiona I	no serious risk of bias ²	serious ³	serious ³	serious⁵	Limited industry involvement All except 1 study conducted in a high incidence country ⁶	2555	91.4% (95% CI 87.5 to 94.2%)	VERY LOW
Specificity	r ¹									
Xpert MTB/RIF only	18	cross- sectiona I	no serious risk of bias ²	serious ³	serious ³	no serious imprecision	Limited industry involvement All except 1 study conducted in a high incidence country ⁶	2555	99.5% (95% CI 98.6 to 99.8%)	LOW

¹ Forest plots for sensitivity and specificity (Xpert MTB/RIF assay):

²Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Reference standard varied widely from study to study, using different culture techniques and in some cases employing a number of additional reference criteria (e.g. clinical characteristics or smear status)

⁴ Wide confidence intervals

⁵ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

⁶ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Use of antituberculosis antibodies to detect tuberculosis in urine compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-negative

	Number of	Quality a	ssessment				Number of			
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	1									
LAM	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistenc y	no serious indirectness	no serious imprecision	No information available on industry involvement	397	52% 95% CI (43 to 62%)	MODERATE

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
							Conducted in a high incidence country ⁶			
Specificity	/ ¹									
LAM	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistenc y	no serious indirectness	no serious imprecision	No information available on industry involvement Conducted in a high incidence country ⁶	397	86% (95% CI 77 to 93%)	MODERATE
¹ Mutetwa,	2009									

²Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Unclear if a consecutive or random sample used

⁴ Unlcear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Interferon-gamma release assays compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-negative

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	,									
Interferon -gamma release assays ⁷	2	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	no serious imprecision	Test kits supplied by industry Conducted in a high incidence country ⁸	275	90.6% (95% CI 84.2 to 94.6%)	LOW
QuantiFE RON-TB Gold	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	no serious imprecision	Test kits supplied by industry Conducted in a	138	89.2% (95% CI 81.7 to 96.8%)	LOW

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
							high incidence country ⁸			
T- SPOT.TB	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	no serious imprecision	Test kits supplied by industry Conducted in a high incidence country ⁸	137	92.2% (95% CI 85.6 to 98.8%)	LOW
Specificity	,									
QuantiFE RON-TB Gold	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	no serious imprecision	Test kits supplied by industry Conducted in a high incidence country ⁸	138	49.3% (95% CI 37.9 to 60.8%)	LOW
T- SPOT.TB	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	no serious imprecision	Test kits supplied by industry Conducted in a high incidence country ⁸	137	46.6% (95% CI 35.1 to 58.0%)	LOW

¹ Kang, 2007

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Inappropriate exclusions were not avoided – excluded patients with high clinical likelihood of active TB and a negative mycobacterial culture finding but good clinical and radiographic responses to anttuberculosis treatment

⁴ Unclear if test interpretation was blinded

⁵ Unclear how many participants, if any, were under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁶ Reference standard included histology as an alternative to culture

⁷ QuantiFERON-TB Gold and T-SPOT.TB

⁸ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Tuberculin skin tests compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIVnegative

details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	findings	
Sensitivity	1									
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	serious ⁷	Test kits for IGRA component of trial supplied by industry Conducted in a high incidence country ⁸	141	68.2% (95% CI 56.9 to 79.4%)	VERY LOW
Specificity	,									
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	serious ^{5,6}	serious ⁷	Test kits for IGRA component of trial supplied by industry Conducted in a high incidence country ⁸	141	50.7% (95% CI 39.4 to 62.0%)	VERY LOW

¹ Kang, 2007

²Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Inappropriate exclusions were not avoided – excluded patients with high clinical likelihood of active TB and a negative mycobacterial culture finding but good clinical and radiographic responses to anttuberculosis treatment

⁴ Unclear if test interpretation was blinded

⁵ Unclear how many participants, if any, were under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁶ Reference standard included histology as an alternative to culture

⁷ Wide confidence interval

⁸ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

A.2.2 Diagnosis of active pulmonary tuberculosis in adults who are HIV-positive

Smear microscopy compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

		Quality a	ssessment					Number of		
Test	Number of evaluation			Inconsisten	Indirectnes		Other considerations	patients/ specimen	Summary of	
details	S	Design	Risk of bias	су	S	Imprecision	considerations	S	findings	Quality

		Quality a	ssessment				Number of			
Test details	Number of evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity	/ ²									
All technique s	3 ^{1,2}	cross- sectiona I ³	no serious risk of bias	serious ⁴	no serious indirectness ⁷	serious ⁹	No industry involvement All except 1 study conducted in a high incidence country ¹⁰	1094	40.8% (95% CI 18.6 to 67.6%)	MODERA E
Fluoresce nce microsco py	Chaidir, 2013 ¹	cross- sectiona I ³	serious ^{5,6}	serious ⁴	no serious indirectness ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ¹⁰	256	65.2% (95% CI 59.4 to 71.0%)	LOW
Ziehl- Neelson microsco py	Chaidir, 2013 ¹	cross- sectiona I ³	serious ^{5,6}	serious ⁴	no serious indirectness ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ¹⁰	256	58.0% (95% Cl 52.0 to 64.0%)	LOW
Specificity	/ ¹¹									
Fluoresce nce microsco py	Lawn, 2011 Lawn, 2012 Chaidir, 2013	cross- sectiona I ³	serious ^{5,6}	serious ⁴	no serious indirectness ⁷	no serious imprecision	No industry involvement Conducted in high incidence countries ¹⁰	445 516 256	100% (95% CI 100 to 100%) 99.8% (95% CI 99.3 to 100%) 90.4% (95% CI 86.8 to 94.0%)	LOW
Ziehl- Neelson microsco py	Carriquiry, 2012 Chaidir, 2013	cross- sectiona I ³	serious ^{5,6}	serious ⁴	no serious indirectness ⁷	no serious imprecision	No industry involvement All except 1 study conducted in a high incidence country ¹⁰	133 256	96.6% (95% CI 92.8 to 100%) 96.3% (95% CI 94.0 to 98.6%)	LOW

¹ Insufficient data provided to use Chaidir (2013) in the meta-analysis
 ² Forest plots for sensitivity and specificity (grouped by technique used):

		Quality a	ssessment					Number of		Quality
Test details	Number of evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	
³ Both ind	ex test and refe	rence stan	dard performed	in every patient	, with an approp	priate period of ti	ime between the two			
⁴ Reference	ce standard var	ies across :	studies: culture	technique not c	onsistent					
⁵ Unclear	if a consecutive	or random	sample of parti	cipants used in	Chaidir (2013)					
⁶ Unclear	if inappropriate	exclusions	were avoided in	n Chaidir (2013))					
⁷ Chaidir (2013) provide r	no details o	f the age of the	study population	n; however, it is	not anticipated	that the results will be	significantly a	ffected by this	
³ Wide co	nfidence interva	ıl	-						·	
⁹ Significa	nt variation in th	ne point est	imates, as well	as wide confide	nce intervals wi	th limited overla	р			
¹⁰ Countrie	es/territories wit	h an estima		ate of 40 per 10	0,000 or greate		to have a high incide	ence of tubercu	ulosis, as defined b	by Public

¹¹ Meta-analysis of relevant data not possible in STATA or R

Microscopy, chest radiography and symptoms compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

	Quality a	ssessment					Number		
Number of evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	of patients/ specimen s	Summary of findings	Quality
1 ²	cross- sectiona I ³	serious ^{4,5,6}	no serious inconsistenc y	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁸	445	53.7% (95% CI 40.4 to 67.0%)	MODERATE
1 ²	cross- sectiona I ³	serious ^{4,5,6}	no serious inconsistenc y	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁸	445	76.2% (95% CI 72.0 to 80.4%)	MODERATE
	evaluation s 1 ²	Number of evaluation sDesign12cross- sectiona 1312cross- sectiona 1312cross- sectiona	evaluation sDesignRisk of bias12Cross- sectiona l3serious4,5,612Cross- sectionaserious4,5,612Cross- sectionaserious4,5,6	Number of evaluation sDesignRisk of biasInconsisten cy12Cross- sectiona l³serious4,5,6no serious inconsistenc y12Cross- sectionaserious4,5,6no serious inconsistenc y	Number of evaluation sDesignRisk of biasInconsisten cyIndirectnes s12cross- sectiona 13serious4,5,6no serious inconsistenc yno serious indirectness12cross- sectionaserious4,5,6no serious inconsistenc yno serious indirectness12cross- sectionaserious4,5,6no serious indirectnessno serious indirectness	Number of evaluation sDesignRisk of biasInconsisten cyIndirectnes sImprecision12cross- sectiona 13serious4.5.6no serious inconsistencyno serious indirectnessno serious indirectness12cross- sectionaserious4.5.6no serious inconsistencyno serious indirectnessno serious indirectness12cross- sectionaserious4.5.6no serious inconsistencno serious indirectnessno serious imprecision	Number of evaluation sDesignRisk of biasInconsisten cyIndirectnes sImprecisionOther considerations12Cross- sectiona l³serious4.5.6no serious inconsistenc yno serious indirectnessno serious imprecisionNo industry involvement Conducted in a high incidence country812Cross- sectiona l³serious4.5.6no serious yno serious indirectnessno serious imprecisionNo industry involvement Conducted in a high incidence country812Cross- sectiona l³serious4.5.6no serious yno serious inconsistenc yno serious indirectnessNo industry involvement Conducted in a high incidence country8	Number of evaluation sDesignRisk of biasInconsisten cyIndirectnes sImprecisionOther considerationsof patients/ specimen s12Cross- sectiona l³serious4.5.6no serious inconsistenc yno serious indirectnessno serious indirectnessNo industry involvement Conducted in a high incidence country844512Cross- sectiona l³serious4.5.6no serious inconsistenc yno serious indirectnessNo industry involvement Conducted in a high incidence country844512Cross- sectiona l³serious4.5.6no serious inconsistenc yno serious indirectnessNo industry involvement Conducted in a high incidence445	Number of evaluation sDesignRisk of biasInconsisten cyIndirectnes sImprecisionOther considerationsof patients/ specimenSummary of findings12cross- sectiona 13serious ^{4.5.6} no serious inconsistenc yno serious indirectnessno serious imprecisionNo industry involvement Conducted in a high incidence country844553.7% (95% CI 40.4 to 67.0%)12cross- sectiona 13serious ^{4.5.6} no serious inconsistenc yno serious indirectnessno serious imprecisionNo industry involvement Conducted in a high incidence country844553.7% (95% CI 40.4 to 67.0%)12cross- sectiona 13serious ^{4.5.6} no serious inconsistenc yno serious indirectnessno serious imprecisionNo industry involvement Conducted in a high incidence country844576.2% (95% CI 72.0 to 80.4%)

¹ Any 1 of the following 4 symptoms: cough, fever, weight loss and night sweats ² Swindells, 2013

		Quality a	ssessment					Number		
Test details	Number of evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	of patients/ specimen s	Summary of findings	Quality
³ Both inde	x test and refe	rence stand	dard performed	in every patient	, with an approp	oriate period of ti	me between the two	Ì		

⁴ Unclear if inappropriate exclusions were avoided
 ⁵ Unclear if test interpretation was blinded in all or most of the included comparisons

⁶ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁷ Unclear how many participants, if any, are under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁸ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public

Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Commercial nucleic acid amplification techniques compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	1									
Xpert MTB/RIF	16	cross- sectiona I	no serious risk of bias ⁴	serious ⁵	serious ⁵	serious ⁷	Limited industry involvement All except 2 studies conducted in a high incidence country ⁸	2990	80.9% (95% CI 72.9 to 86.9%)	VERY LOW
Specificity	1									
Xpert MTB/RIF	16	cross- sectiona I	no serious risk of bias ⁴	serious⁵	serious⁵	no serious imprecision	Limited industry involvement All except 2 studies conducted in a high incidence country ⁸	2990	98.8% (95% CI 97.8 to 99.4%)	LOW
¹ Forest plo	ots for sensitivi	ty and spec	cificity (Xpert M	[B/RIF assay):			-			

	Number of	Quality a	ssessment					Number of		
Test	evaluation			Inconsisten	Indirectnes		Other	patients/	Summary of	
details	S	Design	Risk of bias	су	S	Imprecision	considerations	specimens	findings	Quality

⁴ Both index test and reference standard performed in every patient, with an appropriate period of time between the two

⁵ Reference standard varied widely from study to study, using different culture techniques and in some cases employing a number of additional reference criteria (e.g. clinical characteristics or smear status)

⁶ Wide confidence interval

⁷ Significant variation in the point estimates with limited overlap of wide confidence intervals

⁸ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Use of antituberculosis antibodies to detect tuberculosis in urine compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

·	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	/ ¹									
LAM	26	cross- sectiona I	no serious risk of bias	no serious inconsistenc y	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁸	1032	27.7% (95% CI 21.5 to 34.8%)	HIGH
LAM	Mutetwa, 2009 ⁶	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistenc y	no serious indirectness	no serious imprecision	Unclear if there was industry involvement Conducted in a high incidence country ⁸	397	52% 95% Cl (43 to 62%)	MODERA TE
Specificity	/ ^{1,9}									
LAM	Lawn, 2012 Lawn, 2012 Mutetwa, 2012	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistenc y	no serious indirectness	serious ⁷	Unclear if there was industry involvement in 1 study; no involvement in the other Conducted in high incidence	516 516 397	98.1% (95% CI 96.9 to 99.4%) 98.6% (95% CI 97.5 to 99.7%) 86% (95% CI	LOW

	Number of	Quality a	ssessment			Number of				
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
							countries ⁸		77 to 93%)	
¹ Forest p	olots:									
⁴ Unclear	if a consecutive if inappropriate	exclusions	were avoided in	n Mutetwa (2009	•					
	if test interpreta			. ,						
6 Insuffici	if test interpreta ent data to inclu n in the point es	de Mutetwa	a (2009) in the n	neta-analysis	ence intervals					

Interferon-gamma release assays compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	/									
QuantiFE RON-TB Gold In- Tube	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	no serious indirectness	serious ⁵	No industry involvement Conducted in a high incidence country ⁶	52	85.3% (95% CI 73.4 to 97.2%)	VERY LOW
Specificity	/									
QuantiFE RON-TB Gold In- Tube	1 ²	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	no serious indirectness	serious⁵	No industry involvement Conducted in a high incidence country ⁶	52	44.4% (95% CI 21.5 to 67.4%)	LOW

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

	Number of	Quality a	ssessment					Number of		
Test	evaluation			Inconsisten	Indirectnes		Other	patients/	Summary of	
details	S	Design	Risk of bias	су	S	Imprecision	considerations	specimens	findings	Quality

³ Consecutive or random sample not used

⁴ Unclear if test interpretation was blinded

⁵ Wide confidence interval

⁶ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Tuberculin skin tests compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are HIV-positive

	Number of	Quality a	ssessment					Number of		
Test details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	Summary of findings	Quality
Sensitivity	,									
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	no serious indirectness	serious ⁵	No industry involvement Conducted in a high incidence country ⁶	52	25.0% (95% CI 12.2 to 37.8%)	VERY LOW
Specificity	,									
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistenc y	no serious indirectness	serious ⁵	No industry involvement Conducted in a high incidence country ⁶	52	72.7% (95% CI 54.1 to 91.3%)	LOW

¹ Kabeer, 2009

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Consecutive or random sample not used

⁴ Unclear if test interpretation was blinded

⁵ Wide confidence interval

⁶ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

A.2.3 Diagnosis of active pulmonary tuberculosis in adults

	Number	Quality a	ssessment					Number of		
Test details	of evaluatio ns	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques (Ziehl- Neelson, fluorescence, cold stain)	84	cross- sectiona I ²	serious ^{2,3,4,5,6}	serious ^{7.8.9}	no serious indirectness ¹	serious ¹¹	Degree of industry involvement unclear in many studies; amongst those for which information is given, just under half had industry involvement Approximately half of studies were conducted in a high incidence country ¹³	59984	65.6% (95% CI 61.1 to 69.9%)	VERY LOW
Specificity ¹										
All techniques (Ziehl- Neelson, fluorescence, cold stain)	84	cross- sectiona I ²	serious ^{2,3,4,5,6}	serious ^{7,8,9}	no serious indirectness ¹	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which information is given, just under half had industry involvement Approximately half of studies were conducted in a high	59984	97.9% (95% Cl 97.1 to 98.5%)	LOW

Smear microscopy compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

	Number	Quality a	ssessment					Number of		
Test details	of evaluatio ns	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							incidence country ¹³			

¹ Forest plots for sensitivity and specificity (grouped by technique used):

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Unclear if a consecutive or random sample of participants used in all or most of the included comparisons

⁴ Unclear if inappropriate exclusions were avoided in all or most of the included comparisons

⁵ Unclear if test interpretation was blinded in all or most of the included comparisons

⁶ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁷ Index test varies across studies: microscopy technique varies across studies

⁸ Reference standard varies across studies: culture technique not consistent

¹⁰ A number of studies include a small proportion of participants who are under 18 years old or provide no details of the age of the study population; however, it is not anticipated that the results will be significantly affected by this

¹¹ Significant variation in the point estimates, with limited overlap in confidence intervals

¹² Wide confidence interval

¹³ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Chest radiography compared to culture-based reference standard in people with suspected pulmonary tuberculosis

				Quality assessm	ient		Number of		
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity									
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥23 points ¹	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	95% (95% CI 91 to 98%)	MODERAT E
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	85% (95% CI 79 to 90%)	MODERAT E

				Quality assessm	nent		Number of		
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
interpretation: ≥56 points ¹									
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥74 points ¹	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	77% (95% CI 71 to 83%)	MODERAT E
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥95 points ¹	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	47% (95% CI 40 to 54%)	MODERAT E
Chest radiograph – 'expert reader' Threshold for interpretation: category 4 ⁴	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	59% (95% CI 52 to 66%)	MODERAT E
Chest radiograph – 'expert reader' Threshold for interpretation: category 3 or	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	78% (95% CI 71 to 83%)	MODERAT E

				Quality assessm	Number of				
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
4 ⁴									
Chest radiograph – clinical officer with practical experience, but not considered 'expert' Threshold for interpretation: category 4 ⁴	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	7% (95% CI 4% to 12%)	MODERAT E
Chest radiograph – clinical officer with practical experience, but not considered 'expert' Threshold for interpretation: category 3 or 4 ⁴	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	76% (95% CI 69 to 82%	MODERAT E
Specificity									
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥23 points ¹	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	33% (95% CI 27 to 39%)	MODERAT E

				Quality assessm	ient		Number of		
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ Imprecision specimens		Quality
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥56 points ¹	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	69% (95% CI 62 to 75%)	MODERAT
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: \geq 74 points ¹	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	79% (95% CI 74 to 84%)	MODERAT E
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: ≥95 points ¹	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	94% (95% CI 91 to 97%)	MODERAT
Chest radiograph – 'expert reader' Threshold for interpretation:	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	98% (95% CI 95 to 99%)	MODERAT E

				Number of		1			
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Inconsistency Indirectness		patients/ specimens	Summary of findings	Quality
category 4 ⁴									
Chest radiograph – 'expert reader' Threshold for interpretation: category 3 or 4 ⁴	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	81% (95% CI 80 to 89%)	MODERAT E
Chest radiograph – clinical officer with practical experience, but not considered 'expert' Threshold for interpretation: category 4 ⁴	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	97% (95% CI 94 to 99%)	MODERAT E
Chest radiograph – clinical officer with practical experience, but not considered 'expert' Threshold for interpretation: category 3 or 4 ⁴	12	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	65% (95% CI 58 to 71%)	MODERAT E

and image level – scores generated by these subsystems are as an abnormality score for the presence of active disease ² Breuninger, 2014

				Quality assessm	Number of					
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality	
³ Protocol permitted the inclusion of children										
⁴ Categories:	Categories:									
1. normal	normal									
2. abnorm	2. abnormal, findings not suggestive for active TB (TB sequel possible)									
3. abnormal, findings consistent with active TB, but TB sequel or other lung pathology possible										

Chest radiography plus an algorithm of signs, symptoms and risk factors compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Chest radiography plus signs, symptoms and risk factors ²	10	systema tic review ³	serious ^{4,5,6}	very serious ^{7,8}	no serious indirectness ⁹	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	5375	94% (24– 100%)	VERY LOW
Specificity ¹										
Chest radiography plus signs, symptoms and risk factors ²	10	systema tic review ³	serious ^{4,5,6}	very serious ^{7,8}	no serious indirectness ⁹	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	5375	56% (21– 93.1%)	VERY LOW
¹ Sensitivity ar	nd specificity:									
	Study			Sensitivity (95% CI)		Specificity (95% C	1)		

		Quality a	ssessment				Number of				
Test details	Number of evaluation s	Design	Risk of bias	Inco y	onsistenc	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary findings	of Quality
	Bock, 1996	5			81% (66 to	91%)		62% (56 to 68%)			
	El-Solh, 19	El-Solh, 1997				100% (78 to 100%) 50% (4			50% (44 to 57%)		
	El-Solh, 19	1999			100% (91 to 100%)			72% (65 to 77%)			
	Lagrange->	Kelot, 2010	elot, 2010			96% (80 to 100%)			21% (14 to 30%)		
	Moran, 200)9			96% (91 to 99%)			49% (47 to 51%)			
	Mylotte, 19	utte, 1997			88% (47 to100%)			63% (56 to 70%)			
	Solari, 200	ri, 2008			93% (86 to 97%)			42% (36 to 49%)			
	Soto, 2008				93%			92%			
	Soto, 2011				24% (18 to	31%)		93% (91 to 95%)			
	Wisnivesky	<i>ı</i> , 2005			95% (74 to	100%)		35% (31 to 40%)			

² Scoring systems used:

Study	Details of chest radiograph scoring system
Bock, 1996	1) chest X-ray with upper lobe infiltrate, 2) chest X-ray with cavity, 3) contact with someone with active tuberculosis, 4) self-report of positive tuberculin skin test in the past, 5) self-report of isoniazid preventive therapy in the past Test-positive: any of 1 to 3 or 4 (in the absence of 5)
El-Solh, 1997	Test-negative: upper zone disease and fever absent, or upper zone disease absent and fever present, if no weight loss and CD4+ >200 Test-positive: upper zone disease and weight loss
El-Solh, 1999	Age, CD4+ counts, diabetes mellitus, HIV, tuberculin skin test positivity; chest pain, weight loss, cough, night sweats, fever, shortness of breath; upper or lower lobe infiltrate, upper or lower lobe cavity, adenopathy, unilateral or bilateral pleural effusion, pleural thickening, miliary pattern
Lagrange-Xelot, 2010	Tuberculosis risk factors or chronic symptoms – scores 4; self-report of positive tuberculin skin test in the past – scores 5; shortness of breath – scores -3; temperature $<38.5^{\circ}C$ – scores 0; temperature $38.5-39^{\circ}C$ – scores 3; temperature $>39^{\circ}C$ – scores 6; crackles on physical examination – scores -3; upper lobe disease on chest x-ray – scores 6
	Test-positive: score of 1 or above
Moran, 2009	1) apical infiltrate, 2) cavitation, 3) immigrant, 4) weight loss, 5) positive tuberculosis history, 6) homeless, 7) incarcerated Test-positive: any of 1 to 7
Mylotte, 1997	AFB-positive smear – scores 3; localised chest X-ray change – scores 2; incarcerated – scores 2; history of weight loss – scores 1 Test-positive: score of 3 or above
Solari, 2008	Age <35 years – scores 0; age 35-60 years – scores -1; age 60 or over – scores -2; weight loss – scores 5; history of pulmonary tuberculosis – scores -3; miliary pattern – scores 10; cavity – scores 5; upper lobe infiltrate – scores 9 Test-positive: score of 3 or above

		Quality a	assessment					Number of		
Test details	Number evaluations		Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Soto, 2008	, 2008 Haemoptysis – scores 2; weight loss – scores 1; age >45 years – scores -1; expectoration – scores -1; apical infiltrate – scores 3; miliar scores 4 Score >4 = high probability								scores 3; miliary ir	nfiltrate –
Soto, 2011		Haemoptysis – scores 4 Score ≥5 = hig		oss – scores 1; ag	je >45 years – so	cores -1; expecto	ration – scores -1; ap	ical infiltrate – s	scores 3; miliary ir	nfiltrate –
Wisnivesky, 2		scores -3; tem scores -3; upp		- scores 0; temper chest x-ray – scor	ature 38.5-39°C		rculin skin test in the erature >39°C – scor			

³ Data presented only for cross-sectional studies; case-control excluded

⁴ Unclear if interpretation of reference standard was blind to the results of the index test in a number of studies (5 of 10), although interpretation of the index test was always conducted blind to the reference standard

⁵ Unclear if a consecutive or random sample of participants used

⁶ Unclear if inappropriate exclusions were avoided

⁷ Index test varies significantly across studies

⁸ Reference standard was permitted by reviewers to be liquid or solid culture; consistency in the exact techniques used across studies is not clear

⁹ Reviewers provide no details of the age of the study population; however, it is not anticipated that the results will be significantly affected by this

¹⁰ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

Chest radiography plus an algorithm of signs, symptoms and risk factors compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are smear-negative

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Chest radiography plus signs, symptoms and risk factors ²	4	systema tic review ³	serious ^{4,5,6}	very serious ^{7,8}	no serious indirectness ⁹	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in	1575	94% (24– 96%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluatio s		Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							which studies were conducted			
Specificity ¹										
Chest radiography plus signs, symptoms and risk factors ²	4	systema tic review ³	serious ^{4,5,6}	very serious ^{7,8}	no serious indirectness ⁹	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	1575	94% (24– 96%)	VERY LOW
¹ Sensitivity ar	nd specificity	y:		I			1			
	Study			Sensitivity			Specificity (95% C	:1)		
	Lagrang	e-Xelot, 2010		96% (80 to	100%)		21% (14 to 30%)			
	Soto, 20	800		93%			92%			
	Soto, 20)11		24% (18 to	31%)		93% (91 to 95%)			
	Wisnive	sky, 2005		95% (74 to	100%)		35% (31 to 40%)			
² Scoring syste	ems used:									
Study		Details of ches	t radiograph scor	ing system						
Lagrange-Xel	ot, 2010	scores -3; temp scores -3; upp	perature <38.5°C	– scores 0; temper n chest x-ray – sco	ature 38.5-39°C		erculin skin test in the perature >39°C – sco			
Soto, 2008	\$	Haemoptysis – scores 4 Score >4 = hig		loss – scores 1; a	ge >45 years – s	cores -1; expecto	pration – scores -1; a	pical infiltrate –	scores 3; miliary i	nfiltrate –
Soto, 2011	\$	Haemoptysis – scores 4 Score ≥5 = hig		loss – scores 1; ag	ge >45 years – s	cores -1; expecto	pration – scores -1; a	pical infiltrate –	scores 3; miliary i	nfiltrate –
Wisnivesky, 2	2005 9	scores -3; tem	perature <38.5°C		rature 38.5-39°C		erculin skin test in the perature >39°C – sco			

Appendix E: GRADE profiles

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
	Tes	st-positive: s	score of 1 or above	9		·		·		

³ Data presented only for cross-sectional studies; case-control excluded

⁴ Unclear if interpretation of reference standard was blind to the results of the index test in a number of studies (2 of 4), although interpretation of the index test was always conducted blind to the reference standard

⁵ Unclear if a consecutive or random sample of participants used

⁶ Unclear if inappropriate exclusions were avoided

⁷ Index test varies significantly across studies

⁸ Reference standard was permitted by reviewers to be liquid or solid culture; consistency in the exact techniques used across studies is not clear

⁹ Reviewers provide no details of the age of the study population; however, it is not anticipated that the results will be significantly affected by this

¹⁰ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

Commercial nucleic acid amplification techniques compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques	137	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, less than half of studies were	85438	89.0% (95% CI 87.2 to 90.6%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							conducted in a high incidence country ¹⁵			
Amplicor	31	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately two-thirds had industry involvement Where information available, a quarter of studies were conducted in a high incidence country ¹⁵	29937	84.8% (95% Cl 81.1 to 87.9%)	VERY LOW
Amplified M. Tuberculosis Direct Test	33	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear in many studies; amongst those for which information is given, less than half had industry involvement Where information available, a quarter of studies	17701	91.9% (95% Cl 88.1 to 94.6%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							were conducted in a high incidence country ¹⁵			
BDProbeTec	3	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear Where information available, study was conducted in a high incidence country ¹⁵	1416	94.4% (95% Cl 90.2 to 96.8%)	VERY LOW
BDProbeTec ET	11	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear in many studies; information was available for 1 study, which was industry sponsored Where information available, half of studies were conducted in a high incidence country ¹⁵	6847	88.0% (95% CI 82.8 to 91.9%)	VERY LOW
Cobas Amplicor	18	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Degree of industry involvement unclear in many studies;	18000	87.2% (95% Cl 80.2 to 92.0%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information was available for 3 studies, of which 1 was industry sponsored Where information available, half of studies were conducted in a high incidence country ¹⁵			
Enhanced Amplified M. Tuberculosis Direct Test	3	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹⁴	Information on industry involvement available for 2 studies, of which 1 was industry sponsored 2 of 3 studies were conducted in a high incidence country ¹⁵	1359	78.9% (95% CI 66.6 to 87.5%)	VERY LOW
MTBDRplus assay	1 ³	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹³	Conducted in a high incidence country ¹⁵	177	76% (95% CI 64 to 85%)	VERY LOW
TB-Biochip	1 ⁴	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Conducted in a high incidence country ¹⁵	105	97.3% (95% CI 93.5 to 100%)	VERY LOW
Xpert MTB/RIF	37	cross- sectiona I	serious ^{2,7}	serious ¹²	serious ¹²	serious ¹⁴	Degree of industry involvement unclear in many studies; information	10073	90.0% (95% CI 86.5 to 92.7%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							provided for 5 studies, none of which were industry sponsored Majority of studies were conducted in a high incidence country ¹⁵			
Specificity ¹							·			
All techniques	137	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, less than half of studies were conducted in a high incidence country ¹⁵	85438	98.1% (95% CI 97.6 to 98.5%)	VERY LOW
Amplicor	31	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which	29937	97.5% (95% Cl 96.2 to 98.3%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information is given, approximately two-thirds had industry involvement Where information available, a quarter of studies were conducted in a high incidence country ¹⁵			
Amplified M. Tuberculosis Direct Test	33	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which information is given, less than half had industry involvement Where information available, a quarter of studies were conducted in a high incidence country ¹⁵	17701	97.2% (95% CI 95.5 to 98.3%)	VERY LOW
BDProbeTec	3	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear Where	1416	See forest plot below ^{1,16}	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information available, study was conducted in a high incidence country ¹⁵			
BDProbeTec ET	11	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear in many studies; information was available for 1 study, which was industry sponsored Where information available, half of studies were conducted in a high incidence country ¹⁵	6847	97.4% (95% Cl 96.0 to 98.3%)	VERY LOW
Cobas Amplicor	18	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Degree of industry involvement unclear in many studies; information was available for 3 studies, of which 1 was industry sponsored Where information available, half of studies were conducted in a	18000	99.1% (95% CI 98.2 to 99.6%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							high incidence country ¹⁵			
Enhanced Amplified M. Tuberculosis Direct Test	3	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Information on industry involvement available for 2 studies, of which 1 was industry sponsored 2 of 3 studies were conducted in a high incidence country ¹⁵	1359	See forest plot below ^{1,16}	VERY LOW
MTBDRplus assay	1 ³	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	no serious imprecision	Conducted in a high incidence country ¹⁵	177	97% (95% CI 92 to 99%)	VERY LOW
TB-Biochip	14	cross- sectiona I	very serious ^{2,7,8,9,10}	serious ¹²	serious ^{11,12}	serious ¹³	Conducted in a high incidence country ¹⁵	105	78.1% (95% CI 63.8 to 92.5%)	VERY LOW
Xpert MTB/RIF	37	cross- sectiona I	serious ^{2,7}	serious ¹²	serious ¹²	no serious imprecision	Degree of industry involvement unclear in many studies; information provided for 5 studies, none of which were industry sponsored Majority of studies were conducted in a high incidence country ¹⁵	10073	98.9% (95% CI 98.3 to 99.3%)	VERY LOW

Appendix E: GRADE profiles

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
¹ Forest plots Amplicor	for sensitivity a	and specific	city (grouped by to	echnique used):						
Amplified M. T	uberculosis D	irect Test								
BDProbeTec										
BDProbeTec I	ET									
Cobas Amplic	or									
Enhanced Am	plified M. Tub	erculosis D	irect Test							
Xpert MTB/RI	F assay									
² Both index te ³ Scott, 2011 ⁴ Kurbatova, 2		ice standar	d performed in ev	very patient, with	an appropriate ı	period of time be	etween the two			
⁷ Many studies ⁸ Unclear if ina	s did not use a appropriate exc	clusions we	re avoided	nple or did not rep			t			
¹⁰ Unclear if a ¹¹ Unclear how ¹² Reference s	threshold for t v many particip tandard varied	est interpre pants, if any d widely from	tation was presp y, are under 18 ye		ost of the includ r, it is not anticip	ed comparisons bated that the res	sults will be significa ases employing a n			riteria (e.g. cli
characteristics	s or smear stat	tus)								

Number of evaluation Inconsistenc Indirectnes Other considerations patients/ specimen S		Quality a	ssessment					Number of		
Test details s Design Risk of bias y s Imprecision s fi	details	 Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations		Summary of findings	Quality

¹³ Wide confidence interval

¹⁴ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

¹⁵ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health Englar current estimates of incidence for in the UK are 13.9 per 100,000

¹⁶ Meta-analysis of relevant data not possible in STATA or R

Commercial nucleic acid amplification techniques compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are smear-positive

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques	66	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, half of studies were conducted in a high incidence country ¹³	5205	98.7% (95% CI 97.8 to 99.2%)	VERY LOW
Amplicor	8	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many	1248	95.5% (95% CI 83.7 to 98.8%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							studies; amongst 5 studies for which information is given, 1 had industry involvement 1 study was conducted in a high incidence country ¹³			
Amplified M. Tuberculosis Direct Test	11	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst 4 studies for which information is given, 3 had industry involvement Where information was available, 3 studies were conducted in a high incidence country ¹³	1204	99.6% (95% CI 98.1 to 99.9%)	VERY LOW
BDProbeTec	1 ³	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear	83	98.8% (95% CI 96.5 to 100%)	VERY LOW
BDProbeTec ET	4	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement	113	97.6% (95% Cl 89.6 to 99.5%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							unclear Where information was available, 1 of 2 studies were conducted in a high incidence country ¹³			
Cobas Amplicor	7	cross- sectiona I	very serious ^{4.5.6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many studies; only study to report had no industry involvement Where information was available, 2 of 6 studies were conducted in a high incidence country ¹³	492	Median (range) = 96.2% (79.2– 97.0%)	VERY LOW
Enhanced Amplified M. Tuberculosis Direct Test	2	cross- sectiona I	very serious ^{4.5.6.7.8}	serious ¹⁰	serious ^{9,10}	serious ¹¹	Degree of industry involvement reported in 1 study, which did not receive industry support	45	93.0% (95% CI 75.9 to 98.2%)	VERY LOW
Xpert MTB/RIF	33	cross- sectiona I	serious ^{4,5}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many studies; information	2020	98.5% (95% CI 97.5 to 99.1%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							provided for 4 studies, none of which were industry sponsored Majority of studies were conducted in a high incidence country ¹³			
Specificity ¹										
All techniques	66	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	serious ¹¹	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, half of studies were conducted in a high incidence country ¹³	5205	30.1% (95% CI 10.3 to 61.8%)	VERY LOW
Amplicor	8	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	serious ^{11,12}	Degree of industry involvement unclear in many studies; amongst 5 studies for which	1248	78.0% (95% CI 47.3 to 93.3%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information is given, 1 had industry involvement 1 study was conducted in a high incidence country ¹³			
Amplified M. Tuberculosis Direct Test	11	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	serious ¹¹	Degree of industry involvement unclear in many studies; amongst 4 studies for which information is given, 3 had industry involvement Where information was available, 3 studies were conducted in a high incidence country ¹³	1204	90.4% (95% Cl 68.1 to 97.7%)	VERY LOW
BDProbeTec	1 ³	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	serious ¹¹	Degree of industry involvement unclear	83	50.0% (95% CI 0.0 to 100%)	VERY LOW
BDProbeTec ET	4	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	serious ^{11,12}	Degree of industry involvement unclear Where information was	113	63.8% (95% Cl 6.6 to 97.8%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							available, 1 of 2 studies were conducted in a high incidence country ¹³			
Cobas Amplicor	7	cross- sectiona I	very serious ^{4.5.6.7.8}	serious ¹⁰	serious ^{9,10}	serious ¹²	Degree of industry involvement unclear in many studies; only study to report had no industry involvement Where information was available, 2 of 6 studies were conducted in a high incidence country ¹³	492	See forest plot below ^{1,14}	VERY LOW
Enhanced Amplified M. Tuberculosis Direct Test	2	cross- sectiona I	very serious ^{4,5,6,7,8}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement reported in 1 study, which did not receive industry support	45	See forest plot below ^{1,14}	VERY LOW
Xpert MTB/RIF	33	cross- sectiona I	serious ^{4.5}	serious ¹⁰	serious ^{9,10}	no serious imprecision	Degree of industry involvement unclear in many studies; information provided for 4 studies, none of which were industry	2020	See forest plot below ^{1,14}	VERY LOW

		Quality a	assessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							sponsored Majority of studies were conducted in a high incidence country ¹³			
¹ Forest plots Amplicor	for sensitivity a	and specifi	city (grouped by t	echnique used):						
Amplified M. T	Tuberculosis D	irect Test								
BDProbeTec I	ET									
Cobas Amplic	or									
Enhanced Am	plified M. Tub	erculosis D	irect Test							
Xpert MTB/RI	F assay									
 ⁵ Many studies ⁶ Unclear if ina ⁷ Many studies ⁸ Unclear if a t ⁹ Unclear how ¹⁰ Reference s ¹¹ Wide confid ¹² Significant w 	est and referer s did not use a appropriate exe s did not blind threshold for te many particip standard varied teristics or sm ence interval variation in the	a consecuti clusions we test interpre eats, if any d widely fro lear status)	ve or random sar ere avoided retation or did not tation was prespe r, are under 18 ye m study to study, nates, as well as	, using different cu wide confidence in	ort the samplin e of blinding use st of the include it is not anticipa ilture technique	g approach used ed ad comparisons ated that the res s and in some c nited overlap		umber of additi	onal reference cr	

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Health Englan		mates of in	cidence for in the	UK are 13.9 per	100,000					,

¹⁴ Meta-analysis of relevant data not possible in STATA or R

Commercial nucleic acid amplification techniques compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are smear-negative

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques	65	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ¹¹	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, half of studies were conducted in a high incidence country ¹²	24499	72.6% (95% Cl 68.1 to 76.8%)	VERY LOW
Amplicor	8	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ^{10,11}	Degree of industry involvement unclear in many studies; amongst 4 studies for which	2739	78.0% (95% CI 60.9 to 89.0%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information is given, 1 had industry involvement 1 study was conducted in a high incidence country ¹²			
Amplified M. Tuberculosis Direct Test	11	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ^{10,11}	Degree of industry involvement unclear in many studies; amongst 6 studies for which information is given, 2 had industry involvement Where information was available, 3 studies were conducted in a high incidence country ¹²	5922	84.6% (95% Cl 71.6 to 92.3%)	VERY LOW
BDProbeTec ET	4	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ^{10,11}	Degree of industry involvement unclear Where information was available, 1 of 2 studies were conducted in a high incidence country ¹²	2391	70.4% (95% Cl 54.4 to 82.5%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Cobas Amplicor	7	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ¹¹	Degree of industry involvement unclear in many studies; only study to report had no industry involvement Where information was available, 2 of 6 studies were conducted in a high incidence country ¹²	5040	56.9% (95% CI 48.3 to 65.1%)	VERY LOW
Enhanced Amplified M. Tuberculosis Direct Test	2	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	serious ^{10,11}	Degree of industry involvement reported in 1 study, which did not receive industry support	1233	67.7% (95% CI 48.4 to 82.4%)	VERY LOW
Xpert MTB/RIF	3	cross- sectiona I	serious ^{3,4}	serious ⁹	serious ^{8,9}	serious ¹¹	Degree of industry involvement unclear in many studies; information provided for 4 studies, none of which were industry sponsored Majority of studies were conducted in a high incidence	619	71.1% (95% CI 65.5 to 76.0%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							country ¹²			_
Specificity ¹										
All techniques	65	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst those for which information is given, approximately half had industry involvement Where information available, half of studies were conducted in a high incidence country ¹²	24499	98.6% (95% CI 97.9 to 99.0%)	VERY LOW
Amplicor	8	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement unclear in many studies; amongst 4 studies for which information is given, 1 had industry involvement 1 study was conducted in a high incidence country ¹²	2739	96.5% (95% Cl 92.3 to 98.5%)	VERY LOW
Amplified M.	11	cross-	very	serious ⁹	serious ^{8,9}	no serious	Degree of	5922	98.0% (95%	VERY

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Tuberculosis Direct Test		sectiona I	serious ^{3,4,5,6,7}			imprecision	industry involvement unclear in many studies; amongst 6 studies for which information is given, 2 had industry involvement Where information was available, 3 studies were conducted in a high incidence country ¹²		CI 94.7 to 99.2%)	LOW
BDProbeTec ET	4	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement unclear Where information was available, 1 of 2 studies were conducted in a high incidence country ¹²	2391	96.4% (95% CI 94.2 to 97.8%)	VERY LOW
Cobas Amplicor	7	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement unclear in many studies; only study to report had no industry involvement Where	5040	99.3% (95% CI 98.1 to 99.8%)	VERY LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							information was available, 2 of 6 studies were conducted in a high incidence country ¹²			
Enhanced Amplified M. Tuberculosis Direct Test	2	cross- sectiona I	very serious ^{3,4,5,6,7}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement reported in 1 study, which did not receive industry support	1233	See forest plot below ^{1,14}	VERY LOW
Xpert MTB/RIF	33	cross- sectiona I	serious ^{3,4}	serious ⁹	serious ^{8,9}	no serious imprecision	Degree of industry involvement unclear in many studies; information provided for 4 studies, none of which were industry sponsored Majority of studies were conducted in a high incidence country ¹²	7180	99.0% (95% Cl 98.3 to 99.4%)	VERY LOW

¹ Forest plots for sensitivity and specificity (grouped by technique used): Amplicor

Amplified M. Tuberculosis Direct Test

BDProbeTec ET

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Cobas Amplic	or									
Enhanced Am	plified M. Tube	erculosis D	irect Test							
Xpert MTB/RI	F assay									
 ⁵ Unclear if ina ⁶ Many studies ⁷ Unclear if a t 	appropriate exc s did not blind threshold for te many particip	clusions we test interpre est interpret ants, if any	re avoided etation or did not ation was prespe , are under 18 ye	report the degree ecified in all or most ars old; however, using different cul	of blinding use st of the include it is not anticipa	d d comparisons ated that the res	ults will be significar			

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Phage- based tests	5 ²	cross- sectiona I	serious ^{4,5,6,7,8}	serious ⁹	serious ^{10,11}	serious ¹²	Industry involvement unclear Unclear TB incidence in	3033	69.5% (95% Cl 47.5 to 85.1%)	VERY LOW

		Quality a	issessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							countries in which studies were conducted			
Specificity ¹										
Phage- based tests	5 ²	cross- sectiona I	serious ^{4,5,6,7,8}	serious ⁹	serious ^{10,11}	serious ¹²	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	3033	See forest plot below ^{1,13}	VERY LOW

² Dinnes, 2007

⁴ Both index test and reference standard performed in every patient, with an appropriate period of time between the two

⁵ Unclear if a consecutive or random sample was used

⁶ Unclear if inappropriate exclusions were avoided

⁷ Unclear if test interpretation was blinded

⁸ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁹ Reference standard varied widely from study to study

¹⁰ Unclear how many participants, if any, are under 18 years old; however, it is not anticipated that the results will be significantly affected by this

¹¹ Reference standard sometimes included more than just culture, for example X-ray, clinical features and treatment response

¹² Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

 $^{\rm 13}$ Meta-analysis of relevant data not possible in STATA or R

Phage-based tests compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are smearpositive

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
FASTPlaque TB	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	no serious imprecision	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	277	86.3% (95% CI 81.4 to 90.1%)	VERY LOW
Specificity ¹										
FASTPlaque TB	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹²	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	277	See forest plot below ^{1,11}	VERY LOW
¹ Forest plots:							were conducted			

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Unclear if a consecutive or random sample was used

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁷ Reference standard varied widely from study to study

⁸ Unclear how many participants, if any, are under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁹ Reference standard sometimes included more than just culture, for example X-ray, clinical features and treatment response

¹⁰ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

¹¹ Meta-analysis of relevant data not possible in STATA or R

Phage-based tests compared to culture-based reference standard in adults with suspected pulmonary tuberculosis who are smearnegative

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
FASTPlaque TB	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	1016	58.6% (95% Cl 39.6 to 75.3%)	VERY LOW
Specificity ¹										
FASTPlaque TB	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	no serious imprecision	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	1016	See forest plot below ^{1,11}	VERY LOW

¹ Forest plots:

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Unclear if a consecutive or random sample was used

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁷ Reference standard varied widely from study to study

⁸ Unclear how many participants, if any, are under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁹ Reference standard sometimes included more than just culture, for example X-ray, clinical features and treatment response

¹⁰ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

 $^{\rm 11}$ Meta-analysis of relevant data not possible in STATA or R

		_	ssessment					Number of	,	
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Antitubercul osis antibody detection tests	9	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹⁰	Degree of industry involvement unclear in many studies; 1 of the 2 studies that provided information had industry involvement Both studies for which information available were conducted in a high incidence country ¹¹	2703	68.2% (95% CI 40.9 to 86.9%)	VERY LOW
Specificity ¹										
Antitubercul osis antibody detection tests	9	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹⁰	Degree of industry involvement unclear in many studies; 1 of the 2 studies that provided information had industry involvement Both studies for which information available were conducted in a high incidence	2703	85.3% (95% CI 76.8 to 91.0%)	VERY LOW

Antituberculosis antibody detection compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							country ¹¹			
¹ Forest plots:										
⁴ Unclear if ina ⁵ Unclear if tes	appropriate exc st interpretation	clusions we n was blind	ed	cified in all or mo	st of the include	ed comparisons				
		•	n study to study							
	••••••		· · · · · · · · · · · · · · · · · · ·		•		ults will be significar		/ this	
							treatment response			
		•		wide confidence i		•				
				of 40 per 100,000 UK are 13.9 per		considered to ha	ive a high incidence	of tuberculosis	s, as defined by F	Public

Use of antituberculosis antibodies (LAM) to detect tuberculosis in serum
--

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Antitubercul osis antibody detection tests	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹⁰	Industry involvement unclear Unclear TB incidence in countries in which studies were conducted	370	54.1% (95% CI 30.4 to 76.2%)	VERY LOW
Specificity ¹										
Antitubercul osis antibody	2	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	no serious imprecision	Industry involvement unclear	370	See forest plot below ^{1,11}	VERY LOW

	Quality a	ssessment					Number of	Summary of findings	
Test details	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s		Quality
detection tests						Unclear TB incidence in countries in which studies were conducted			

¹ Forest plots:

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Unclear if a consecutive or random sample was used

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Unclear if a threshold for test interpretation was prespecified in all or most of the included comparisons

⁷ Reference standard varied widely from study to study

⁸ Unclear how many participants, if any, are under 18 years old; however, it is not anticipated that the results will be significantly affected by this

⁹ Reference standard sometimes included more than just culture, for example X-ray, clinical features and treatment response

¹⁰ Significant variation in the point estimates, as well as wide confidence intervals with limited overlap

¹¹ Meta-analysis of relevant data not possible in STATA or R

Use of antituberculosis antibodies (LAM) to detect tuberculosis in urine

		Quality a	ssessment							
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerati ons	Number of patients/ specimens	Summary of findings	Quality
Sensitivity ¹										
Antitubercul osis antibody detection tests	3	cross- sectiona I	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	serious ¹⁰	No industry involvement Conducted in a high incidence country ¹¹	1429	32.9% (95% CI 22.6 to 45.2%)	VERY LOW
Specificity ¹										
Antitubercul osis	3	cross- sectiona	serious ^{2,3,4,5,6}	serious ⁷	serious ^{8,9}	no serious	No industry	1429	See forest plot	VERY

		Quality a	issessment							
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerati ons	Number of patients/ specimens	Summary of findings	Quality
antibody detection tests		1				imprecision	involvement Conducted in a high incidence country ¹¹		below ^{1,12}	LOW
 ³ Unclear if a d ⁴ Unclear if ina ⁵ Unclear if test 	consecutive or appropriate exc st interpretation	random sa clusions we n was blind	ample was used ere avoided led	very patient, with			etween the two			
		•	n study to study			a compansons				
				ears old; however,			-		d by this	
				st culture, for exar wide confidence i			r treatment resp	onse		
¹¹ Countries/te	erritories with a	n estimate	d incidence rate		or greater are o	-	ave a high incide	ence of tubercu	losis, as defined by	/ Public

¹² Meta-analysis of relevant data not possible in STATA or R

Interferon-gamma release assays compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

	Number	Quality as	sessment					ľ		
	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecisio n	Other considerations	Number of patients/ specimens	Summary of findings	Quality	
Sensitivity ¹	l									
IGRAs	3 ^{2,3}	cross- sectional	serious ^{4,5,6,7}	serious ⁸	serious ^{9,10}	no serious imprecision	Industry involvement in Kang (2007) Conducted in a high incidence country ¹²	327	89.3% (95% CI 83.4 to 93.3%)	VERY LOW
Specificity ¹	l									

Test details	Number	Quality as	ssessment							
	of evaluatio ns	Design	Risk of bias	Inconsistenc y	Indirectness	Imprecisio n	Other considerations	Number of patients/ specimens	Summary of findings	Quality
IGRAs	3 ^{2,3}	cross- sectional	serious ^{4,5,6,7}	serious ⁸	serious ^{9,10}	no serious imprecision	Industry involvement in Kang (2007) Conducted in a high incidence country ¹²	327	See forest plot below ^{1,13}	VERY LOW

Forest plots:

² Kabeer, 2009

³ Kang, 2007

⁴ Both index test and reference standard performed in every patient, with an appropriate period of time between the two

⁵ Consecutive or random sample not used in Kabeer (2009)

⁶ Inappropriate exclusions were not avoided – Kang (2007) excluded patients with high clinical likelihood of active TB and a negative mycobacterial culture finding but good clinical and radiographic responses to anttuberculosis treatment

⁷ Unclear if test interpretation was blinded

⁸ Reference standard varied

⁹ Unclear how many participants, if any, were under 18 years old in Kang (2007); however, it is not anticipated that the results will be significantly affected by this

¹⁰ Reference standard included histology as an alternative to culture in Kang (2007)

¹¹ Wide confidence interval

¹² Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

¹³ Meta-analysis of relevant data not possible in STATA or R

Tuberculin skin tests compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

		Quality a	ssessment				Number o			
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Mantoux	2	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ^{7,8}	serious ¹⁰	Degree of industry involvement unclear 1 study;	108	46.1% (95% CI 12.1 to 84.2%)	VERY LOW

		Quality a	ssessment				Number of	of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							amongst the 2 for which information is given, 1 had industry involvement Where information available, both studies were conducted in a high incidence country ¹¹			
Specificity ¹										
Mantoux	2	cross- sectiona I	serious ^{2.3,4,5}	serious ⁶	serious ^{7,8}	serious ¹⁰	Degree of industry involvement unclear 1 study; amongst the 2 for which information is given, 1 had industry involvement Where information available, both studies were conducted in a high incidence country ¹¹	108	See forest plot below ^{1,12}	VERY LOW

¹ Forest plots:

² Both index test and reference standard performed in every patient, with an appropriate period of time between the two

³ Consecutive or random sample not used in Kabeer (2009)

⁴ Inappropriate exclusions were not avoided – Kang (2007) excluded patients with high clinical likelihood of active TB and a negative mycobacterial culture finding but

	Number of	Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
good clinical a	and radiograph	ic response	es to anttuberculo	sis treatment		·				
⁵ Unclear if tes	st interpretation	n was blind	ed							
⁶ Reference st	andard varied									
⁷ Unclear how	many particip	ants, if any	, were under 18 y	ears old in Kang	(2007); howeve	r, it is not anticip	bated that the results	s will be signific	cantly affected by	this
⁸ Reference st	tandard include	ed histolog	, as an alternativ	e to culture in Kai	ng (2007)			-		
⁹ Wide confide	ence interval									
10 Significant V	ariation in the	point estim	ates, as well as v	wide confidence i	ntervals with lim	ited overlap				
¹¹ Countries/te	erritories with a	n estimate	d incidence rate of		or greater are o	•	ve a high incidence	of tuberculosis	s, as defined by P	Public

¹² Meta-analysis of relevant data not possible in STATA or R

Gas chromatography mass spectrometry for tuberculostearic acid compared to culture-based reference standard in adults with suspected pulmonary tuberculosis

	Number	Quality a	ssessment					Number of		
Test details	of evaluatio ns	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Gas chromatograp hy mass spectrometry for tuberculostear ic acid	1 ¹	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency ⁷	no serious indirectness	serious ⁸	Degree of industry involvement unclear	145	55.3% (95% CI 39.5 to 71.1%)	LOW
Specificity										
Gas chromatograp hy mass spectrometry for tuberculostear ic acid	1 ¹	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency ⁷	no serious indirectness	serious ⁸	Degree of industry involvement unclear	145	86.9% (80.5% to 93.3%)	LOW

	Number	Quality a	ssessment				Number			
Test details	of evaluatio ns	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
¹ Savić, 1992										
² Both index tes	t and referen	ce standar	d performed in ev	ery patient, with a	an appropriate p	period of time be	tween the two			
³ Unclear if a co	onsecutive or	random sa	mple of patients	were enrolled						
⁴ Unclear if the	study avoide	d inappropr	riate exclusions							
⁵ Unclear if test	interpretation	n was blind	ed							
⁶ Unclear if a te	st threshold v	was prespe	cified							
 ⁷ Unclear how n ⁸ Wide confident 		ants, if any	, were under 18 y	ears old; howeve	er, it is not antici	pated that the re	esults will be signification	antly affected b	by this	

Time-to-detection

Test	Time	Reference
Time to diagnosis (median (range), unless otherwis	se indicated)	
Xpert MTB/RIF	0 days	Balcells, 2012
	0 (0–1) days	Boehme, 2011
	2 hours	Helb, 2010
	4 (3–6) days	Lawn, 2011
	<2 hours	Marlowe, 2011
	113 minutes	Miller, 2011
	2 hours	Moure, 2011
	within two hours	Rachow, 2011
	results available the same day	Van Rie, 2013
	3 to 24 hours	Zeka, 2011
Microscopy	1 (IQR 0–1) days	Boehme, 2011
	3 (2–5) days	Lawn, 2011
	minimum of 1 day; routinely available within 3 days	Kambashi, 2001
Liquid culture	10 (5–22) days	Balcells, 2012
	16 (13–21) days	Boehme, 2011
	smear-positive: 12 (10–14) days smear-negative: 20 (17–27) days	Lawn, 2011
	mean (range) = 19 (3–42) days	
Solid culture	30 (23–43) days	Boehme, 2011
Time to treatment initiation (median (range) or [inte	rquartile range])	
Xpert MTB/RIF	before Xpert MTB/RIF introduced: 56 (39–81) days after Xpert MTB/RIF introduced: 5 (2–8) days	Boehme, 2011
	Xpert MTB/RIF positive patients: 0 (0–0) days patients diagnosed by other methods: 13 (10–20) days	Van Rie, 2013

A.3 RQ D

A.3.1 Diagnosis of active pulmonary tuberculosis in children and young people who are HIV-negative

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis who are HIV-negative

	Number of evaluation Test details Sensitivity ¹ Kpert	Quality a	ssessment					Number of		
Test details	evaluation	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Xpert MTB/RIF	4	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ^{6,7}	No industry involvement All studies conducted in a high incidence country ⁸	1428	65.4% (95% CI 53.1 to 76.0%)	LOW
Specificity ¹										
Xpert MTB/RIF	4	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement All studies conducted in a high incidence country ⁸	1428	See forest plot below ^{1,9}	MODER ATE

¹ Forest plots for sensitivity and specificity:

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Random sample of patients enrolled in Zar (2012); unclear if consecutive or random sample of patients enrolled in Bates (2013)

⁴ Blinding of test interpretation employed in Zar (2012); unclear if blinding of test interpretation employed in Bates (2013)

⁵ Threshold for interpretation unclear

⁶ Significant variation in point estimates with little overlap in confidence intervals

⁷ Wide confidence interval

⁸ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

⁹ Meta-analysis of relevant data not possible in STATA or R

Interferon-gamma release assays compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis who are HIV-negative

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
QuantiFERO N-TB Gold In-Tube	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ⁹	362	79.7% (95% CI 72.7 to 86.7%)	VERY LOW
Specificity										
QuantiFERO N-TB Gold In-Tube	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	serious ⁸	No industry involvement Conducted in a high incidence country ⁹	362	16.7% (95% CI 11.9 to 21.4%)	VERY LOW

¹ Lodha, 2013

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Not all diagnoses were made with the same reference standard

⁷ Reference diagnoses could be made by microscopy alone

⁸Wide confidence interval

⁹ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Tuberculin skin tests compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis who are HIV-negative

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Soncitivity										

Sensitivity

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ⁹	362	89.8% (95% Cl 84.6 to 95.1%)	VERY LOW
Specificity										
Mantoux	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ⁹	362	5.1% (95% CI 2.3 to 8.0%)	VERY LOW

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Not all diagnoses were made with the same reference standard

⁷ Reference diagnoses could be made by microscopy alone

⁸Wide confidence interval

⁹ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

A.3.2 Diagnosis of active pulmonary tuberculosis in children and young people who are HIV-positive

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis who are HIV-positive

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
Xpert	4	cross-	serious ^{2,3,4,5}	no serious	no serious	serious ⁶	No industry	513	82.0% (55.2	LOW

		Quality a	ssessment				Number of			
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
MTB/RIF		sectiona I		inconsistency	indirectness		involvement Conducted in a high incidence country ⁷		to 94.4%)	
Specificity ¹										
Xpert MTB/RIF	4	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁷	513	99.5% (96.2 to 99.9%)	MODER ATE

Forest plots for sensitivity and specificity:

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Random sample of patients enrolled in Zar (2012); unclear if consecutive or random sample of patients enrolled in Bates (2013)

⁴ Blinding of test interpretation employed in Zar (2012); unclear if blinding of test interpretation employed in Bates (2013)

⁵ Threshold for interpretation unclear

⁶ Significant variation in point estimates with little overlap/wide confidence intervals

⁷ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

A.3.3 Diagnosis of active pulmonary tuberculosis in children and young people

Smear microscopy compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis

		Quality as	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques	8	cross- sectional	serious ^{2,3,4,5,6}	serious ⁷	no serious indirectness	serious ⁹	Limited industry involvement,	2491	56.3% (95% CI 32.7 to	VERY LOW

		Quality as	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							although 2 studies do not provide any information on this All except 1 study conducted in a high incidence country ⁹		77.4%)	
Fluorescenc e microscopy	6	cross- sectional	serious ^{2,3,5,6}	no serious inconsistency	no serious indirectness	serious ⁹	No industry involvement All studies conducted in high incidence countries ⁹	2384	43.1% (95% Cl 22.5 to 66.4%)	LOW
Ziehl- Neelson microscopy	1	cross- sectional	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁸	No information available on industry involvement	60	81.5% (95% CI 66.8 to 96.1%)	LOW
Specificity ¹										
All techniques	8	cross- sectional	serious ^{2,3,4,5,6}	serious ⁷	no serious indirectness	no serious imprecision	Limited industry involvement, although 2 studies do not provide any information on this All except 1 study conducted in a high incidence country ⁹	2491	99.7% (95% CI 98.8 to 99.9%)	LOW
Fluorescenc e	6	cross- sectional	serious ^{2,3,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement	2384	See forest plot below ^{1,10}	MODER ATE

		Quality as	ssessment			Number of				
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
microscopy							All studies conducted in high incidence countries ⁹			
Ziehl- Neelson microscopy	1	cross- sectional	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	No information available on industry involvement	60	97.6% (95% CI 90.9 to 100%)	MODER ATE

¹ Forest plots for sensitivity and specificity (grouped by technique used):

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Random sample of patients enrolled in Zar (2012 and 2013); unclear if consecutive or random sample of patients enrolled in Bates (2013), El-Sayed Zaki (2008) and Shata (1996)

⁴ Unclear if El-Sayed Zaki (2008) avoided inappropriate exclusions

⁵ Blinding of test interpretation employed in Zar (2012 and 2013); unclear if blinding of test interpretation employed in Bates (2013), El-Sayed Zaki (2008) and Shata (1996)

⁶ Threshold for interpretation unclear

⁷ Shata (1996) uses a different culture technique as a reference standard than the other included studies (solid *vs* liquid culture)

⁸ Significant variation in point estimates with little overlap in or wide confidence intervals

⁹ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

¹⁰ Meta-analysis of relevant data not possible in STATA or R

Chest radiography compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Chest X-ray	1 ¹	cross- sectiona I	serious ^{2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	No information available on industry	110	72%	LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							involvement			
							Conducted in a high incidence country ⁶			
Specificity										
Chest X-ray	11	cross- sectiona I	serious ^{2,3,4}	no serious inconsistency	no serious indirectness	serious ⁵	No information available on industry involvement Conducted in a high incidence country ⁶	110	54%	LOW
 ³ Unclear if stu ⁴ Index test int ⁵ Insufficient d 	udy avoided in terpretation wa lata to assess	appropriate is blinded, f imprecision	exclusions though it was und	clear if interpretati	on of the refere	nce standard wa	e between the two as also blinded ve a high incidence o	of tuberculosis	as defined by P	ublic

Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity ¹										
All techniques	9	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁸	Limited industry involvement, although 1 study did not provide any information on this	2828	71.3% (95% CI 54.3 to 83.8%)	LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							All studies except 1 conducted in a high incidence country ⁹			
Amplified M. Tuberculosis Direct Test	1	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	No information available on industry involvement	60	97.5% (95% CI 92.7 to 100%)	MODER ATE
Xpert MTB/RIF	8	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	serious ⁸	No industry involvement All studies conducted in a high incidence country ⁹	2768	65.0% (95% CI 51.9 to 76.1%)	LOW
Specificity ¹										
All techniques	9	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	Limited industry involvement, although 1 study did not provide any information on this All studies except 1 conducted in a high incidence country ⁹	2828	98.6% (95% Cl 98.0 to 99.1%)	MODER ATE
Amplified M. Tuberculosis Direct Test	1	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	No information available on industry involvement	60	97.6% (95% CI 90.9 to 100%)	MODER ATE
Xpert MTB/RIF	8	cross- sectiona I	serious ^{2,3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement All studies conducted in a high incidence country ⁹	2768	98.7% (95% CI 98.1 to 99.1%)	MODER ATE

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
¹ Forest plots	for sensitivity a	and specific	tity (grouped by t	echnique used):						
 ³ Random/con enrolled in Bat ⁴ Unclear if El- ⁵ Blinding of te and Sekadde 	secutive samp tes (2013) and Sayed Zaki (2 est interpretation (2013)	ble of patier El-Sayed 2 008) avoid on employe	nts enrolled in Nic Zaki (2008) ed inappropriate	col (2011), Sekad exclusions	de (2013) and Z	2012 and 20	e between the two 13); unclear if cons employed in Bates (
6 Threshold fo	r interpretation	unclear								
⁷ Wide confide										
•	•		•	o in or wide confid						
				f 40 per 100,000 UK are 13.9 per		onsidered to hav	e a high incidence	of tuberculosis	, as defined by P	ublic

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	No industry involvement Conducted in a high incidence country ⁷	930	63.2% (95% CI 41.5 to 84.9%)	LOW
Specificity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁷	930	99.8% (95% CI 99.3 to 100%)	MODEF ATE

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children under 2 years old

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

	Number of evaluation	Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc v	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
³ Unclear if co	nsecutive or ra	•	ple of patients wa	as enrolled						
⁴ Unclear if tes			• •							
⁵ Threshold fo	•									
⁶ Wide confide	nce interval									
7 Countrios/tou	ritories with ar	estimated	incidence rate of	40 per 100 000	or greater are c	onsidered to hav	ve a high incidence d	of tuborculosis	as defined by P	ublic

⁷ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children between 2 and 4 years old

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	No industry involvement Conducted in a high incidence country ⁷	201	66.7% (95% CI 44.9 to 88.4%)	LOW
Specificity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁷	201	99.5% (95% CI 98.4 to 100%)	MODER ATE

¹ Bates, 2013

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if test interpretation was blinded

⁵ Threshold for interpretation unclear

⁶ Wide confidence interval

⁷ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children between 5 and 9 years old

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2.3.4.5}	no serious inconsistency	no serious indirectness	serious ⁶	No industry involvement Conducted in a high incidence country ⁷	124	50.0% (95% CI 10.0 to 90.0%)	LOW
Specificity										
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2.3.4.5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁷	124	97.5% (95% Cl 94.6 to 100%)	MODER ATE

¹ Bates, 2013

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if test interpretation was blinded

⁵ Threshold for interpretation unclear

⁶ Wide confidence interval

⁷ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Commercial nucleic acid amplification techniques compared to culture-based reference standard in children and young people between 10 and 15 years old

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
All techniques	2 ^{1,8}	cross- sectiona I	serious ^{2,3,4,5,7}	no serious inconsistency	no serious indirectness	serious ⁶	Limited industry involvement, although 1 study	198	96.5% (95% CI 87.0 to 99.1%)	LOW

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
							did not provide any information on this All studies except 1 conducted in a high incidence country ⁹			
Amplified M. Tuberculosis Direct Test	1 ⁸	cross- sectiona I	serious ^{2,3,4,5,7}	no serious inconsistency	no serious indirectness	no serious imprecision	No information available on industry involvement	60	97.5% (95% CI 92.7 to 100%)	MODER ATE
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2.3.4.5}	no serious inconsistency	no serious indirectness	serious ⁶	No industry involvement Conducted in a high incidence country ⁹	138	96.8% (95% CI 88.0 to 100%)	LOW
Specificity										
Amplified M. Tuberculosis Direct Test	1 ⁸	cross- sectiona I	serious ^{2,3,4,5,7}	no serious inconsistency	no serious indirectness	no serious imprecision	No information available on industry involvement	60	100% (95% CI 100% to 100%)	MODER ATE
Xpert MTB/RIF	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	no serious imprecision	No industry involvement Conducted in a high incidence country ⁹	138	98.4% (95% CI 96.1 to 100%)	MODER ATE

¹ Bates, 2013

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if test interpretation was blinded

⁵ Threshold for interpretation unclear

⁶ Wide confidence interval

⁷ Unclear if El-Sayed Zaki (2008) avoided inappropriate exclusions

⁸ El-Sayed Zaki (2008)

		Quality a	ssessment					Number of		
Test details	Number of evaluation s		Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
⁹ Countries/ter	ritories with ar	n estimated	incidence rate of	40 per 100,000 d	or greater are co	onsidered to hav	e a high incidence c	of tuberculosis,	as defined by Pu	ublic

Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Interferon-gamma release assays compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
QuantiFERO N-TB Gold In-Tube	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	no serious imprecision	No industry involvement Conducted in a high incidence country ⁹	5886	79.7 (72.7 to 86.7)	VERY LOW
Specificity										
QuantiFERO N-TB Gold In-Tube	1 ¹	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	serious ⁸	No industry involvement Conducted in a high incidence country ⁹	5886	16.7 (11.9 to 21.4)	VERY LOW

¹ Lodha, 2013

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Not all diagnoses were made with the same reference standard

⁷ Reference diagnoses could be made by microscopy alone

⁸ Significant variation in point estimates with little overlap in confidence intervals

⁹ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

Tuberculin skin tests compared to culture-based reference standard in children and young people with suspected pulmonary tuberculosis

		Quality a	ssessment					Number of		
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
Sensitivity										
Mantoux	2 ^{1,9}	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	no serious imprecision	Limited industry involvement, although 1 study did not provide any information on this Conducted in a high incidence country ⁹	5543	89.8 (84.6 to 95.1) ¹ 47 ⁹	VERY LOW
Specificity							,			
Mantoux	2 ^{1,9}	cross- sectiona I	serious ^{2,3,4,5}	serious ⁶	serious ⁷	serious ⁸	Limited industry involvement, although 1 study did not provide any information on this Conducted in a high incidence country ⁹	5543	5.1 (2.3 to 8.0) ¹ 60 ⁹	VERY LOW

² Both index test and reference standard performed in the every patient, with an appropriate period of time between the two

³ Unclear if consecutive or random sample of patients was enrolled in Lodha (2013) and Mahomed (2013)

⁴ Unclear if inappropriate exclusions were avoided

⁵ Unclear if test interpretation was blinded

⁶ Not all diagnoses were made with the same reference standard

⁷ Reference diagnoses could be made by microscopy alone

⁸ Significant variation in point estimates with little overlap in confidence intervals

⁹ Iriso, 2005

¹⁰ Countries/territories with an estimated incidence rate of 40 per 100,000 or greater are considered to have a high incidence of tuberculosis, as defined by Public Health England; current estimates of incidence for in the UK are 13.9 per 100,000

WHO scoring system compared to culture-based reference standard in children and young people with suspected pulmonary	
tuberculosis	

		Quality a	ssessment					Number of			
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality	
Sensitivity											
Scoring system	1 ²	cross- sectiona I	serious ^{3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	No information available on industry involvement Conducted in a high incidence country ⁷	110	86%	LOW	
Specificity											
Scoring system	1 ²	cross- sectiona I	serious ^{3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	No information available on industry involvement Conducted in a high incidence country ⁷	110	22%	LOW	
¹ WHO scoring • duration of ill • weight for ag • nutrition • family history • tuberculin sk • unexplained • presence of ll ² Iriso, 2005	ness e v of tuberculos in test fever and nigh	it sweats	e swelling, abdor	ninal mass or asc	ites, central ner	vous system sig	ns, or kyphosis of th	ne spine			
 ³ Both index te ⁴ Unclear if stu ⁵ Unclear if tes ⁶ Insufficient d 	idy avoided ina at interpretation ata to assess i	appropriate n was blind imprecision	exclusions ed				e between the two				
				f 40 per 100,000 UK are 13.9 per		onsidered to hav	ve a high incidence	of tuberculosis	as defined by P	ublic	

Time-to-detection

Test	Time	Reference
Time from obtaining specimen to reporting to c	linician (median (interquartile range))	
Xpert MTB/RIF	0 (0–3) days	Zar, 2012
	1 (1–1) days	Zar, 2013
Culture	15 (12–20) days	Zar, 2012
	16 (13–19) days	Zar, 2013

A.4 RQ G

A.4.1 Diagnosis of active bone and joint tuberculosis

Use of interferon gamma release assays in the diagnosis of people with suspected bone and joint tuberculosis

Number of evaluations			Quality assessme	ent		Number of		
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
1 ¹	cross- sectional	serious ²	serious ³	no serious indrectness ³	serious ⁴	36	86.7% (95% CI 69.5 to 100%)	VERY LOW
Specificity								
1 ¹	cross- sectional	serious ²	serious ³	no serious indrectness ³	serious ⁴	36	61.9% (95% Cl 41.1 to 82.7%)	VERY LOW
	interpretation und ed different refere							

⁴ Wide confidence interval

A.4.2 Diagnosis of active central nervous system tuberculosis

ise of micro			Quality assessm	nent	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
6 ^{2,3,4,5,6,14}	cross- sectional	serious ^{8,9,10,11}	no serious inconsistency	no serious indirectness	serious ^{12,13}	706	Pooled sensitivity ¹ (95% CI) = 68.8% (32.7 to 90.9%)	LOW
Specificity								
6 ^{2,3,4,5,6,14}	cross- sectional	serious ^{8,9,10,11}	no serious inconsistency	no serious indirectness	no serious imprecision	706	See forest plot below ^{1,7}	MODERATE
¹ Forest plots for	or sensitivity a	nd specificity:						
 ⁸ Unclear if a ra ⁹ Unclear if test ¹⁰ Interpretation ¹¹ Unclear if a the 	00 Jamieson, 20 11 of relevant dandom or cons interpretation of reference hreshold for te ariation in poir	ata not possible ir secutive sample w was blinded: Bor standard not bling est interpretation w	STATA or R as used: Bonington ington, 2000; Ched led: Teo, 2011; Fen vas used and prede ttle overlap in confic	ore and Jamieson g, 2014 fined: Bonington, 2	, 2003; Malbruny,	2011		

Use of microscopy in the diagnosis of people with suspected central nervous system tuberculosis

cross-

¹⁴ Feng, 2014

Number of **Quality assessment** Number of patients/ evaluations Design **Risk of bias** Inconsistency Imprecision **Summary of findings** Quality Indirectness specimens Sensitivity 29^{1,7} serious^{2,3,4} Pooled sensitivity (95% CI) = serious⁵ serious⁶ 2810 LOW crossno serious 70.6% (53.3 to 83.5%) sectional indirectness Specificity **29**^{1,7,8} serious^{2,3,4} serious⁵ See forest plot below^{1,8} LOW

serious⁶

2810

no serious

Use of commercial nucleic acid amplification tests in the diagnosis of people with suspected central nervous system tuberculosis

Appendix E: GRADE profiles

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/	Summary of findings	Quality
evaluations	Design	TTISK OF DIAS	meensistency	mancethess	imprecision	specimens	ounnary or mangs	Quanty
	sectional			indirectness				

¹ Forest plots for sensitivity and specificity:

² Unclear if a random or consecutive sample was used in a number of studies

³ Unclear if test interpretation was blinded in a number of studies

⁴ Unclear if a threshold for test interpretation was used and predefined in a number of studies

⁵ A number of different reference standards were used, both across and within studies

⁶ Significant variation in point estimates with little overlap in confidence intervals
 ⁷ Systematic reviews: Denkinger (2014), Pai (2003); additional studies: Al-Ateah (2012), Bemer-Melchior (1998),

Chedore and Jamieson (2003), Malbruny (2011), Teo (2011)

⁸ Meta-analysis of relevant data not possible in STATA or R

			Quality assessm	ent	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
3 ^{1,2,3,4}	cross- sectional	serious ^{6,7,8,9,10}	no serious inconsistency	no serious indirectness	serious ¹¹	141	Pooled sensitivity (95% CI) = 84.2% (71.9 to 91.7%)	LOW
Specificity								
3 ^{1,2,3,4,5}	cross- sectional	serious ^{6,7,8,9,10}	no serious inconsistency	no serious indirectness	serious ¹¹	141	See forest plot below ^{1,5}	LOW
 ⁶ Unclear if a rat ⁷ Unclear if inap ⁸ Test interpreta ⁹ Unclear if test ¹⁰ PCR (one of the set of th	of relevant da ndom or cons propriate excl tion unblinded interpretation the reference	ata not possible in s ecutive sample wa usions were avoid d: Kim, 2008 was blinded: Liao, standards in Kim (s used: Liao, 2009 ed		ndard			

Use of interferon gamma release assays in the diagnosis of people with suspected central nervous system tuberculosis

Use of tuberculin skin test in the diagnosis of people with suspected central nervous system tuberculosis

			Quality assessm	ent	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	35	45.5% (95% CI 16.0 to 74.9%)	VERY LOW
Specificity								
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	35	66.7% (95% CI 47.8 to 85.5%)	VERY LOW
¹ Kim, 2008 ² Unclear if inapp ³ Test interpretat		usions were avoid I	ed					

Appendix E: GRADE profiles

			Quality assessm	ent	Number of			
Number of					patients/			
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality
⁴ PCR is not a va	alidated refere	ence standard						

⁵ Patients did not all receive the same reference standard (PCR or culture)
 ⁶ Wide confidence interval

Use of adenosine deanimase assays in the diagnosis of people with suspected central nervous system tuberculosis

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
Threshold for	positivity: 4 L	ו/נ						
13 ^{1,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	no serious imprecision	1092	Pooled sensitivity (95% CI) = 92.7% (89.1 to 95.4%)	VERY LOW
Threshold for	positivity: 8 L	ו/נ						
13 ^{2,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ⁹	1092	Pooled sensitivity (95% CI) = 63.0% (57.1 to 68.6%)	VERY LOW
Threshold for	positivity: 10	U/I						
13 ^{3,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ⁹	1092	Pooled sensitivity (95% CI) = 49.5% (43.6 to 55.4%)	VERY LOW
Specificity								
Threshold for	positivity: 4 L	ו/נ						
13 ^{1,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ⁹	1092	Pooled specificity (95% CI) = 72.3% (69.0 to 75.4%)	VERY LOW
Threshold for	positivity: 8 L	ו/נ						
13 ^{2,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ⁹	1092	Pooled specificity (95% CI) = 84.8% (82.1 to 87.3%)	VERY LOW
Threshold for	positivity: 10	U/I						
13 ^{3,4}	cross- sectional	very serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ⁹	1092	Pooled specificity (95% CI) = 90.7% (88.5 to 92.7%)	VERY LOW
¹ Forest plots fo			hreshold for positivit					

² Forest plots for sensitivity and specificity at a threshold for positivity of 8 U/I:

Appendix E: GRADE profiles

Number of evaluations			Quality assessm	ent	Number of			
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
³ Forest plots for	- sensitivity ar	nd specificity at a t	hreshold for positivit	y of 10 U/I:				
⁴ Systematic rev ⁵ Included studie		010) a case-control desi	an					
⁶ Unclear if inap	propriate excl	lusions were avoid	ed					
⁸ Different refere	ence standard	d were not blinded Is used in each stu	ıdy					
⁹ Significant vari	ation in point	estimates with little	e overlap in confider	ice intervals				

Diagnosis of active genitourinary tuberculosis A.4.3

			Quality assessm	ient	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
2 ^{1,2,3}	cross- sectional	serious ^{5,6,7,8}	no serious inconsistency	no serious indirectness	serious ⁹	72	Pooled sensitivity (95% CI) = 36.3% (19.2 to 57.8%)	LOW
Specificity								
2 ^{1,2,3,4}	cross- sectional	serious ^{5,6,7,8}	no serious inconsistency	no serious indirectness	no serious imprecision	72	See forest plot below ^{1,4}	MODERATE
¹ Forest plots fo	r sensitivity ar	nd specificity:						
⁵ Unclear if a co	nsecutive or r	ita not possible in andom sample wa usions were avoid	is used					
⁷ Unclear if test	interpretation	was blinded						
⁹ Wide confiden		lex test interpretati	on was used					

Use of microscopy in the diagnosis of people with suspected genitourinary tuberculosis

⁹ Wide confidence interval

Use of radiology¹ in the diagnosis of people with suspected genitourinary tuberculosis

			Quality assessm	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
1 ²	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	42	91.4% (95% CI 82.2 to 100%)	MODERATE
Specificity								
1 ²	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious7	42	28.6% (95% CI 0.0 to 62.0%)	LOW

			Quality assessm	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
¹ Includes renal c	alcification, o	caliceal destruction	, infundibular stenos	is, cavitation, uret	eral stricture, vesi	icoureteral reflux	and small capacity bladder	
² Hemal, 2000								
³ Unclear if a con	secutive or ra	andom sample was	sused					
⁴ Unclear if inapp	ropriate exclu	usions were avoide	ed					
⁵ Unclear if test in	terpretation	was blinded						
⁶ Unclear if a thre	shold for ind	ex test interpretation	on was used					
⁷ Wide confidence	e interval							

Use of commercial nucleic acid amplification tests in the diagnosis of people with suspected genitourinary tuberculosis

			Quality assessm	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
4 ^{1,2,3,4,6}	cross- sectional	serious ^{7,8,9,10}	no serious inconsistency	no serious indirectness	serious ^{11,12}	208	Pooled sensitivity (95% CI) = 56.9% (34.9 to 76.4%)	LOW
Specificity								
4 ^{1,2,3,4,5,6}	cross- sectional	serious ^{7,8,9,10}	no serious inconsistency	no serious indirectness	serious ^{11,12}	208	See forest plot below ^{1,5}	LOW
 ⁶ Systematic revi ⁷ Unclear if a cor ⁸ Unclear if inapp ⁹ Unclear if test i ¹⁰ Unclear if a thr 	(2 evaluation 5 of relevant dat ew: Dinnes (2 nsecutive or ra propriate exclu nterpretation v reshold for ind iation in point	s) a not possible in a 2007) andom sample was usions were avoide was blinded in 3 of lex test interpretatio	d the 4 evaluations					

Use of interferon gamma release assays in the diagnosis of people with suspected genitourinary tuberculosis

			Quality assessm	Number of				
Number of				patients/				
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality

			Quality assessm	ient		Number of		Quality
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	
Sensitivity								
1 ¹	cross- sectional	serious ^{2,3,4}	no serious inconsistency	no serious indirectness	serious ⁵	30	91.7% (95% CI 76.0 to 100%)	LOW
Specificity								
1 ¹	cross- sectional	serious ^{2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	30	88.9% (95% CI 74.4 to 100%)	LOW
	propriate excluinterpretation v	andom sample was usions were avoide was blinded						

A.4.4 Diagnosis of active gastrointestinal tuberculosis

Use of microscopy in the diagnosis of people with suspected gastrointestinal tuberculosis

			Quality assessm	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
3 ^{1,2,3}	cross- sectional	serious ^{5,6,7,8,9}	serious12	no serious indirectness	serious ^{10,11}	124	Pooled sensitivity (95% CI) = 42.4% (12.2 to 79.6%)	VERY LOW
HIV-negative								
1 ³	cross- sectional	serious ^{5,6,7,8,9}	no serious inconsistency	no serious indirectness	serious ¹¹	41	85.7% (95% CI 35.6 to 98.5%)	LOW
Specificity								
3 ^{1,2,3,4}	cross- sectional	serious ^{5,6,7,8,9}	serious ¹²	no serious indirectness	serious ¹⁰	124	See forest plot below ^{1,4}	VERY LOW
HIV-negative								
1 ³	cross- sectional	serious ^{5,6,7,8,9}	no serious inconsistency	no serious indirectness	serious ¹¹	41	71.1% (95% CI 55.2 to 83.0%)	LOW
¹ Forest plots for	sensitivity and	d specificity:						

			Quality assessm	Number of				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
² Cho, 2011								
³ Saleh, 2012 ⁴ Meta-analysis	of relevant da	ita not possible in a	available statistical so	ftware				
		andom sample use						
		usions were avoide						
		tation was blinded		0)				
		t interpretation was	s blinded: Saleh (201 s used	2)				
			e overlap in confider	ce intervals				
¹¹ Wide confider								
¹² Patients recei	ved different i	reference standard	s: Cho (2011)					

Use of interferon gamma release assays in the diagnosis of people with suspected gastrointestinal tuberculosis

			Quality assessm	ent		Number of				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality		
Sensitivity										
14 ^{1,2}	cross- sectional	serious ^{3,4,5}	serious ⁶	no serious indirectness	serious ⁷	965	Pooled sensitivity (95% CI) = 89.7% (82.6 to 94.1%)	VERY LOW		
Specificity										
14 ^{1,2}	cross- sectional	serious ^{3,4,5}	serious ⁶	no serious indirectness	serious ^{7,8}	965	Pooled specificity (95% CI) = 93.3% (82.9 to 97.6%)	VERY LOW		
¹ Forest plots for	sensitivity an	d specificity:								
			s: Cho (2011), Liao (2009)						
		andom sample use usions were avoide								
		was blinded in a nu								

⁶ Patients received different reference standards, both within and between studies
 ⁷ Significant variation in point estimates with little overlap in confidence intervals
 ⁸ Wide confidence interval

Use of adenosine deanimase assays in the diagnosis of people with suspected gastrointestinal tuberculosis

	Number of	Quality assessment	Number of	Summary of findings	Quality
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Sensitivity	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens		
47 156								
17 ^{1,5,6}	cross- sectional	serious ^{7,8,9,10}	serious ¹¹	serious ¹²	serious ¹³	1617	Pooled sensitivity (95% CI) = 94.9% (89.7 to 97.5%)	VERY LOW
Threshold for p	ositivity: <10	U/I						
1 ^{2,5}	cross- sectional	serious ^{7,8,9,10}	no serious inconsistency	serious ¹²	serious ¹⁴	368	58.8% (95% CI 35.4 to 82.2%)	VERY LOW
Threshold for p	ositivity: 20 te	o 29 U/I						
1 ^{3,5}	cross- sectional	serious ^{7,8,9,10}	no serious inconsistency	serious ¹²	no serious imprecision	52	92.6% (95% CI 82.7 to 100%)	LOW
Threshold for p	ositivity: >30	U/I						
15 ^{4,5,6}	cross- sectional	serious ^{7,8,9,10}	serious ¹¹	serious ¹²	serious ¹³	1197	Pooled sensitivity (95% CI) = 94.7% (91.5 to 96.7%)	VERY LOW
Specificity								
17 ^{1,5,6}	cross- sectional	serious ^{7,8,9,10}	serious ¹¹	serious ¹²	serious ¹³	1617	Pooled specificity (95% CI) = 96.2% (93.9 to 97.7%)	VERY LOW
Threshold for p	ositivity: <10	U/I						
1 ^{2,5}	cross- sectional	serious*	serious*	serious*	no serious imprecision	368	95.4% (95% CI 93.3 to 97.6%)	VERY LOW
Threshold for p	ositivity: 20 te	o 29 U/I						
1 ^{3,5}	cross- sectional	serious*	serious*	serious*	serious ¹⁴	52	84.0% (95% CI 69.6 to 98.4%)	VERY LOW
Threshold for p	ositivity: >30	U/I						
15 ^{4,5,6}	cross- sectional	serious ^{7,8,9,10}	serious ¹¹	serious ¹²	serious ¹³	1197	Pooled specificity (95% CI) = 96.7% (94.3 to 98.1%)	VERY LOW
¹ Forest plots for	sensitivity and	l specificity:						
² Hillebrand, 199 ³ Kang, 2012 ⁴ Forest plots for		I specificity at a th	reshold for positivity	of >30 U/I				

⁵ Systematic review: Shen (2013)
⁶ Additional study: Brant (1995)
⁷ Unclear if a consecutive or random sample used
⁸ Unclear if inappropriate exclusions were avoided

		Quality assessment						
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
 ¹⁰ Unclear if a three ¹¹ Patients receive ¹² Review include 	eshold for tes ed different re d inappropria ation in point	t interpretation was rerence standards te reference stand	, both within and bet					

A.4.5 Diagnosis of active lymph node tuberculosis

Quality assessment Number of Number of patients/ **Risk of bias** evaluations Design Inconsistency Indirectness Imprecision Summary of findings Quality specimens Sensitivity **7**^{1,2} 799 Pooled sensitivity (95% CI) = LOW serious^{5,6,7} serious^{8,9} crossno serious no serious 36.4% (27.5 to 46.5%) sectional inconsistency indirectness Children 1³ serious^{5,6,7} no serious no serious serious⁹ 129 44.3% (95% CI 33.9 to 54.7%) LOW crosssectional indirectness inconsistency **HIV-positive 1**⁴ serious6,7 no serious serious⁹ 344 51.0% (95% CI 43.0 to 59.0%) LOW no serious crossinconsistency sectional indirectness Specificity **7**^{1,2} serious^{8,9} 799 Pooled specificity (95% CI) = LOW serious^{5,6,7} crossno serious no serious 94.4% (78.4 to 98.8%) sectional inconsistency indirectness Children 1³ serious^{5,6,7} serious⁹ 129 58.5% (95% CI 43.5 to 73.6%) crossno serious no serious LOW indirectness sectional inconsistency **HIV-positive 1**⁴ serious^{6,7} serious⁹ 344 96.0% (95% CI 93.1 to 98.7%) LOW crossno serious no serious sectional inconsistency indirectness

Use of microscopy in the diagnosis of people with suspected lymph node tuberculosis

			Quality assessm	nent		Number of		
Number of evaluations ¹ Forest plots for	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens		Quality
¹ Forest plots for	sensitivity and	d specificity:						
 ³ Fanny, 2012 ⁴ Van Rie, 2013 ⁵ Unclear if a ran 	dom or conse	cutive sample use	; Kerleguer, 2004; N	lies	nek, 2002, Van Ri	e, 2013		
		clusions were avoid vas blinded in any	led in a number of st of the studies	udies				
⁸ Significant varia	ation in point e		overlap in confidence	e intervals				
⁹ Wide confidence	e interval							

Use of cytology¹ in the diagnosis of people with suspected lymph node tuberculosis

			Quality assessm	nent		Number of				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality		
Sensitivity										
1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	250	99.2% (95% CI 97.7 to 100%)	HIGH		
Specificity										
1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	250	49.2% (95% CI 40.2 to 58.1%)	MODERATE		
- ·	¹ Including the presence or absence of granulomas, Langerhan's giant cells, plasma cells, lymphocytes, macrophages, neutrophils and necrosis; the cytological criteria for									

diagnosis of tuberculous lymphadenitis were defined as epithelioid cell granulomas with or without multinucleate giant cells and caseation necrosis ² Nataraj, 2002
 ³ Wide confidence interval

Use of commercial nucleic acid amplification tests in the diagnosis of people with suspected lymph node tuberculosis

			Quality assessm		Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
26 ^{1,2}	cross- sectional	serious ^{4,5,6,7}	serious ⁸	no serious indirectness	serious ^{9,10}	1824	Pooled sensitivity (95% CI) = 86.5% (78.5 to 91.8%)	VERY LOW

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
HIV-positive								
1 ³	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	no serious imprecision	344	85.8% (95% CI 80.4 to 91.2%)	MODERATE
Specificity								
26 ^{1,2}	cross- sectional	serious ^{4,5,6,7}	serious ⁸	no serious indirectness	serious ^{9,10}	1824	Pooled specificity (95% CI) = 92.4% (88.7 to 95.0%)	VERY LOW
HIV-positive								
1 ³	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	no serious imprecision	344	94.5% (95% CI 91.2 to 97.8%)	MODERATE

¹ Forest plots for sensitivity and specificity:

² Systematic reviews: Denkinger (2014), Dinnes (2007); additional studies: Gamboa (1997b), Kerleguer (2004), Lithelm (2011), Malbruny (2011), Osores (2006), Pfyffer (1996), Van Rie (2013)

³ Van Rie, 2013

⁴ Unclear if a random or consecutive sample used in a number of studies

⁵ Unclear if inappropriate exclusions were avoided in a number of studies

⁶ Unclear if test interpretation was blinded in any of the studies

⁷ Unclear if the threshold for test positivity was predefined in a number of studies

⁸ Patients received different reference standards, both within and across studies

⁹ Significant variation in point estimates with little overlap in confidence intervals

¹⁰ Wide confidence interval

A.4.6 Diagnosis of active pericardial tuberculosis

Use of commercial nucleic acid amplification tests in the diagnosis of people with suspected pericardial tuberculosis

		P	a u	.				
			Quality assess	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
2 ^{1,3,4}	cross- sectional	serious ^{5,6,7}	serious ⁸	no serious indirectness	serious ^{9,10}	115	Pooled sensitivity (95% CI) = 51.5% (13.8 to 87.6%)	VERY LOW
Specificity								
2 ^{1,2,3,4}	cross- sectional	serious ^{5,6,7}	serious ⁸	no serious indirectness	no serious imprecision	115	See forest plot below ^{1,4}	LOW
 ³ Lee, 2002 ⁴ Reuter, 2006 ⁵ Unclear if index ⁶ Unclear if referent ⁷ Unclear if a three 	< test interpreta ence standard eshold for test	tion was blinded: was blinded positivity was pree	vailable statistical so Reuter (2006) defined: Reuter (200 and across studies					
⁹ Significant varia ¹⁰ Wide confiden		stimates with little	overlap in confidence	ce intervals				

Use of adenosine deanimase assays in the diagnosis of people with suspected pericardial tuberculosis

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
5 ^{1,2}	cross- sectional	serious ^{3,4,5}	serious ⁶	no serious indirectness	serious ⁷	421	Pooled sensitivity (95% CI) = 88% (82 to 91%)	VERY LOW

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Specificity								
5 ^{1,2}	cross- sectional	serious ^{3,4,5}	serious ⁶	no serious indirectness	serious ⁷	421	Pooled specificity (95% CI) = 83% (78 to 88%)	VERY LOW
¹ Forest plots for ² Tuon, 2006								
⁴ Unclear if test in	nterpretation w	sions were avoide as blinded ot always predefir						
⁶ Different referen	nce standards	used, both within	and across studies lap in confidence in	tonyala				

Use of tuberculin skin tests in the diagnosis of people with suspected pericardial tuberculosis

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
Threshold for p	ositivity: 10 n	nm						
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	52	88.9% (95% CI 78.6 to 99.2%)	VERY LOW
Threshold for p	ositivity: 15 n	nm						
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	52	44.4% (95% CI 28.2 to 60.7%)	VERY LOW
Specificity								
Threshold for p	ositivity: 10 n	nm						
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	52	56.3% (95% CI 31.9 to 80.6%)	VERY LOW
Threshold for p	ositivity: 15 n	nm						
1 ¹	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	no serious imprecision	52	93.8% (95% CI 81.9 to 100%)	LOW
¹ Reuter, 2006 ² Unclear if index								

³ Unclear if reference standard was blinded

			Quality assessm	nent		Number of		
Number of						patients/		
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality
⁴ Unclear if a three	eshold for test	positivity was pred	lefined					
⁵ Different refere	nce standards	used						

⁶ Wide confidence interval

A.4.7 Diagnosis of active pleural tuberculosis

Use of microscopy in the diagnosis of people with suspected pleural tuberculosis

			Quality assessm	ient		Number of	Pooled sensitivity (95% CI) = LOW 10.5% (3.7 to 26.4%)		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality	
Sensitivity ¹									
6 ^{2,3,4,5,6}	cross- sectional	serious ^{8,9,10,11}	no serious inconsistency	no serious indirectness	serious ^{12,13}	294	Pooled sensitivity (95% CI) = 10.5% (3.7 to 26.4%)	LOW	
Specificity ^{1,7}									
6 ^{2,3,4,5,6}	cross- sectional	serious ^{8,9,10,11}	no serious inconsistency	no serious indirectness	no serious imprecision	294	See forest plot below ^{1,7}	MODERATE	
 ⁸ Unclear if a rand ⁹ Unclear if inapp ¹⁰ Unclear if test if ¹¹ Unclear if the test 	3 (2 evaluation 3 (2 evaluation f relevant data dom or consec ropriate exclu- nterpretation est positivity the in point estim	a not possible in S cutive sample was sions were avoide was blinded in mo nreshold was pred	used d in all studies						

Use of commercial nucleic acid amplification tests in the diagnosis of people with suspected pleural tuberculosis

		(Quality assessme	ent		Number of		
Number of						patients/		
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality

			Quality assessm	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity ¹								
26 ^{2 to 14}	cross- sectional	serious ^{16,17,18,19}	serious ²⁰	no serious indirectness	serious ^{21,22}	1686	Pooled sensitivity (95% CI) = 53.0% (33.2 to 71.9%)	VERY LOV
Specificity ¹								
26 ^{2 to 14}	cross- sectional	serious ^{16,17,18,19}	serious ²⁰	no serious indirectness	no serious imprecision	1686	Pooled specificity (95% CI) = 99.4% (98.1 to 99.8%)	LOW
 ¹⁶ Random or col ¹⁷ Unclear if inap ¹⁸ Blinding of test ¹⁹ Unclear if thres ²⁰ Different refere 	95 views: Denking nsecutive san propriate excl t interpretatior shold for test ence standard iation in point	n not performed in a positivity predefined s used, both within	studies Il studies I in all studies	ce intervals				

Use of cytology¹ in the diagnosis of people with suspected pleural tuberculosis

		Quality assessment						
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
1 ²	cross-	serious ^{3,4}	no serious	no serious	serious ⁵	45	Sensitivity (95% CI) = 53.9%	LOW

		(Quality assessme	ent		Number of				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality		
	sectional		inconsistency	indirectness			(34.7 to 73.0%)			
Specificity										
1 ²	cross- sectional	serious ^{3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	45	Specificity (95% CI) = 97.4% (90.4 to 100%)	MODERATE		
 ² Hasaneen, 200 ³ Unclear if a rar ⁴ Unclear if the t 	¹ Histopathologic examination of pleural biopsy specimen fixed in formalin for caseating granuloma ² Hasaneen, 2003 ³ Unclear if a random or consecutive sample was used ⁴ Unclear if the test positivity threshold was predefined ⁵ Wide confidence interval									

Use of interferon gamma release assays in the diagnosis of people with suspected pleural tuberculosis

			Quality assessme	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity ¹								
5 ^{2,3,4}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ^{13,14}	150	Pooled sensitivity (95% CI) = 75.5% (60.9 to 85.8%)	VERY LOW
Specificity ^{1,5}								
5 ^{2,3,4}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ^{13,14}	16 ² 23 ² 40 ³ 39 ³ 32 ⁴	See forest plot below ^{1,5}	VERY LOW
 ⁸ Unclear if a ran ⁹ Unclear if inapp ¹⁰ Unclear if test ¹¹ Unclear if the ¹² Different reference 	evaluations) valuations) of relevant da dom or cons propriate excl interpretatior test positivity ence standard	ata not possible in S ecutive sample was usions were avoide n was blinded threshold was prec ds used, both withir	sused					

		(Quality assessme	ent	Number of			
Number of						patients/		
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality
¹⁴ Wide confiden	ce interval							

Use of lipoarabinomannan assays in the diagnosis of people with suspected pleural tuberculosis

			Quality assessm	ent		Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality	
Sensitivity									
Threshold for p	positivity: 30	g/l							
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁵	50	Sensitivity (95% CI) = 93.8% (86.9 to 100%)	VERY LOW	
Threshold for p	positivity: 60	g/l							
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁵	50	Sensitivity (95% CI) = 91.7% (80.6 to 100%)	VERY LOW	
Specificity									
Threshold for p	oositivity: 30	g/l							
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁵	50	Specificity (95% CI) = 11.5% (0.0 to 23.8%)	VERY LOW	
Threshold for p	positivity: 60	g/l							
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁵	50	Specificity (95% CI) = 92.3% (82.1 to 100%)	VERY LOW	
¹ Dheda, 2009 ² Unclear if test ³ Unclear if the t ⁴ Different refere ⁵ Wide confident	est positivity t ence standard	hreshold was prede	efined						

Use of adenosine deanimase assays in the diagnosis of people with suspected pleural tuberculosis

			Quality assessm	nent	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
65 ^{1,11}	cross-	serious ^{8,9,10,11}	serious ¹²	no serious	serious ¹³	8222	Pooled sensitivity (95% CI) =	VERY LOW

			Quality assessm	nent		Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality	
	sectional			indirectness			94.2% (91.5 to 96.0%)		
Threshold for	positivity: 10	to <15 U/l2							
1 ^{3,11}	cross- sectional	serious ^{10,11}	serious ¹²	no serious indirectness	no serious imprecision	74	Sensitivity (95% CI) = 99.0% (90.9 to 99.9%)	LOW	
Threshold for	positivity: 15	to <20 U/I4							
1 ^{5,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	no serious imprecision	69	Sensitivity (95% CI) = 95.7% (85.8 to 98.8%)	LOW	
Threshold for	positivity: 30	to 35 U/I							
19 ^{6,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	1461	Pooled sensitivity (95% CI) = 94.2% (88.2 to 97.2%)	VERY LOV	
Threshold for	positivity: >3	5 to 40 U/I							
15 ^{7,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	1951	Pooled sensitivity (95% CI) = 94.3% (89.1 to 97.1%)	VERY LOV	
Threshold for	positivity: >4	0 to 45 U/I							
9 ^{8,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹⁴	1203	Pooled sensitivity (95% CI) = 89.5% (79.7 to 94.9%)	VERY LOV	
Threshold for	positivity: >4	5 to 50 U/I							
14 ^{9,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	2072	Pooled sensitivity (95% CI) = 92.6% (84.1 to 96.8%)	VERY LOV	
Threshold for	positivity: >5	0 U/I							
7 ^{10,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	no serious imprecision	1448	Pooled sensitivity (95% CI) = 98.1% (88.3 to 99.7%)	LOW	
Specificity ¹									
65 ^{1,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	8222	Pooled specificity (95% CI) = 91.3% (89.1 to 93.1%)	VERY LOV	
Threshold for	positivity: 10	to <15 U/I2							
1 ^{3,11}	cross- sectional	serious ^{10,11}	serious ¹²	no serious indirectness	serious ¹⁴	74	Specificity (95% CI) = 38.5% (22.4 to 57.5%)	VERY LOV	
Threshold for	positivity: 15	to <20 U/I4							
1 ^{5,11}	cross-	serious ^{8,9,10,11}	serious ¹²	no serious	serious ¹⁴	69	Specificity (95% CI) = 90.9%	VERY LOW	

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
	sectional			indirectness			(72.2 to 97.5%)	
Threshold for p	ositivity: 30	to 35 U/I						
19 ^{6,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	1461	Pooled specificity (95% CI) = 94.0% (89.3 to 96.7%)	VERY LOW
Threshold for p	ositivity: >3	5 to 40 U/I						
15 ^{7,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	1951	Pooled specificity (95% CI) = 90.4% (83.3 to 94.7%)	VERY LOW
Threshold for p	ositivity: >4	0 to 45 U/I						
9 ^{8,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	no serious imprecision	1203	Pooled specificity (95% CI) = 93.0% (89.4 to 95.4%)	LOW
Threshold for p	ositivity: >4	5 to 50 U/I						
14 ^{9,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	serious ¹³	2072	Pooled specificity (95% CI) = 87.7% (82.1 to 91.7%)	VERY LOW
Threshold for p	ositivity: >5	D U/I						
7 ^{10,11}	cross- sectional	serious ^{8,9,10,11}	serious ¹²	no serious indirectness	no serious imprecision	1448	Pooled specificity (95% CI) = 91.7% (87.8 to 94.4%)	LOW

			Quality assessn	nent		Number of				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality		
¹ Forest plots for	r sensitivity ar	nd specificity:								
² 13 U/I ³ Dheda, 2009 ⁴ 20 U/I ⁵ Andreasyan ⁶ Forest plots for	r sensitivity ar	nd specificity at a t	hreshold for positivit	y of 30 to 35 U/I:						
⁷ Forest plots for sensitivity and specificity at a threshold for positivity of >35 to 40 U/I:										
⁸ Forest plots for	r sensitivity ar	nd specificity at a t	hreshold for positivit	y of >40 to 45 U/I:						
⁹ Forest plots for	r sensitivity ar	nd specificity at a t	hreshold for positivit	y of >45 to 50 U/I:						
¹⁰ Forest plots for	or sensitivity a	and specificity at a	threshold for positivi	ty of >50 U/I:						
 ⁹ Unclear if inapp ¹⁰ Unclear if test ¹¹ Unclear if the ¹² Different refer 	ndom or cons propriate excl interpretatior test positivity ence standar riation in poin	ecutive sample wa lusions were avoid n was blinded threshold was pre ds used, both withi	ed in all studies							

Use of adenosine deanimase assays in conjunction with the lymphocyte-neutrophil ratio in the diagnosis of people with suspected pleural tuberculosis

			Quality assessm	ient		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	no serious imprecision	303	88.1% (95% CI 82.8 to 93.4%)	LOW
Specificity								
1 ¹	cross- sectional	serious ^{2,3}	serious ⁴	no serious indirectness	no serious imprecision	303	95.0% (95% CI 91.6 to 98.4%)	LOW
¹ Burgess, 1996								

			Quality assessm	nent	Number of						
Number of						patients/					
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality			
² Unclear if test i	nterpretation v	vretation was blinded									

³ Test positivity threshold was not predefined ⁴ Different reference standards used

A.5 RQ I

A.5.1 Dosing frequencies in children

Intervention: daily (unsupervised) dosing

Comparator: intermittent (DOT) dosing

Site of tuberculosis: pulmonary/intrathoracic

		Qualit	y assessment			Number of	patients	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) dosing	Intermittent (DOT) dosing	Relative (95% CI)	Absolute (95% Cl)	Quality
Relapse (n	umber to experie	nce clinical or r	adiological recurre	ence; follow-up 24	to 60 months ¹)					
2 ^{2,3}	randomised trials	Very Serious ^{4,5,6,7,} 8,9	very serious ^{10,11,12}	serious ¹³	very serious ^{14,15}	1/184 (0.54%)	1/155 (0.65%)	OR 0.87 (0.08 to 9.85) ^{16,17}	0 fewer per 100 (from 1 fewer to 5 more)	VERY LOW
 ³ Swaminat ⁴ Te Water ⁵ Swaminat ⁶ Allocation ⁷ Te Water ⁸ Swaminat 	han et al, 2005: i concealment un Naude et al, 200	0: randomisatic nethod of rand clear 0: blinding abse aside from the l intent-to-treat p	omisation unclear ent or unclear blinding of the radio principle	ologist and paedia	atrician assessed	lysis is at the level of the the children's chest x-ray	ys, blinding is unclea		ficient data to co	rrect

¹⁷ Forest plot:

Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

Intervention: daily (unsupervised) dosing

Comparator: twice-weekly (DOT) followed by thrice-weekly (DOT) dosing

Site of tuberculosis: pulmonary

		Qualit	ty assessment			Number of	patients	Effect		
Number of studies	· · · · · · · · · · · · · · · · · · ·	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) dosing	Twice-weekly (DOT) followed by thrice-weekly (DOT) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
	number of tuber	culosis-related c	leaths during the s	tudy; follow-up 24	months1)					
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ^{7,8}	serious ⁹	very serious ^{10,11}	1/68 (1.5%)	2/69 (2.9%)	OR 0.50 (0.04 to 5.65) ¹²	1 fewer per 100 (from 3 fewer to 12 more)	VERY LOW
	to treatment - o	disease resolut				at treatment completion		s ¹³)		
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}	serious ^{7,8}	very serious ^{9,16}	serious ¹⁰	61%	48%	OR 1.69 (0.97 to 2.97) ¹²	13 more per 100 (from 1 fewer to 25 more)	VERY LOW
			ion (% of participa							
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}	serious ^{7,8}	very serious ^{9,16}	serious ¹⁰	82%	89.5%	OR 0.54 (0.20 to 1.48) ¹²	7 fewer per 100 (from 27 fewer to 3 more)	VERY LOW
Response	to treatment - o	disease resolut	tion (% of participa	ants with residual I	esions at treatme	ent completion; follow-up	6-9 months ¹³)			
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}	serious ^{7,8}	very serious ^{9,16}	serious ¹⁰	39%	49%	OR 0.67 (0.38 to 1.17) ¹²	10 fewer per 100 (from 22 fewer to 4 more)	VERY LOW
Response	to treatment - o	disease resolut	tion (% of participa	ants with residual I	esions at 60 mor	nths)				
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}	serious ^{7,8}	very serious ^{9,16}	very serious ^{10,11}	15%	1.5%	OR 11.40 (1.42 to 91.85) ¹²	13 more per 100 (from 1 more to 57 more)	VERY LOW
	to treatment - o	disease resolut	ion (number of pa	rticipants to requir	e treatment exte	nsion due to incomplete i	resolution)			
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ^{7,8}	very serious ^{9,16}	very serious ^{10,11}	5/68 (7.4%)	4/69 (5.8%)	OR 1.29 (0.33 to 5.02) ¹²	2 more per 100 (from 4 fewer to 18 more)	VERY LOW
			radiological recurre		months)					
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}	serious ^{7,8}	serious ⁹	very serious ^{10,11}	1/67 (1.5%)	0/66 (0%)	OR 3.00 (0.12 to 74.98) ¹²	-	VERY LOW
	vents - hepatot	oxicity (number	of patients to exp		icity; follow-up 24	4 months ¹)				
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ^{7,8}	serious ⁹	very serious ^{10,11}	2/68 (2.9%)	1/69 (1.4%)	OR 2.06 (0.18 to 23.27) ¹²	1 more per 100 (from 1 fewer to 24 more)	VERY LOW

¹ After treatment completion ² Ramachrandan et al, 1998

³ Method of randomisation and the use of allocation concealment was unclear

⁴ The groups were not comparable at baseline – more patients in the intermittent group had cavitatory disease at baseline, a sign that the disease in this group may have been more severe at treatment initiation

⁵ Aside from the blinding of the radiologist and paediatrician assessed the children's chest x-rays, blinding is unclear

		Quali	ty assessment			Number of	patients	Effe	ct
							Twice-weekly (DOT) followed by		
Number		Risk of				Daily (unsupervised)	thrice-weekly	Relative	Absolute
of studies	Design	bias	Inconsistency	Indirectness	Imprecision	dosing	(DOT) dosing	(95% CI)	(95% CI)

⁶ Unclear if analysis follows the intent-to-treat principle

⁷ In addition to the use of different treatments, the two groups received different care: the thrice-weekly followed by twice-weekly regimen was supervised in the clinic, whereas the daily regimen was not supervised except on the day of medication collection

⁸ The loss to follow-up in each group is unclear

⁹ Intervention and comparator vary by more than dosing frequency; that is, the intervention studied does not precisely match the intervention of interest

¹⁰ GRADE rule of thumb event number <300

¹¹ Wide confidence intervals

¹² Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

¹³ Treatment period

¹⁴ Swaminathan et al, 2005

¹⁵ Analysis did not follow the intent-to-treat principle

¹⁶ Outcome is a substitute for the outcome of interest (cure, treatment success and treatment failure) Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

Intervention: twice-weekly (DOT) dosing

Comparator: daily (Monday-Friday) (unsupervised) dosing

Site of tuberculosis: intrathoracic

		Qualit	y assessment			Number of	patients	Effec	st	
Number		Risk of				Daily (Monday-Friday)	Twice-weekly	Relative	Absolute	
of studies	Design	bias	Inconsistency	Indirectness	Imprecision	(unsupervised) dosing	(DOT) dosing	(95% CI)	(95% CI)	Quality
Response	to treatment 3 n	nonths after tr	eatment initiation	(measured with: o	composite score	obtained from parent asses	ssment, clinical sympto	oms, weight gain and	chest radiograph	; range of
scores: -4-8	; better indicated	l by higher valu	ies)							
1 ²	randomised	very	serious ⁷	very serious ^{8,9}	no serious	89	70	-	median	VERY
	trial	serious ^{3,4,5,6}			imprecision ¹⁰				difference 0 ¹¹	LOW
Response	to treatment at f	reatment com	pletion (measured	with: composite s	score obtained fro	om parent assessment, clir	nical symptoms, weigh	t gain and chest radio	graph; range of s	cores: -4-8;
	ated by higher va			·				•		
1 ²	randomised	verv	serious ⁷	very serious8,9	no serious	93	70	-	median	VERY
	trial	serious ^{3,4,5,6}		,	imprecision ¹⁰				difference 0 ¹¹	LOW
Response	to treatment 6 n		eatment completion	on (measured with	n: composite sco	re obtained from parent as	sessment. clinical svm	ptoms, weight gain a	nd chest radiogra	ph: range
•			alues; follow-up 12	· · ·		· · · · · · · · · · · · · · · · · · ·	,	p = 0, = 0 = 0 = 0		. , . 5-
1 ²	randomised	very		very serious8,9	no serious	74	65	-	median 1	VERY
	trial	serious ^{3,4,5,6}		· , · · · · ·	imprecision ¹⁰				higher ¹¹	LOW
Response	to treatment 12-		er treatment com	detion (measured		score obtained from parer	nt assessment clinical	symptoms weight a	U	
			gher values; follow					ojp.coo,o.g g.		og.op.,
1 ²	randomised	verv	serious ⁷	very serious8,9	no serious	74	71	-	median	VERY
	trial	serious ^{3,4,5,6}	0011040		imprecision ¹⁰				difference 0 ¹¹	LOW
Symptom i			eight gain from trea	tment initiation un		pletion; better indicated by	higher values: follow-	up 6 months ¹)		
1 ²	randomised	verv	serious ⁷	serious ⁸	no serious	_12	_12	-	median 0.25	VERY
•	trial	serious ^{3,4,5,6}	00110000	5011005	imprecision ¹⁰				kg higher ¹¹	LOW
Polanco (n			adiological recurre	nco: follow up 30					ng nighei	LOW
neiapse (m	uniber to experie		autological recurre	nce, ionow-up 30	monuis)					

		Quali	ty assessment			Number of	patients	Effe	ect	
lumber		Risk of				Daily (Monday-Friday)	Twice-weekly	Relative	Absolute	
studies	Design	bias	Inconsistency	Indirectness	Imprecision	(unsupervised) dosing	(DOT) dosing	(95% CI)	(95% CI)	Quality
	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	very serious ^{14,15}	0/117 (0%)	1/89 (1.1%)	OR 0.25 (0.01 to 6.24) ¹⁶	1 fewer per 100 (from 1 fewer to 5 more)	VERY LOW
dherence	- treatment co	mpletion (num	ber to complete tre	atment on sched	ule; follow-up 6 m	onths ^{1,17})			·	
2	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	serious ¹⁴	114/117 (97.4%)	85/89 (95.5%)	OR 1.79 (0.39 to 8.20) ¹⁶	2 more per 100 (from 6 fewer to 4 more)	VERY LOW
	- number adhe	erent (number o	of children taking ≥			. ,				
2	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	serious ¹⁴	90/117 (76.9%)	70/89 (78.7%)	OR 0.90 (0.47 to 1.76) ¹⁶	2 fewer per 100 (from 15 fewer to 8 more)	VERY LOW
Iherence	- number part	ially adherent	(number of childrer	n taking ≥75% of	the prescribed dos	ses but <75% during any si	ngle 4-week period; f	follow-up 6 months ^{1,17})	
2	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	serious ¹⁴	30/117 (25.6%)	21/89 (23.6%)	OR 1.12 (0.59 to 2.12) ¹⁶	2 more per 100 (from 8 fewer to 16 more)	VERY LOW
dherence	- time to defau	ult by non-adh	erers (days to defa	ult by non-adhere	ers, defined as the	ose taking <75% of the pres	scribed doses; better	indicated by higher va	alues; follow-up 6	months ¹)
	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	no serious imprecision ¹⁰	117	89	-	median 30 days lower ¹¹	VERY LOW
		ult by partial ad		efault by partial a		hose taking ≥75% of the pr	escribed doses but <	75% during any single		
	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	no serious imprecision ¹⁰	117	89	-	median 23 days lower ¹¹	VERY LOW
	- proportion o	f prescribed d	· · ·	prescribed doses	taken; better indic	ated by higher values; follo	ow-up 6 months ^{1,17})			
	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	no serious imprecision ¹⁰	117	89	-	median 2% Iower ¹¹	VERY LOW
Randomis Allocation Blinding a Analysis o Weight fo their tuber Interventic Outcome Data is gi Data is gi Data is gi Total nun In additio on the day	concealment u bsent or unclear lid not follow the r age' and the 'r culosis was less on and compara is a substitute fo iven as median nber of participa	priate: randomis nclear r aumber who we s severe than th tor vary by more or the outcome and interquartile s not provided b ints not stated different treatme collection	orinciple re culture positive' e daily group e than dosing frequ of interest (cure, tre e range; imprecisio by authors; calculat ents, the two group	was significantly uency; that is, the eatment success n cannot be judg ed by reviewer a	lower in the intern intervention studi and treatment fail ed s (median _{twice-weekly}		e that the intermittent	group were less likely interest		
Wide con	fidence interval	s	s not provided by a	uthors; calculated	l by reviewer					

¹⁷ Treatment period

		Quali	ty assessment			Number of	oatients	Effe	ct	
Number		Risk of				Daily (Monday-Friday)		Relative	Absolute	
of studies	Design	bias	Inconsistency	Indirectness	Imprecision	(unsupervised) dosing	(DOT) dosing	(95% CI)	(95% CI)	Quality
Abbreviation	ns: CI, confidenc	e interval; DOT	T, directly observed	l therapy; OR, odd	ls ratio					

Intervention: daily (unsupervised) followed by twice-weekly (unsupervised) dosing

Comparator: daily (unsupervised) dosing

Site of tuberculosis: pulmonary

		Quali	ty assessment			Numl	ber of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) dosing	Daily (unsupervised) followed by twice- weekly (unsupervised) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
Response	to treatment - o	disease resolut	tion (number of pa	rticipants to compl	etely resolve; foll	ow-up 12 months ¹)				
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	very serious ^{8,9}	serious ¹⁰	9/15 (60%)	8/18 (44.4%)	OR 1.88 (0.47 to 7.53) ¹¹	16 more per 100 (from 17 fewer to 41 more)	VERY LOW
	to treatment - I	radiologic impr	ovement (number	of participants to	show radiologic ir	mprovement; follow-u	p 12 months ¹)			
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	very serious ^{8,9}	very serious ^{10,12}	15/15 (100%)	18/18 (100%)	OR 0.84 (0.12 to 44.73) ¹¹	-	VERY LOW
Response	to treatment - f	time to clinical	response (therapy	period for an ear	ly clinical respons	se; better indicated by	/ lower values; follow-up 12 m	ionths1)		
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	very serious ^{8,9}	serious ¹²	15	18	-	MD 1.6 months lower in the daily group (from 6.56 lower to 3.36 higher) ¹³	VERY LOW
Symptom i	mprovement -	weight gain (no	umber to experience	e weight gain; foll	ow-up 12 months	¹ ; better indicated by	higher values)		ũ ,	
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	serious ⁸	no serious imprecision	15	18	-	MD 0.09 kg higher in the daily group (from 1.15 lower to 1.33 higher) ¹³	VERY LOW
	umber to experi	ence clinical or	radiological recurre		oths after treatme	nt completion ¹)				
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	serious ⁸	very serious ^{10,12}	0/15 (0%)	0/18 (0%)	OR 1.19 (0.02 to 63.73) ¹¹	-	VERY LOW
Adverse ev	vents - hepatot	oxicity (numbe	r to experience ele	vated levels of ser	um aspartate am	inotransferase and al	anine aminotransferase; follo	w-up 12 months ¹)		
1 ²	randomised trial	very serious ^{3,4,5,6,} 14	serious ⁷	serious ⁸	very serious ^{10,12}	1/15 (6.7%)	0/18 (0%)	OR 3.83 (0.14 to 101.08) ¹¹	-	VERY LOW
Adherence	(number exclu	ded due to "poo	r compliance"; follo	w-up 12 months ¹)						
1 ²	randomised trial	very serious ^{3,4,5,15}	no serious inconsistency	serious ⁸	serious ¹⁰	3/18 (16.7%)	0/18 (0%)	OR 8.35 (0.40 to 174.51) ¹¹	-	VERY LOW

		Quali	ity assessment			Numb	per of patients	i	Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) dosing	Daily (unsupervised) followed by twice- weekly (unsupervised) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
After treatr	ment completior	้า					-			
Kansoy et i	al, 1998									
	randomisation u									
Allocation	concealment un	nclear								
Blinding ur										
	id not follow the									
Loss to foll daily group	•	etween the two	arms: 3 of 18 patie	ents were exclude	d from the analys	sis in the daily followed	I by twice-weekly group for "p	oor compliance	", none were exc	luded from th
, , ,		or vary by more	e than dosing fregu	ency: that is, the	intervention studi	ed does not precisely	match the intervention of inte	rest		
			of interest (cure, tre							
⁹ GRADE ru	ule of thumb eve	ent number <30	00			,				
¹ Odds ratio	o and 95% confi	idence intervals	s not provided by a	uthors; calculated	by reviewer					
² Wide cont	fidence intervals	s			-					
³ Mean diffe	erence and 95%	6 confidence int	tervals not provided	d by authors; calc	ulated by reviewe	r; mean difference = (I	mean _{daily+twice-weekly} — mean _{daily})			
						e aminotransferase no				
⁵ Outcome	definition not pr	rovided								

¹⁵ Outcome definition not provided Abbreviations: CI, confidence interval; DOT, directly observed therapy; MD, mean difference; OR, odds ratio

Intervention: twice-weekly (DOT) dosing

Comparator: daily (unsupervised) followed by twice-weekly (DOT) dosing

Site of tuberculosis: cross-site

		Quali	ty assessment			Numbe	er of patients	Effe	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Twice-weekly (DOT) dosing	Daily (unsupervised) followed by twice- weekly (DOT) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (n	umber of death	s during the stu	dy; follow-up <12-2	24 months)						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	1/37 (2.7%) ⁸	1/39 (2.6%) ⁸	OR 1.06 (0.06 to 17.52) ⁹	0 more per 100 (from 2 fewer to 29 more)	VERY LOW
Response t	o treatment - n	narked respon	se (number of pati	ents with marked r	esponse to treatr	nent ¹² ; follow-up <12-2	24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,10}	serious ¹¹	very serious ^{6,7}	25/37 (67.6%) ⁸	28/39 (71.8%) ⁸	OR 0.82 (0.31 to 2.18) ⁹	4 fewer per 100 (from 28 fewer to 13 more)	VERY LOW
Response t	o treatment - n	noderate respo	onse (number of pa	atients with modera	ate response to tr	eatment ¹² ; follow-up <	12-24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,10}	serious ¹¹	very serious ^{6,7}	11/37 (29.7%) ⁸	3/39 (7.7%) ⁸	OR 5.08 (1.29 to 20.03) ⁹	22 more per 100 (from 2 more to 55 more)	VERY LOW

		Qual	ity assessment			Nur	nber of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Twice-weekly (DOT) dosing	Daily (unsupervised) followed by twice- weekly (DOT) dosing	Relative (95% CI)	Absolute (95% Cl)	Quality
Response	to treatment -	ooor response	(number of patient	s with poor respo	nse to treatment ¹²	; follow-up <12-24 r	months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,10}	serious ¹¹	very serious ^{6,7}	1/37 (2.7%) ⁸	1/39 (2.6%) ⁸	OR 1.06 (0.06 to 17.52) ⁹	0 more per 100 (from 2 fewer to 29 more)	VERY LOW
Relapse (n	umber to experi	ence clinical or	radiological recurre	ence; follow-up <1	2-24 months)					
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious6,7	0/35 (0%) ⁸	0/35 (0%) ⁸	OR 1.00 (0.02 to 51.81) ⁹	-	VERY LOW
Adverse ev	vents - side eff	ects requiring	modification of tre	eatment (number	of participants that	at experienced side	effects that required modification	tion of treatment; fo	llow-up <12-24 i	months)
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious6,7	0/37 (0%)	0/39 (0%)	OR 1.05 (0.02 to 54.45) ⁹	-	VERY LOW
Adverse ev	ents - hyperse	ensitivity react	ions (number of pa	rticipants that exp	erienced a hypers	sensitivity reaction;	follow-up <12-24 months)	,		
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/37 (0%)	0/39 (0%)	OR 1.05 (0.02 to 54.45) ⁹	-	VERY LOW
Adverse ev	vents - haemate	ologic effects	(number of participation	ants that experien	ced haematologic	effects; follow-up <	(12-24 months)	,		
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/37 (0%)	0/39 (0%)	OR 1.05 (0.02 to 54.45) ⁹	-	VERY LOW
 ³ Blinding u. ⁴ In addition regimen w ⁵ Follow-up ⁶ GRADE ru ⁷ Wide conf 	concealment un nclear n to the use of d vas not supervis varied consider ule of thumb even ïdence intervals	ifferent treatme sed except on th rably between p ent number <30	he day of medicatio participants	n collection		, , , , , , , , , , , , , , , , , , ,	rvised in the clinic, whereas th	ne daily part of the d	daily followed by	twice-weekly

⁹ Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer
 ¹⁰ Unclear length of follow-up
 ¹¹ Outcome is a substitute for the outcome of interest (cure, treatment success and treatment failure)

¹² See evidence table for criteria

Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

Intervention: twice-weekly (DOT) dosing

Comparator: daily (unsupervised) followed by twice-weekly (DOT) dosing

Site of tuberculosis: pulmonary

		Quali	ty assessment			Number of	patients	Effe	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) followed by twice- weekly (unsupervised) dosing	Daily (unsupervised) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (n	number of death	s during the stu	dy; follow-up <12-2	4 months)						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	1/20 (5%)	1/23 (4.3%)	OR 1.16 (0.07 to 19.80) ⁸	1 more per 100 (from 4 fewer to 43 more)	VERY LOW
Response	to treatment - n	narked respons	se (number of patie	ents with marked r	esponse to treatn	nent ¹¹ ; follow-up <12-24 mo	nths)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	serious ⁶	13/20 (65%)	16/23 (69.6%)	OR 0.81 (0.23 to 2.92) ⁸	5 fewer per 100 (from 35 fewer to 17 more)	VERY LOW
Response	to treatment - n	noderate respo	nse (number of pa	atients with modera	ate response to tr	eatment ¹¹ ; follow-up <12-24	I months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious6,7	1/20 (5%)	0/23 (0%)	OR 3.62 (0.14 to 93.85) ⁸	-	VERY LOW
Response	to treatment - p	oor response	(number of patients	s with poor respon	se to treatment11;	follow-up <12-24 months)				
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious6,7	1/20 (5%)	0/23 (0%)	OR 3.62 (0.14 to 93.85) ⁸	-	VERY LOW
Relapse (nu	umber to experie	ence clinical or r	adiological recurre	nce; follow-up <12	2-24 months)					
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/20 (0%)	0/23 (0%)	OR 1.15 (0.02 to 60.41) ⁸	-	VERY LOW
¹ Kumar et a	ai, 1990									

² Allocation concealment unclear

³ Blinding unclear

⁴ In addition to the use of different treatments, the two groups received different care: twice-weekly dosing was supervised in the clinic, whereas the daily part of the daily followed by twice-weekly regimen was not supervised except on the day of medication collection

⁵ Follow-up varied considerably between participants

⁶ GRADE rule of thumb event number <300

⁷ Wide confidence intervals

⁸ Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

⁹ Unclear length of follow-up

¹⁰ Outcome is a substitute for the outcome of interest (cure, treatment success and treatment failure)

¹¹ See evidence table for criteria

Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

Intervention: twice-weekly (DOT) dosing

Comparator: daily (unsupervised) followed by twice-weekly (DOT) dosing

Site of tuberculosis: **lymph node**

		Qual	ity assessment			Nu	umber of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Twice-weekly (DOT) dosing	Daily (unsupervised) followed by twice-weekly (DOT) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (r	number of death	is during the stu	dy; follow-up 15-24	I months)						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious6,7	0/15 (0%)	0/12 (0%)	OR 0.81 (0.01 to 43.60) ⁸	-	VERY LOW
Response	to treatment -	marked respon		ents with marked	response to treatr	nent ¹¹ ; follow-up 15	5-24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	serious ⁶	10/15 (66.7%)	8/12 (66.7%)	OR 1.00 (0.20 to 5.00) ⁸	0 fewer per 100 (from 38 fewer to 24 more)	VERY LOW
Response	to treatment -	moderate resp		atients with mode	rate response to tr	eatment11; follow-u	ip 15-24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	5/15 (33.3%)	3/12 (25%)	OR 1.50 (0.28 to 8.14) ⁸	8 more per 100 (from 16 fewer to 48 more)	VERY LOW
Response	to treatment -	poor response	(number of patient	s with poor respor	nse to treatment ¹¹	follow-up 15-24 m	ionths)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	0/15 (0%)	1/12 (8.3%)	OR 0.25 (0.01 to 6.64) ⁸	6 fewer per 100 (from 8 fewer to 29 more)	VERY LOW
Relapse (n	umber to experi	ence clinical or	radiological recurre	ence; follow-up 15	-24 months)					
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious6,7	0/15 (0%)	0/12 (0%)	OR 0.81 (0.01 to 43.60) ⁸	-	VERY LOW
 ³ Blinding u ⁴ In addition regimen v ⁵ Follow-up ⁶ GRADE ru 	concealment un inclear n to the use of d	ifferent treatmei sed except on th rably between p ent number <300	e day of medicatio articipants		t care: twice-week	ly dosing was supe	ervised in the clinic, whereas the	daily part of the da	aily followed by	twice-weekly

Wide confidence intervals

⁸ Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

⁹ Unclear length of follow-up
 ¹⁰ Outcome is a substitute for the outcome of interest (cure, treatment success and treatment failure)

¹¹ See evidence table for criteria

Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

Intervention: twice-weekly (DOT) dosing

Comparator: daily (unsupervised) followed by twice-weekly (DOT) dosing

Site of tuberculosis: disseminated

		Quali	ty assessment			Nu	mber of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Twice-weekly (DOT) dosing	Daily (unsupervised) followed by twice-weekly (DOT) dosing	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (n	umber of death	s during the stu	dy; follow-up <12-2	4 months)						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/2 (0%)	0/4 (0%)	OR 1.80 (0.03 to 121.71) ⁸	-	VERY LOW
Response t	o treatment - r	narked respon	se (number of patie	ents with marked r	esponse to treatm	nent ¹¹ ; follow-up <1	2-24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	serious ⁶	2/2 (100%)	4/4 (100%)	OR 0.56 (0.01 to 37.57) ⁸	-	VERY LOW
Response t	o treatment - r	noderate respo	onse (number of pa	tients with modera	ate response to tre	eatment ¹¹ ; follow-up	p <12-24 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	0/2 (0%)	0/4 (0%)	OR 1.80 (0.03 to 121.71) ⁸	-	VERY LOW
Response t	o treatment - p	oor response	(number of patients	with poor respon	se to treatment ¹¹ ;	follow-up <12-24 n	nonths)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	0/2 (0%)	0/4 (0%)	OR 1.80 (0.03 to 121.71) ⁸	-	VERY LOW
¹ Kumar et a ² Allocation o ³ Blinding un	concealment un	oclear								

⁴ In addition to the use of different treatments, the two groups received different care: twice-weekly dosing was supervised in the clinic, whereas the daily part of the daily followed by twice-weekly regimen was not supervised except on the day of medication collection

⁵ Follow-up varied considerably between participants

⁶ GRADE rule of thumb event number <300

⁷ Wide confidence intervals

⁸ Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

⁹ Unclear length of follow-up

¹⁰ Outcome is a substitute for the outcome of interest (cure, treatment success and treatment failure)

¹¹ See evidence table for criteria

Abbreviations: CI, confidence interval; DOT, directly observed therapy; OR, odds ratio

A.6 RQ K

A.6.1 People coinfected with tuberculosis and HIV

Rifabutin-containing regimens compared with the standard recommended regimen

Quality assessment No of patients Effect Quality Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifabutin- containing regimen (2HRbZE/4HRb)	Standard recommended regimen (2HRZE/4HR)	Relative (95% Cl)	Absolute		
Mortality	(follow-up 6 m	nonths; assess	ed with: number of	of deaths during	the study period)							
1 ¹	randomised trials	no serious risk of bias⁴	no serious inconsistency	no serious indirectness	very serious ^{5,6}	none	4/25 (16%)	2/25 (8%)	OR 2.19 (0.36 to 13.22) ³	8 more per 100 (from 5 fewer to 45 more)	LOW	
hanges	in signs and	symptoms –	radiographic cha	ange (follow-up 6	6 months; assess	ed with: number of	patients in whom ra	adiographic improv	ement was o	observed)		
1	randomised trials	no serious risk of bias ⁴	no serious inconsistency	no serious indirectness	very serious ^{5,6}	none	24/25 (96%)	25/25 (100%)	OR 0.32 (0.01 to 8.25) ³	-	LOW	
•		•	•			nber of patients to u ce of sputum produ	undergo sputum cor iction)	version, defined a	s 3 consecu	tive negative	sputum sn	nears and
1		no serious risk of bias ⁴	no serious inconsistency	serious ²	serious ⁶	none	22/25 (88%)	22/25 (88%)	OR 1.00 (0.18 to 5.51) ³	0 fewer per 100 (from 31 fewer to 10 more)	LOW	
² Substitu ³ Odds ra ⁴ Patients	were able to a	onfidence inter see the differe		ts, but they were	not informed abo	out their content; st	udy nurses and phy o not to be blinded v			quest informa	ation about	medication

⁵ Wide confidence interval

⁶ GRADE rule of thumb: <300 events

Ciprofloxacin-containing regimens compared with the standard recommended regimen

			Quality asse	essment			No of p	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin- containing regimen (4HRC/2HR)	Standard recommended regimen (2HRZE/2HRZ/ 2HR)	Relative (95% Cl)	Absolute	Quality	Importance
Relapse	(follow-up 12 r	months (6 mor	ths after treatmen	t completion); as	sessed with: nun	nber of patients to	experience culture-	confirmed relapse)				
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,6}	no serious indirectness	very serious ^{7,8}	none	4/26 (15.4%)	0/32 (0%)	OR 13.00 (0.67 to 253.61) ⁹	-	VERY LOW	
Respons	se to treatmen	t – culture co	nversion (follow-	up 12 months (6	months after trea	tment completion);	; measured with: tim	e to first negative	test results;	better indicat	ed by lowe	r values)
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,6}	serious ¹⁰	no serious imprecision ¹¹	none	26	32	-	MD 0.9 higher ^{12,13}	VERY LOW	
² Unblind ³ Precise	y et al 1996 ed, except for definition of ou	utcome not pro	ovided, and it is un	nclear if the meth	od used to deterr	nine the outcome v	vas valid and reliab	'e				

⁴ Unclear if the groups were comparable at baseline
 ⁵ Unclear the comparison groups received the same care apart from the interventions studied
 ⁶ Unclear if the groups were comparable for treatment completion and availability of outcome data

			Quality asse	essment			No of p	atients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin- containing regimen (4HRC/2HR)	Standard recommended regimen (2HRZE/2HRZ/ 2HR)	Relative (95% Cl)	Absolute	Quality	Importance
⁷ Wide co	onfidence inter	val										
⁸ GRADE	rule of thumb	: <300 events										
⁹ Odds ra	atio and 95% c	onfidence inte	rval not provided b	by authors; calcu	lated by reviewe	r						
¹⁰ Substit	tute outcome											
¹¹ Unable	to calculate c	confidence inte	rval; insufficient da	ata								
¹² Mean o		provided by au	uthors; calculated l	by reviewer								

 $^{13} p = 0.0003$

Non-rifampicin-containing regimens compared with rifampicin-containing regimens

			Quality asse	essment			No of p	atients	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency		Imprecision	Other considerations	Non-rifampicin- containing regimens	Rifampicin- containing regimens	Relative (95% CI)	Absolute	Quality	Importance
Mortality	(univariate ana		w-up 1 years; asse		er of deaths duri	ng study period)						
1 ¹	observational studies ²	serious ^{3,4}	very serious ^{5,6,7}	serious ⁸	no serious imprecision ⁹	none	-	-	OR 1.82 (1.17 to 2.84) ¹⁰	-	VERY LOW	
Mortality	(multivariate a	nalysis) (foll	low-up 1 years; as	sessed with: nun	nber of deaths du	uring study period)						
1 ¹	observational studies ²	serious ^{3,4}	very serious ^{5,6,7}	serious ⁸	no serious imprecision ⁹	none	-	-	OR 1.21 (0.74 to 1.97) ^{11,12}	-	VERY LOW	
² Prospec		• •	atment groups is r	elated to potentia	al confounding fa	octors			,			

⁴ Unclear if blinded, though unlikely

⁵ Unclear if the groups were comparable at baseline

⁶ Unclear the comparison groups received the same care apart from the interventions studied

⁷ Unclear if the groups were comparable for treatment completion and availability of outcome data

⁸ Unclear if the intervention exactly matches the intervention of interest, details provided are limited

⁹ Unclear if GRADE rule of thumb (300 events) met

 $^{10} p = 0.0079$

¹¹ 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 ¹² p = 0.447

Ethambutol-containing continuation phase compared with the standard recommended regimen

			Quality asses	sment		No of	patients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	continuation	Standard recommended regimen		Absolute	Quality	Importance

Mortality (2HRZE₇/6HE₇ or 2HRZE₃/6HE₇ compared to 2HRZE₇/4HR₇) (follow-up 12 months after treatment completion; assessed with: number of deaths)

			Quality asse	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ethambutol- containing continuation phase	Standard recommended regimen	Relative (95% Cl)	Absolute	Quality	Importance
1 ¹	randomised trials ²	serious ⁴	serious ^{17,18}	very serious ^{19,20}	serious ¹²	none	13/90 (14.4%)	4/37 (10.8%)	OR 1.39 (0.52 to 4.59) ¹³	4 more per 100 (from 6 fewer to 25 more)	VERY LOW	
	(2HRZE7/6HE7	compared to 2		ow-up 12 months	s after treatment	completion; assess	ed with: number	of deaths)				
1 ¹	randomised trials ²	serious ⁴	serious ^{17,18}	very serious ^{19,20}	very serious ^{12,21}	none	10/45 (22.2%)	4/37 (10.8%)	OR 2.36 (0.67 to 8.25) ¹³	11 more per 100 (from 3 fewer to 39 more)	VERY LOW	
			RZE/6HR or 2HR			ssed with: number of						
1 ¹⁶	observational studies ²	very serious ^{3,4,5}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	27/136 (19.9%)	113/413 (27.4%)	OR 0.66 (0.41 to 1.06) ¹³	7 fewer per 100 (from 14 fewer to 1 more)	VERY LOW	
	(2HRZE/6HE c	compared to 2H	RZE/6HR) (follow			er of deaths)						
1 ¹⁶	observational studies ²	very serious ^{3,4,5}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	27/136 (19.9%)	62/266 (23.3%)	OR 0.82 (0.49 to 1.35) ¹³	3 fewer per 100 (from 10 fewer to 6 more)	VERY LOW	
Treatme	nt failure (2HR2	ZE/6HE compar	red to 2HRZE/6HF	R or 2HRZE/4HR) (follow-up 2 yea	ars; assessed with:	number of patier	nts to experience t	reatment fai			
1 ¹⁶	observational studies ²	very serious ^{3,4,5,14}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	8/136 (5.9%)	12/413 (2.9%)	OR 2.09 (0.84 to 5.22) ¹³	3 more per 100 (from 0 fewer to 11 more)	VERY LOW	
Treatme	nt failure (2HR2	ZE/6HE compar	red to 2HRZE/6HF	R) (follow-up 2 ye	ars; assessed w	ith: number of patie	nts to experience	e treatment failure)			
1 ¹⁶	observational studies ²	very serious ^{3,4,5,14}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	8/136 (5.9%)	7/266 (2.6%)	OR 2.31 (0.82 to 6.52) ¹³	3 more per 100 (from 0 fewer to 12 more)	VERY LOW	
						sed with: number o	f patients to expe	erience relapse, de	efined as the	e developmer	nt of active	tuberculosis
after suce	cessful completi observational		course of treatmer verv	nt during 24 mont serious ^{10,11}	hs of follow-up a serious ¹²	none	23/136	30/413	OR 2.60	10 more	VERY	
	studies ²	serious ^{3,4,5}	serious ^{6,7,8,9}	SCHOUS -	SCHUUS	none	(16.9%)	(7.3%)	(1.45 to 4.65) ¹³	per 100 (from 3 more to 19 more)	LOW	
			RZE/6HR) (follow- ent during 24 mon			er of patients to exp	erience relapse,	defined as the de	velopment o	f active tuber	culosis afte	r successful
1 ¹⁶	observational studies ²		very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	23/136 (16.9%)	14/266 (5.3%)	OR 3.66 (1.82 to	12 more per 100	VERY LOW	

			Quality asses	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ethambutol- containing continuation phase	Standard recommended regimen	Relative (95% Cl)	Absolute	Quality	Importance
									7.38) ¹³	(from 4 more to 24 more)		
			e outcome (2HRZ			red to 2HRZE ₇ /4HF	R ₇) (follow-up 12	months after treat	ment comple	etion; assess	ed with: nu	mber of
1 ¹	randomised trials ²	serious ⁴	serious ^{17,18}	very serious ^{19,20,15}	very serious ^{12,21}	none	13/90 (14.4%)	1/37 (2.7%)	OR 6.08 (0.77 to 48.27) ¹³	12 more per 100 (from 1 fewer to 55 more)	VERY LOW	
Respons		- culture conve	ersion (2HRZE/6	HE compared to	2HRZE/6HR or 2	2HRZE/4HR) (follow	-up 2 years; ass	essed with: numbe	er of patients	,	e-negative	after 2 months
1 ¹⁶	observational studies ²	very serious ^{3,4,5,14}	very serious ^{6,7,8,9}	very serious ^{10,11,15}	serious ¹²	none	101/136 (74.3%)	364/413 (88.1%)	OR 0.39 (0.24 to 0.63) ¹³	14 fewer per 100 (from 6 fewer to 24 fewer)	VERY LOW	
	ce - treatment	completion (2H	IRZE/6HE compa	red to 2HRZE/6H		R) (follow-up 2 year	rs; assessed witl	n: number of patier		,		
16	observational studies ²	very serious ^{3,4,5,14}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	89/136 (65.4%)	317/413 (76.8%)	OR 0.57 (0.39 to 0.87) ¹³	11 fewer per 100 (from 3 fewer to 20 fewer)	VERY LOW	
dheren	ce - treatment	completion (2F	IRZE/6HE compa	red to 2HRZE/6H	R) (follow-up 2	years; assessed wit	h: number of pat	ients to complete	therapy)	20.000.)		
16	observational studies ²	very serious ^{3,4,5,14}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	89/136 (65.4%)	195/266 (73.3%)	OR 0.69 (0.44 to 1.08) ¹³	8 fewer per 100 (from 19 fewer to 1 more)	VERY LOW	
 ² Prospect ³ Unclear ⁴ Unclear ⁵ Attempt ⁵ Groups ⁵ Groups was dir ³ Groups 2HRZE 	if method of allo r if blinded, thoug ts were not made were not compa- total white blood did not receive rectly observed not followed up 5/6HE group	gh unlikely e within the des arable at baselir cell counts the same care a for an equal an	ign or analysis to ne - 2HRZE/4HR g apart from the inte d appropriate leng	balance the grou group were signif rvention(s) studi gth of time - med	ips for potential c icantly older, 2Hi ed - rifampicin re ian follow-up in tl	ors - allocation was confounders RZE/6HR group had gimens (2HRZE/4H he 2HRZE/4HR gro ompleted treatment	d significantly hig IR and 2HRZE/6 up was 512 day:	ther levels of haer HR) were self-adn 5, 533 days in the	ninistered, no 2HRZE/6HR	on-rifampicin group, and	regimen (2 661 days in	PHRZE/6HE)

65% completed treatment in the 2HRZE/6HE group ¹⁰ Population appears to match the population of interest, although unclear if there was any drug resistance at baseline ¹¹ 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) ¹² GRADE rule of thumb: <300 events

			Quality asses	ssment			No of	patients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ethambutol- containing continuation phase	Standard recommended regimen	Relative (95% Cl)	Absolute	Quality	Importance
			al not provided by		ed by reviewer							
		precise definiti	on of the outcome	9								
	ute outcome											
	a et al, 2006											
			baseline as basel			/ HIV status						
,	,		on, though rates v	•	U ,							
¹⁹ Popula	tion may not exa	actly match the	population of inter	rest: some drug r	esistance at bas	eline, although uncl	lear if any within	the HIV subgroup	as baseline	characteristi	cs not repo	rted by HIV
status												
	-				-	e than the combina		0 0				
	longer than tho le, whereas all	se with an R-co	ntinuation phase,	and some patien	ts receiving an E	-continuation phas	e had an initial d	osing schedule of	3-times wee	kly and som	e had a dai	ly dosing
²¹ Wide c	onfidence interv	al										
²² Failure	was defined as	a culture of 20	or more colonies	at month 6 or 8, o	or a change of tre	eatment by the loca	l investigator ow	ing to treatment fa	ilure			

²³ 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

A.6.2 People with tuberculosis and liver disease

Fluoroquinolone-containing regimen compared with rifampicin-containing regimen

			Quality asses	sment			No of pat	ients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone -containing regimen	Rifampicin- containing regimen	Relative (95% CI)	Absolute	Quality	Importance
Mortality	- all-cause (2H	ZEO/10HEO co		E/7HR) (follow-u	p 3 months after	treatment was stop	ped; assessed with:	number of pati	ents to die	from any cau	se)	
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5}	serious ⁶	very serious ^{7,8}	none	1/16 (6.3%) ⁹	0/15 (0%)	OR 3.00 (0.11 to 79.50) ¹⁰	-	VERY LOW	
Mortality	- tuberculosis	-related (2HZE)	O/10HEO compare	ed with 2HRE/7H	HR) (follow-up 3 r	months after treatme	ent was stopped; as	sessed with: nu	mber of tub	erculosis-rela	ated deaths	S)
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5}	serious ⁶	very serious ^{7,8}	none	0/16 (0%)	0/15 (0%)	OR 0.94 (0.02 to 50.32) ¹⁰	-	VERY LOW	
Mortality	- hepatotoxicit	ty-related (2HZ	EO/10HEO compa	ared with 2HRE/	7HR) (follow-up 3	3 months after treat	ment was stopped; a	ssessed with: r	number of h	epatotoxicity	-related de	aths)
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5}	serious ⁶	very serious ^{7,8}	none	0/16 (0%)	0/15 (0%)	OR 0.94 (0.02 to 50.32) ¹⁰	-	VERY LOW	
							nent was stopped; as clusion of superimpo			atients to exp	erience he	patotoxicity,
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5}	serious ⁶	serious ⁸	none	0/16 (0%)	4/15 (26.7%)	OR 0.08 (0.00 to 1.58) ¹⁰	24 fewer per 100 (from 27 fewer to 10 more)	VERY LOW	

Adverse events - hepatotoxicity (HRbAOL compared with HRZS/E) (follow-up unclear; assessed with: number of patients to experience liver dysfunction, defined as ALT >1336 IU/L 2-3 months

			Quality asses	sment			No of pat	ents	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone -containing regimen		Relative (95% CI)		Quality	Importance
after initia	tion of antituber	culosis chemot	herapy)		_							_
1 ¹¹	observationa I studies ¹²	very serious ^{13,14,15} , ¹⁶	serious ^{5,17,18}	serious ¹⁹	serious ²⁰	none	7/23 (30.4%)	19/24 (79.2%)	OR 0.12 (0.03 to 0.43) ¹⁰	48 fewer per 100 (from 17 fewer to 69 fewer)	VERY LOW	

¹ Saigal et al, 2001

² Unclear if there was adequate concealment of allocation

³ Unblinded

⁴ Groups not comparable at baseline - 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

⁵ Unclear if groups received the same care apart from the intervention(s) studied; limited details provided

⁶ 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

⁷ Wide confidence interval

⁸ GRADE rule of thumb: <300 events

⁹ Death resulted from intracranial bleeding unrelated to the antituberculosis chemotherapy during the follow-up

¹⁰ Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer

¹¹ Pan et al, 2005

¹² Prospective

¹³ Unclear if method of allocation to treatment groups is related to potential confounding factors

¹⁴ Blinding unclear

¹⁵ Attempts were not made within the design or analysis to balance the groups for potential confounders

¹⁶ Unclear if follow-up was for an appropriate period of time

¹⁷ Groups appear to be comparable at baseline - authors state that the 'general conditions of the 2 groups were not distinguishable (p > 0.05)', although no further details are provided

¹⁸ Unclear if groups were followed up for an equal length of time

¹⁹ 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)

²⁰ GRADE rule of thumb: <300 events

A.7 RQ L

A.7.1 Duration of treatment in adults with respiratory tuberculosis

SMEAR-POSITIVE, CULTURE-POSITIVE

4 vs 6 months

Age: mix

HIV status: not specified - negative?

Disease status: smear- and culture-positive

Site of disease: pulmonary

Drug sensitivity: susceptible only

		Quality asse	essment			Number o	of patients	Eff	iect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality
Response to treatm	ent - favourable	status (assessed	with: number of s	mear-positive cul	ture-positive patie	nts to achieve a fa	avourable status a	at the end of treat	ment)	
1 ¹	randomised trials	very serious ^{2,3}	serious ⁴	serious ^{5,6}	serious ⁷	161/161 (100%)	169/169 (100%)	OR 0.95 (0.02 to 48.31) ⁸	-	VERY LOW
Relapse (follow-up 5	to 8 years after tr			umber of smear-p	ositive culture-po	sitive patients to e	experience relapse	e ⁹)		
1 ¹	randomised trials	very serious ^{2,3}	serious ^{4,10}	serious ^{5,6}	very serious ^{7,11}	20/131 (15.3%)	3/138 (2.2%)	OR 8.11 (2.35 to 28) ⁸	13 more per 100 (from 3 more to 36 more)	VERY LOW
 ¹ Singapore TB Servi ² Blinding unclear ³ Analysis is not inter ⁴ Unclear if the loss to ⁵ Intervention does no ⁶ Population does no ⁷ Wide confidence int ⁸ Odds ratio and 95% ⁹ See evidence table ¹⁰ Unclear if length of ¹¹ GRADE rule of thu Abbreviations: CI, co 	t-to-treat of ollow-up was si of exactly match th ervals of confidence inten for the full definiti follow-up period mb: <300 events	milar in the 2 grou he intervention of e population of ini vals calculated by on was the same in t	ups interest: did not c terest: unclear if c reviewer			ecommended drug	gs			

3 vs 4.5 months

Age: mix

HIV status: not specified - negative?

Disease status: smear-positive, culture-positive

Site of disease: pulmonary

Drug sensitivity: unclear

	Quality asse	essment			Number o	of patients	Eff	fect	
				Relative Absolut				Absolute	
Number of studies Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4.5 months	(95% CI)	(95% CI)	Quality

Response to treatment - culture status (intent-to-treat) (assessed with: number of smear-positive, culture-positive patients to be culture-negative at the end of treatment)

		Quality as	sessment			Numbe	er of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4.5 months	(95% CI)	(95% CI)	Quality
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	very serious ^{6,7,12}	very serious ^{8,9}	58/91 (63.7%)	68/89 (76.4%)	OR 0.54 (0.28 to 1.04) ¹⁰	13 fewer per 100 (from 29 fewer to 1 more)	VERY LOW
Response to treatment	ent - culture st	atus (among tho	se that completed	treatment) (ass	essed with: numbe	er of smear-pos	itive, culture-positiv	ve patients to be cu	Ilture-negative at	the end of
1 ¹	randomised trials	very serious ^{2,3,4,11}	serious⁵	very serious ^{6,7,12}	very serious ^{8,9}	58/58 (100%)	68/68 (100%)	OR 0.85 (0.02 to 43.72) ¹⁰	-	VERY LOW
Changes in signs a appearance 6 month			radiographic stat	us (assessed wit	h: number of smea	ar-positive, cultu	ure-positive patient	s to experience de	terioration in radio	ographic
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	very serious ^{8,9}	0/91 (0%)	0/89 (0%)	OR 0.98 (0.02 to 49.83) ¹⁰	-	VERY LOW
Changes in signs and 6 months after treatm		- no change in ra	diographic status	(assessed with:	number of smear-	positive, culture	-positive patients to	o experience no ch	ange in radiograp	phic appearance
1 ¹	randomised trials	serious ^{2,3,4}	serious ⁵	serious ^{6,12}	very serious ^{8,9}	0/91 (0%)	1/89 (1.1%)	OR 0.32 (0.01 to 8.02) ¹⁰	1 fewer per 100 (from 1 fewer to 7 more)	VERY LOW
Changes in signs a radiographic appeara				raphic status (a	ssessed with: num	ber of smear-po	ositive, culture-posi	tive patients to exp	perience moderate	e improvement in
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	serious ⁹	31/91 (34.1%)	39/89 (43.8%)	OR 0.66 (0.36 to 1.21) ¹⁰	10 fewer per 100 (from 22 fewer to 5 more)	VERY LOW
Changes in signs a radiographic appeara				phic status (ass	essed with: numbe	er of smear-posi	tive, culture-positiv	e patients to exper	/	provement in
1 ¹	randomised trials	serious ^{2,3,4}	serious ⁵	serious ^{6,12}	serious ⁹	24/91 (26.4%)	24/89 (27%)	OR 0.97 (0.5 to 1.88) ¹⁰	1 fewer per 100 (from 11 fewer to 14 more)	VERY LOW
Changes in signs a radiographic appeara				phic status (ass	essed with: numbe	er of smear-posi	itive, culture-positiv	e patients to exper	ience marked im	provement in
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	serious ⁹	19/91 (20.9%)	15/89 (16.9%)	OR 1.30 (0.61 to 2.76) ¹⁰	4 more per 100 (from 6 fewer to 19 more)	VERY LOW
Changes in signs a radiographic appeara				phic status (ass	essed with: numbe	er of smear-posi	tive, culture-positiv	e patients to exper	ience marked im	provement in
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	serious ⁹	20/91 (22%)	16/89 (18%)	OR 1.29 (0.62 to 2.68) ¹⁰	4 more per 100 (from 6 fewer to 19 more)	VERY LOW
Adverse events lead	•				· ·		•	0		,
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	very serious ^{8,9}	5/91 (5.5%)	2/89 (2.2%)	OR 2.53 (0.48 to 13.39) ¹⁰	3 more per 100 (from 1 fewer to 21 more)	VERY LOW

		Quality ass	essment			Numbe	r of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4.5 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Adherence – treatmo	ent default (ass	essed with: numbe	er of smear-positiv	e, culture-positive	e patients to defau	ılt ¹³)				
11	randomised trials	serious ^{2,3,4}	serious⁵	serious ^{6,12}	serious ⁹	8/91 (8.8%)	7/89 (7.9%)	OR 1.13 (0.39 to 3.26) ¹⁰	1 more per 100 (from 5 fewer to 14 more)	VERY LOW
Relapse (follow-up 1	year after treatm	nent completion; a	ssessed with: num	ber of smear-pos	sitive, culture-posit	tive patients to	experience relapse	13)		
1 ¹	randomised trials	serious ^{2,3,4}	serious ⁵	serious ^{6,12}	very serious ^{8,9}	1/91 (1.1%)	1/89 (1.1%)	OR 0.98 (0.06 to 15.88) ¹⁰	0 fewer per 100 (from 1 fewer to 14 more)	VERY LOW
Mehotra et al, 1982 Method of randomis Allocation concealm Blinding unclear	ation unclear									

6 vs 8 months

Age: unclear

HIV status: not specified - negative?

Disease status: smear- and culture-positive (?), symptomatic

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asse	ssment			Number o	of patients	Eff	ect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	8 months	(95% CI)	(95% CI)	Quality
Relapse (follow-up 1	2 months after tre	atment completion	n; assessed with:	number of smear-	positive, culture-p	ositive patients to	experience relap	se)		
1 ¹	randomised	very	serious ¹⁰	serious6,7	serious ⁸	1/97	3/96	OR 0.32 (0.03	2 fewer per	VERY LOW
	trials	serious ^{2,3,4,5}				(1%)	(3.1%)	to 3.16) ⁹	100 (from 3	

		Quality ass	essment			Number	r of patients		Effect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	8 months	(95% CI)	(95% CI)	Quality
									fewer to 6 more)	
 ¹ Nayar et al, 1988 ² Method of randomis ³ Allocation concealm ⁴ Blinding unclear ⁵ Analysis does not fc ⁶ Unclear if population ⁷ Intervention does not ⁸ GRADE rule of thun ⁹ Odds ratio and 95% ¹⁰ Follow-up began fro Abbreviations: CI, col 	ent unclear nincludes childre ot exactly match t nb: <300 events confidence inter om treatment initi	n he intervention of vals calculated by ation; therefore, a	reviewer			Ū	ent lengths			

SMEAR-POSITIVE, MIXED/UNSPECIFIED CULTURE

3 vs 6 months

Age: mix

HIV status: not specified - negative?

Disease status: smear-positive \rightarrow negative, culture not specified

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asse	essment			Number o	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	6 months	Relative (95% CI)	Absolute (95% CI)	Quality
Response to treatm treatment)	ent - culture stat	us (assessed with	n: number of initia	lly smear-positive	patients who were	e smear-negative	after 8 weeks of t	reatment to be cu	Iture-negative at t	he end of
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,9,14,15}	very serious ^{10,11}	56/56 (100%)	70/70 (100%)	OR 0.80 (0.02 to 41.03) ¹²	-	VERY LOW
Changes in signs an treatment to experien				· ·		r of initially smear	-positive patients	who were smear-	negative after 8 w	eeks of
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,14,15}	serious ¹⁰	36/56 (64.3%)	57/70 (81.4%)	OR 0.52 (0.23 to 1.2) ¹²	12 fewer per 100 (from 31 fewer to 3 more)	VERY LOW
Changes in signs an to experience slight in					ed with: number c	of initially smear-p	ositive patients wh	no were smear-ne	gative after 8 wee	ks of treatment

		Quality ass	essment			Numbe	er of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	6 months	Relative (95% CI)	Absolute (95% CI)	Quality
11	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,14,15}	serious ¹⁰	9/56 (16.1%)	9/70 (12.9%)	OR 1.30 (0.48 to 3.53) ¹²	3 more per 100 (from 6 fewer to 21 more)	VERY LOW
Changes in signs a experience no change					number of initially	smear-positive	patients who were	e smear-negative af	ter 8 weeks of tre	eatment to
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,14,15}	serious ¹⁰	2/56 (3.6%)	4/70 (5.7%)	OR 0.61 (0.11 to 3.46) ¹²	2 fewer per 100 (from 5 fewer to 12 more)	VERY LOW
Changes in signs a experience deteriora					h: number of initia	ally smear-positiv	ve patients who w	vere smear-negative	after 8 weeks of	treatment to
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,14,15}	very serious ^{10,11}	6/56 (10.7%)	0/70 (0%)	OR 18.15 (0.9995 to 329.54) ¹²	-	VERY LOW
Relapse (follow-up 1		reatment initiation;	assessed with: nu	umber of initially	smear-positive pa				tment to experier	
1 ¹	randomised trials	very serious ^{2,3,4,5}	very serious ^{6,7,13}	very serious ^{8,14,15}	very serious ^{10,11}	12/56 (21.4%)	1/70 (1.4%)	OR 18.82 (2.36 to 149.85) ¹²	20 more per 100 (from 2 more to 67 more)	VERY LOW
 Research Committe Method of randomi. Allocation concealn Blinding unclear Analysis is not inten Comparability of parability of parabil	sation unclear nent unclear nt-to-treat tients at baseline lost to follow-up ot exactly match itute for an outco inter of an outco inter solo events ntervals % confidence inte for treatment ini ot exactly match consistent with th	e unclear in each group is u the intervention of ome of interest ervals calculated b tiation; therefore, a the population of i nose recommende	nclear f interest: did not c y reviewer as different duratio nterest: may includ	ns of treatment v de some children	vere used, follow-	up was for differ	J			

6 vs 9 months

Age: mix

HIV status: unspecified - negative?

Disease status: smear-positive

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality ass	essment			Number of	of patients	Eff	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Cure (assessed with	: number of sputu	m-smear-positive	patients to be sm	ear-negative in th	e last month of tre	atment and on at	least one previou	is occasion)		
11	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁶	25/93 (26.9%)	19/107 (17.8%)	OR 1.73 (0.88 to 3.4) ⁷	9 more per 100 (from 2 fewer to 25 more)	VERY LOW
Treatment failure (a	ssessed with: nur	mber of sputum-si	mear-positive patie	ents to be smear-	positive at 5 mont	ns or later during	treatment)			
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	very serious ^{6,8}	0/93 (0%)	1/107 (0.93%)	OR 0.38 (0.02 to 9.43) ⁷	1 fewer per 100 (from 1 fewer to 7 more)	VERY LOW
Bacteriological rela	pse (assessed wi	ith: number of spu	tum-smear-positiv	ve patients to expe	erience bacteriolog	gical relapse)				
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	very serious ^{6,8}	5/93 (5.4%)	0/107 (0%)	OR 13.36 (0.73 to 244.96) ⁷	-	VERY LOW
 ¹ Ziaullah et al, 2004 ² Method of randomis ³ Allocation concealn ⁴ Blinding unclear ⁵ Population does no 	sation unclear nent unclear	o non-dation of in		ildron (220/ acad	E to 11 years 22	2/ ared 15 to 20 v	(0070)			

⁵ Population does not exactly match the population of interest: includes children (33% aged 5 to 14 years, 33% aged 15 to 29 years) ⁶ GRADE rule of thumb: <300 events

⁷ Odds ratio and 95% confidence intervals calculated by reviewer

⁸ Wide confidence intervals

⁹ Analysis did not follow intent-to-treat principle Abbreviations: CI, confidence interval; OR, odds ratio

CULTURE-POSITIVE, MIXED/UNSPECIFIED SMEAR, CAVITATORY

9 vs 18 months

Age: mix

HIV status: not specified – negative?

Disease status: culture-positive, cavitatory

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality ass	essment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Treatment failure (a	ssessed with: nur	mber of culture-po	sitive patients with	n cavities >2 cm to	o experience treat	ment failure ¹)				
1 ²	randomised trials	serious ^{3,4,5}	no serious inconsistency	very serious6,7	very serious ^{8,9}	0/187 (0%)	0/194 (0%)	1.04 (0.02 to 52.55) ¹⁰	-	VERY LOW
'Alive and well' (ass	essed with: numb	per of culture-posit	tive patients with c	avities >2 cm to b	e considered aliv	e and well after 5	4 months of follow	v-up ¹)		
1 ²	randomised trials	serious ^{3,4,5}	serious ¹¹	very serious ^{6,7,12}	serious ⁹	116/187 (62%)	108/194 (55.7%)	OR 1.30 (0.86 to 1.96) ¹⁰	6 more per 100 (from 4 fewer to 15 more)	VERY LOW
Relapse (follow-up 5	4 months; assess	sed with: number of	of culture-positive	patients with cavit	ties >2 cm to expe	erience relapse ¹)				
1 ²	randomised trials	serious ^{3,4,5}	serious ¹¹	very serious6,7	very serious ^{8,9}	0/187 (0%)	0/194 (0%)	1.04 (0.02 to 52.55) ¹⁰	-	VERY LOW
 ¹ See evidence table ² British Thoracic Sod ³ Method of randomis ⁴ Allocation concealn ⁵ Radiographer blinde ⁶ Intervention does no ⁷ Population does no ⁸ Wide confidence intervention 	ciety, 1975/80 sation unclear nent possible - "ra ed to treatment al ot exactly match th t exactly match th	andom allocations location, but uncle the intervention of	ear if to prognostic interest: does not	factors or if other contain all of or ju	, investigators we ust the 4 standard	recommended d	0	ria = 15 to 70 year	s)	

⁹ GRADE rule of thumb: <300 events

¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer
 ¹¹ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹² Outcome is a substitute for an outcome of interest

Abbreviations: CI, confidence interval; OR, odds ratio

CULTURE-POSITIVE, MIXED/UNSPECIFIED SMEAR, NON-CAVITATORY

6 vs 12 months

Age: mix

HIV status: not specified - negative?

Disease status: culture-positive, non-cavitatory

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asso	essment			Number o	of patients	Efi	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	12 months	(95% CI)	(95% CI)	Quality
Treatment failure (a	ssessed with: nur	nber of culture-po	sitive patients with	nout HIV or cavitie	es or no cavity >2	cm to experience	treatment failure1)		
1 ²	randomised trials	serious ^{3,4,5}	no serious inconsistency	very serious6,7	very serious ^{8,9}	1/214 (0.47%)	0/217 (0%)	OR 3.06 (0.12 to 75.45) ¹⁰	-	VERY LOW
Alive and well' (ass	essed with: numb	er of culture-posit	ive patients without	ut HIV or cavities	or no cavity >2 cm	to be considered	alive and well aff	ter 54 months of f	ollow-up1)	
1 ²	randomised trials	serious ^{3,4,5}	serious ¹¹	very serious ^{6,7,12}	serious ⁹	129/214 (60.3%)	140/217 (64.5%)	OR 0.83 (0.57 to 1.23) ¹⁰	4 fewer per 100 (from 14 fewer to 5 more)	VERY LOW
Relapse (follow-up 5	4 months; assess	ed with: number of	of culture-positive	patients without H	IV or cavities or n	o cavity >2 cm to	experience relaps	se ¹)		
12	randomised trials	serious ^{3,4,5}	serious ¹¹	very serious ^{6,7}	very serious ^{8,9}	9/214 (4.2%)	2/217 (0.92%)	OR 4.72 (1.01 to 22.11) ¹⁰	3 more per 100 (from 0 more to 16 more)	VERY LOW
¹ See evidence table ² British Thoracic Soc ³ Method of randomis	ciety, 1975/80	on								

³ Method of randomisation unclear

⁴ Allocation concealment possible - "random allocations of treatment were made centrally by coordinators"

⁵ Radiographer blinded to treatment allocation, but unclear if to prognostic factors or if other investigators were blinded

⁶ Intervention does not exactly match the intervention of interest: does not contain all of or just the 4 standard recommended drugs

⁷ Population does not exactly match the population of interest: 3.4% drug resistance at baseline, and may include some children (inclusion criteria = 15 to 70 years)

⁸ Wide confidence intervals

⁹ GRADE rule of thumb: <300 events

¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer

¹¹ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹² Outcome is a substitute for an outcome of interest

Abbreviations: CI, confidence interval: OR, odds ratio

CULTURE-POSITIVE, MIXED/UNSPECIFIED SMEAR

6 vs 9 months

Age: adult-only

HIV status: not specified – negative?

Disease status: culture-positive

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality ass	essment			Numbe	r of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Response to treatm	ent - culture st	atus (assessed wi		re-positive patier	nts to be culture-n	egative after 6 n	nonths of treatmer	nt)		
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	very serious9,10	serious ¹¹	287/287 (100%)	157/157 (100%)	OR 1.83 (0.04 to 92.44) ¹²	-	VERY LO
Relapse (follow-up a	minimum of 3 y	ears after treatme	nt completion; asse	essed with: numb	er of culture-posit	tive patients to e	xperience relapse)		
1	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	very serious ^{11,13}	6/287 (2.1%)	2/157 (1.3%)	OR 1.65 (0.33 to 8.3) ¹²	1 more per 100 (from 1 fewer to 8 more)	VERY LO
Adverse events req reatment)	uiring modifica	tion or withdrawa	al of treatment (as	sessed with: nun	nber of culture-po	sitive patients to	experience an ac	lverse event requiri	ng modification o	r withdrawal
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	serious ¹³	19/344 (5.5%)	7/177 (4%)	OR 1.42 (0.59 to 3.44) ¹²	2 more per 100 (from 2 fewer to 8 more)	VERY LO
Adverse events - he	patic (assessed	d with: number of c	ulture-positive pat	ients to experience	e a hepatic adve	rse event)			·	
1	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	serious ¹³	14/287 (4.9%)	7/157 (4.5%)	OR 1.10 (0.43 to 2.78) ¹²	0 more per 100 (from 2 fewer to 7 more)	VERY LO
Adverse events - ra	sh (assessed wi	ith: number of cult	ure-positive patient	ts to experience r	ash)					
11	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	very serious ^{11,13}	13/287 (4.5%)	1/157 (0.64%)	OR 7.40 (0.96 to 57.12) ¹²	4 more per 100 (from 0 fewer to 26 more)	VERY LO
Adverse events - ar	thralgia (assess	sed with: number c			ence arthralgia)					
1	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	very serious ^{11,13}	2/287 (0.7%)	0/157 (0%)	OR 2.76 (0.13 to 57.82) ¹²	-	VERY LO
dherence - treatm	ent default (ass	essed with: number	er of culture-positiv	e patients to defa	ault treatment)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	serious ⁹	serious ¹³	11/344 (3.2%)	4/177 (2.3%)	OR 1.43 (0.45 to 4.55) ¹²	1 more per 100 (from 1 fewer to 7 more)	VERY LO

		Quality asse	essment			Number o	of patients	Eff	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Adherence - isoniaz	id metabolites (a	ssessed with: nu	mber of urine sam	ples from culture	-positive patients	hat were positive	for isoniazid met	abolites ¹⁴)		
11	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	very serious ^{9,10}	no serious imprecision	1334/1379 (96.7%)	1128/1166 (96.7%)	OR 1.00 (0.64 to 1.55) ¹²	0 fewer per 100 (from 2 fewer to 1 more)	VERY LOW
 ² Method of randomis ³ Allocation concealm ⁴ Blinding unclear ⁵ Analysis did not follo ⁶ Unclear if groups ref ⁷ Unclear if the group ⁸ High attrition rate w ⁹ Intervention does no ¹⁰ Outcome is a subs ¹¹ Wide confidence in ¹² Odds ratio and 959 ¹³ GRADE rule of thu ¹⁴ See evidence table Abbreviations: CI, co. 	ent ow the intent-to-tro- ceived the same of swere comparab- ith regards to the ot exactly match the titute for an outco- tiervals % confidence inter mb: <300 events a for the full definit	care except for the le for treatment con number of particip ne intervention of me of interest vals calculated by ion	ompletion pants for whom da interest: did not c		t the 4 standard re	ecommended drug	gs, and the 2 regi	mens vary by mor	e than duration	

SMEAR-NEGATIVE, MIXED/UNSPECIFIED CULTURE

<6 vs 6 months

Age: mix

HIV status: not specified – negative?

Disease status: smear-negative

Site of disease: pulmonary

Drug sensitivity: susceptible / unclear (pooled)

		Quality ass	sessment			Number	r of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	<6 months	6 months	(95% CI)	(95% CI)	Quality
elapse (follow-up 5	· ·	,					· ·			
1	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,9}	very serious ^{10,12}	72/1502 (4.8%)	10/190 (5.3%)	OR 0.91 (0.46 to 1.79) ¹¹	0 fewer per 100 (from 3 fewer to 4 more)	VERY LOW
Bacteriological rela	pse (follow-up 5	years after treatm	nent initiation; asse	ssed with: numbe	er of smear-negati	ve patients to ex	perience bacterio	ologically confirmed	relapse)	
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7}	very serious ^{8,9}	very serious ^{10,12}	32/1502 (2.1%)	4/190 (2.1%)	OR 1.01 (0.35 to 2.89) ¹¹	0 more per 100 (from 1 fewer to 4 more)	VERY LOW
Adverse events (an	y) (assessed wit	h: number of sme	ar-negative patient	s to experience a	ny adverse event)				
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	462/1502 (30.8%)	81/190 (42.6%)	OR 0.60 (0.44 to 0.81) ¹¹	12 fewer per 100 (from 5 fewer to 18 fewer)	VERY LOW
Adverse events req		al of one or mor			mear-negative par					
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	71/1502 (4.7%)	6/190 (3.2%)	OR 1.52 (0.65 to 3.55) ¹¹	2 more per 100 (from 1 fewer to 7 more)	VERY LOW
Adverse events lea	ding to a tempo	orary interruption	in treatment (ass	essed with: numb	er of smear-nega	tive patients to e	xperience an adv	verse event leading	to a temporary in	terruption in
treatment)										
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	153/1502 (10.2%)	25/190 (13.2%)	OR 0.75 (0.48 to 1.18) ¹¹	3 fewer per 100 (from 6 fewer to 2 more)	VERY LOW
Adverse events - cu	itaneous (asses	sed with: number	of smear-negative	patients to experi	ience a cutaneou	s adverse reaction	on)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	110/1502 (7.3%)	16/190 (8.4%)	OR 0.86 (0.5 to 1.49) ¹¹	1 fewer per 100 (from 4 fewer to 4 more)	VERY LOW
Adverse events - ga	astrointestinal (assessed with: nu	mber of smear-neg		experience a gast	rointestinal adve	erse reaction)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	87/1502 (5.8%)	20/190 (10.5%)	OR 0.52 (0.31 to 0.87) ¹¹	5 fewer per 100 (from 1 fewer to 7 fewer)	VERY LOW
Adverse events - ve	estibular (asses	sed with: number	of smear-negative	patients to experi	ence a vestibular	adverse reaction	1)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	69/1502 (4.6%)	7/190 (3.7%)	OR 1.26 (0.57 to 2.78) ¹¹	1 more per 100 (from 2 fewer to 6 more)	VERY LOW
Adverse events - he	epatic (assessed	d with: number of s	smear-negative pat		ce a hepatic adve					
1 ¹	randomised	very serious ^{2,3,4,5}	serious ⁶	very serious ^{8,9}	very serious ^{10,12}	18/1502 (1.2%)	0/190 (0%)	OR 4.75 (0.29 to 79.11) ¹¹	-	VERY LOW

Quality assessment						Number of patients		Effect		
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	<6 months	6 months	(95% CI)	(95% CI)	Quality
² Method of randomis	ation unclear									
Allocation concealm	nent unclear									
Blinding unclear										
Analysis did not follo	ow intent-to-tre	at principle								
Unclear if loss to fol	llow-up was the	same in the 2 grou	ips							
Follow-up began fro	om treatment in	itiation; therefore, a	, s different duration	ns of treatment w	ere used, follow-u	p was for different	lengths			
							lengths			
Intervention does no	ot exactly match	h the intervention of	f interest: did not c	ontain all of the 4	standard recomn	nended drugs		ere possibly 'inact	ive'	
Intervention does not Population does not	ot exactly match t exactly match	h the intervention of	f interest: did not c	ontain all of the 4	standard recomn	nended drugs		ere possibly 'inact	ive'	
Intervention does not Population does not ⁰ Wide confidence in	ot exactly match t exactly match itervals	h the intervention of the population of in	f interest: did not c iterest: includes so	ontain all of the 4	standard recomn	nended drugs		ere possibly 'inact	ive'	
Follow-up began fro Intervention does not Population does not Wide confidence in 1 Odds ratio and 95% 2 GRADE rule of thui	ot exactly match t exactly match tervals % confidence in	h the intervention of the population of in tervals calculated b	f interest: did not c iterest: includes so	ontain all of the 4	standard recomn	nended drugs		ere possibly 'inact	ive'	

4 vs 6 months

Age: mix

HIV status: not specified - negative?

Disease status: smear-negative, radiographically active

Site of disease: pulmonary

Drug sensitivity: susceptible / unclear (pooled)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Relapse (follow-up 5	Relapse (follow-up 5 years after treatment initiation; assessed with: number of smear-negative patients to experience relapse ¹)									
2 ^{2,3}	randomised trials	very serious ^{4,5,6}	very serious ^{7,8,9}	very serious ^{10,11,12,15}	serious ¹³	7/384 (1.8%)	8/231 (3.5%)	OR 0.47 (0.17 to 1.3) ^{14,16}	2 fewer per 100 (from 3 fewer to 1 more)	VERY LOW

¹ See evidence table for the full definitions

² Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989

³ Teo et al, 2002

⁴ Blinding unclear

⁵ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: method of randomisation unclear

⁶ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: allocation concealment unclear

⁷ Teo et al, 2002: comparability of patients at baseline was unclear

⁸ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: number of patients lost to follow-up in each group is unclear

⁹ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹⁰ Teo et al, 2002: intervention does not exactly match the intervention of interest: did not contain all of the 4 standard recommended drugs, and the two arms vary by more than duration alone

¹¹ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: population does not exactly match the population of interest: includes some

Quality assessment					Number of patients		Effect			
							Relative	Absolute		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality

children, and some cases were possibly 'inactive'

¹² Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: intervention does not exactly match the intervention of interest: did not contain all of or just the 4 standard recommended drugs

¹³ GRADE rule of thumb: <300 events

¹⁴ Pooled odds ratio and 95% confidence intervals calculated by reviewer

¹⁵ Teo et al, 2002: population does not exactly match the population of interest: unclear if children are included

¹⁶ Forest plot (relapse):

Abbreviations: CI, confidence interval; OR, odds ratio

Age: mix

HIV status: not specified – negative?

Disease status: smear-negative, culture unspecified, radiographically active

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality as	sessment			Numbe	er of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality
reatment failure (a	assessed with: n	umber of smear-n	egative patients to	experience treatr	ment failure1)					
12	randomised trials	serious ³	serious ⁴	serious ^{5,10}	very serious ^{6,7}	0/59 (0%)	1/54 (1.9%)	OR 0.30 (0.01 to 7.52) ⁸	1 fewer per 100 (from 2 fewer to 11 more)	VERY LOW
Changes in signs a reatment)	nd symptoms -	- no change in ra	diographic status	(assessed with:	number of smear	negative patien	ts to experience n	o change in radiogra	aphic appearance	e at the end of
12	randomised trials	serious ³	serious ⁴	serious ^{5,10}	serious ⁶	0/59 (0%)	0/54 (0%)	OR 0.92 (0.02 to 49.97) ⁸		VERY LOW
								in 50% radiographic		
1 ²	randomised trials	serious ³	serious ⁴	serious ^{5,10}	serious ⁶	0/59 (0%)	0/54 (0%)	OR 0.92 (0.02 to 49.97) ⁸		VERY LOW
Changes in signs a									-	
2	randomised trials	serious ³	serious ⁴	serious ^{5,10}	serious ⁶	52/59 (88.1%)	52/54 (96.3%)	OR 0.29 (0.06 to 1.44) ⁸	8 fewer per 100 (from 35 fewer to 1 more)	VERY LOW
Changes in signs a	nd symptoms -	- complete radio	graphic clearing (a	assessed with: nu	umber of smear-ne	egative patients	to demonstrate ra	diographic clearing	at the end of trea	tment)
12	randomised trials	serious ³	serious ⁴	serious ^{5,10}	very serious ^{6,7}	52/59 (88.1%)	52/54 (96.3%)	OR 0.29 (0.06 to 1.44) ⁸	8 fewer per 100 (from 35 fewer to 1 more)	VERY LOW
Relapse (follow-up 6	60 months after t	reatment initiation	; assessed with: nu	umber of smear-n	egative patients t	o experience re	lapse ¹)			
1 ²	randomised trials	serious ³	very serious ^{4,9}	serious ^{5,10}	serious ⁶	0/59 (0%)	0/54 (0%)	OR 0.92 (0.02 to 49.97) ⁸	-	VERY LOW
 See evidence table Teo et al, 2002 Blinding unclear Comparability of pathematics Intervention does n GRADE rule of thun Wide confidence in Odds ratio and 959 Follow-up began fn Population does n 	atients at baselin tot exactly match mb: <300 events tervals 6 confidence inte om treatment ini	e was unclear the intervention o s ervals calculated b tiation; therefore, a	y reviewer as different duration	ns of treatment w	ere used, follow-u	-		vary by more than d	uration alone	

Abbreviations: CI, confidence interval; OR, odds ratio

2 vs 3 months

Age: mix

HIV status: not specified - negative?

Disease status: smear-negative, culture-positive or negative (i.e. all patients in trial)

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality ass	essment			Number	of patients	Eff	ect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2 months	3 months	(95% CI)	(95% CI)	Quality
Response to treatm	ent - culture sta		h: number of sme	ar-negative patier	nts to be culture-ne	egative at the end	of treatment)			
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{5,6,7}	serious ⁹	303/303 (100%)	307/307 (100%)	OR 0.98 (0.02 to 49.9) ¹⁰	-	VERY LOW
Relapse (follow-up 6	0 months after tr				egative patients to	experience bacte	riological, radiogr	aphic or clinical re	lapse ¹¹)	
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	45/303 (14.9%)	21/307 (6.8%)	OR 2.38 (1.38 to 4.1) ¹⁰	8 more per 100 (from 2 more to 16 more)	VERY LOW
Bacteriological rela	pse (follow-up 60	months after trea	atment initiation; as	ssessed with: nun	nber of smear-neg	ative patients to e	experience bacteri	ologically confirm	ed relapse ¹¹)	
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	30/303 (9.9%)	13/307 (4.2%)	OR 2.49 (1.27 to 4.86) ¹⁰	6 more per 100 (from 1 more to 13 more)	VERY LOW
Adverse events (an	y) (assessed with	n: number of smea	ar-negative patient	s to experience a	ny adverse reaction	on during chemoth	erapy)			
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{5,6}	serious ⁸	76/303 (25.1%)	98/307 (31.9%)	OR 0.71 (0.5 to 1.02) ^{10,13}	7 fewer per 100 (from 13 fewer to 0 more)	VERY LOW
Adverse events req	uiring withdraw	al of chemothera	py (assessed with	: number of smea	ar-negative patient	ts to experience a	ny adverse reaction	on requiring withd	rawal of one or m	ore drug)
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{5,6}	serious ⁸	6/303 (2%)	9/307 (2.9%)	OR 0.67 (0.24 to 1.9) ¹⁰	1 fewer per 100 (from 2 fewer to 2 more)	VERYLOW
 ¹ Hong Kong Chest S ² Method of randomis ³ Allocation concealn ⁴ Blinding unclear ⁵ Population does no ⁶ Intervention does n ⁷ Outcome is a subst ⁸ GRADE rule of thui 	sation unclear nent unclear t exactly match tl ot exactly match itute for an outco	he population of in the intervention of	terest: some case	s were drug resis	tant, and the popu	lation may includ		nclusion criteria =	15-75 years)	

⁸ GRADE rule of thumb: <300 events ⁹ Wide confidence intervals

¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer

¹¹ See evidence table for the full definition ¹² Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

		Quality asse	essment			Number o	of patients	Eff	ect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2 months	3 months	(95% CI)	(95% CI)	Quality
¹³ note: most adverse	e reactions were r	eported by the au	thors to be "trivial	or mild cutaneous	s, vestibular or gas	strointestinal episo	odes"			

Abbreviations: CI, confidence interval; OR, odds ratio

SMEAR-NEGATIVE, CULTURE-POSITIVE

4 vs 6 months

Age: mix

HIV status: not specified – negative?

Disease status: smear-negative, 1 or more positive culture, radiographically active

Site of disease: pulmonary

Drug sensitivity: susceptible only

		Quality asse	essment			Number o	of patients	Eff	ect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality
Response to treatm	ent - culture sta	tus (assessed wit	n: number of smea	ar-negative patier	ts with 1 or more	initial culture posit	tive to be culture-r	negative at the en	d of treatment)	
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ⁶	very serious ^{7,8,9}	serious ¹⁰	325/325 (100%)	177/177 (100%)	OR 1.83 (0.04 to 92.82) ¹¹	-	VERY LOW
Relapse (follow-up 5	years after treatr	nent initiation; ass	essed with: numb	er of smear-nega	tive patients with '	1 or more initial cu	Iture positive to e	xperience relapse	e)	
1 ¹	randomised trials	very serious ^{2,3,4,5}	very serious ^{6,12}	very serious ^{7,8}	serious ¹⁰	7/325 (2.2%)	8/177 (4.5%)	OR 0.47 (0.17 to 1.3) ¹¹	2 fewer per 100 (from 4 fewer to 1 more)	VERY LOW
Bacteriological rela confirmed relapse)	pse (follow-up 5 y	ears after treatme	ent initiation; asse	ssed with: numbe	r of smear-negativ	ve patients with 1	or more initial cult	ure positive to exp	perience bacteriol	ogically
1 ¹	randomised trials	very serious ^{2,3,4,5}	very serious ^{6,12}	very serious ^{7,8}	serious ¹⁰	5/325 (1.5%)	3/177 (1.7%)	OR 0.90 (0.21 to 3.84) ¹¹	0 fewer per 100 (from 1 fewer to 5 more)	VERY LOW
 ¹ Hong Kong Chest S ² Method of randomis ³ Allocation concealm ⁴ Blinding unclear ⁵ Analysis is not inter ⁶ Number of patients ⁷ Intervention does not ⁸ Population does not 	ation unclear nent unclear nt-to-treat lost to follow-up i ot exactly match t	n each group is ui he intervention of	nclear interest: did not c	ontain all of or jus	t the 4 standard re	ecommended drug		ossibly 'inactive'		

⁹ Outcome is a substitute for an outcome of interest

¹⁰ GRADE rule of thumb: <300 events

¹¹ Odds ratio and 95% confidence intervals calculated by reviewer

		Quality asse	essment			Number o	f patients	Eff	ect	1
								Relative	Absolute	1
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality
¹² Follow-up began fro	om treatment initia	ation; therefore, a	s different duratio	ns of treatment w	ere used, follow-u	p was for different	lengths			

Abbreviations: CI, confidence interval; OR, odds ratio

2 vs 3 months

Age: mix

HIV status: not specified - negative?

Disease status: smear-negative, culture-positive

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality asse	essment			Number of	of patients	Eff	ect	
	Dealar	Disksfilles	1	In dimension		0 m an tha	0	Relative	Absolute	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2 months	3 months	(95% CI)	(95% CI)	Quality
Response to treatm	ent - culture stat	us (assessed with	n: number of smea	ar-negative patien		initial culture posi	tive to be culture-r	negative at the end	d of treatment)	
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{5,6,7}	very serious ^{8,9}	71/71 (100%)	68/68 (100%)	OR 1.04 (0.02 to 53.35) ¹⁰	-	VERY LOW
Relapse (follow-up 6 clinical relapse ¹¹)	0 months after tre	atment initiation;	assessed with: nu	mber of smear-ne	egative patients wi	ith 1 or more initia	l culture positive t	o experience bact	eriological, radiog	raphic or
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	23/71 (32.4%)	9/68 (13.2%)	OR 3.14 (1.33 to 7.42) ¹⁰	19 more per 100 (from 4 more to 40 more)	VERY LOW
Bacteriological rela confirmed relapse ¹¹)	pse (follow-up 60	months after trea	tment initiation; as	ssessed with: num	ber of smear-neg	ative patients with	1 or more initial	culture positive to	experience bacte	riologically
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	16/71 (22.5%)	7/68 (10.3%)	OR 2.54 (0.97 to 6.62) ¹⁰	12 more per 100 (from 0 fewer to 33 more)	VERY LOW

		Quality asse	essment			Number o	of patients	I	Effect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2 months	3 months	(95% CI)	(95% CI)	Quality
¹ Hong Kong Chest S	ervice / Tuberculo	osis Research Ce	ntre, Madras / Brit	ish Medical Rese	arch Council, 197	9/84				
² Method of randomis	ation unclear									
³ Allocation concealm	ent unclear									
⁴ Blinding unclear										
⁵ Population does not										
⁶ Intervention does no			interest: did not co	ontain all of or jus	st the 4 standard r	ecommended dru	gs			
⁷ Outcome is a substi		ne of interest								
^e GRADE rule of thun										
⁹ Wide confidence int										
¹⁰ Odds ratio and 95%			/ reviewer							
¹¹ See evidence table										
¹² Follow-up began fro			s different duration	ns of treatment w	ere used, follow-u	p was for differen	t lengths			
Abbreviations: CI, col	nfidence interval;	OR, odds ratio								

SMEAR-NEGATIVE, CULTURE-NEGATIVE

3 vs 4 months

Age: mix

HIV status: not specified – negative?

Disease status: smear-negative, culture-negative

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asso	essment			Number o	of patients	Eff	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4 months	(95% CI)	(95% CI)	Quality
Response to treatme	ent - culture stat	us (assessed wit	h: number of smea	ar-negative patien	ts with all initial cu	ltures negative to	be culture-negati	ive at the end of tr	reatment)	
1	randomised trials	serious ^{2,3,4}	serious⁵	very serious ^{6,7,8}	serious ⁹	759/759 (100%)	359/359 (100%)	OR 2.11 (0.04 to 106.69) ¹⁰	-	VERY LOW
Relapse (follow-up 5	years after treatm	nent initiation; ass	essed with: numb	er of smear-nega	tive patients with a	all initial cultures r	egative to experie	ence relapse)		
1	randomised trials	serious ^{2,3,4}	very serious ^{5,11}	very serious ^{6,7}	serious ¹²	48/759 (6.3%)	12/359 (3.3%)	OR 1.95 (1.02 to 3.72) ¹⁰	3 more per 100 (from 0 more to 8 more)	VERY LOW
acteriological rela	pse (assessed wi	th: number of sme	ear-negative patie	nts with all initial of	cultures negative t	o experience bact	eriologically confi	rmed relapse)		
1	randomised trials	serious ^{2,3,4}	very serious ^{5,11}	very serious ^{6,7}	serious ¹²	20/759 (2.6%)	4/359 (1.1%)	OR 2.40 (0.81 to 7.08) ¹⁰	2 more per 100 (from 0 fewer to 6 more)	VERY LOW
Hong Kong Chest S	ervice / Tuberculo	osis Research Ce	ntre, Madras / Brit	tish Medical Rese	arch Council, 198	9				

		Quality asse	essment			Number o	of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4 months	(95% CI)	(95% CI)	Quality
² Method of randomise	ation unclear									
³ Allocation concealm	ent unclear									
^₄ Blinding unclear										
⁵ Unclear if loss to foll										
⁶ Population does not	exactly match th	e population of int	terest: may includ	e some children (inclusion criteria =	15-75 years), and	d some cases we	re possibly 'inacti	ve'	
⁷ Intervention does no			interest: did not c	ontain all of or jus	st the 4 standard re	ecommended drug	gs			
⁸ Outcome is a substit	tute for an outcor	ne of interest								
⁹ Wide confidence interpretence	ervals									
¹⁰ Odds ratio and 95%	6 confidence inter	rvals calculated by	y reviewer							
¹¹ Follow-up began fro		ation; therefore, a	s different duratio	ns of treatment w	ere used, follow-u	p was for different	t lengths			
¹² GRADE rule of thur	nb: <300 events									
	fidence interval;	<u> </u>								

2 vs 3 months

Age: mix

HIV status: not specified – negative?

Disease status: smear-negative, culture-negative

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality ass	essment			Number o	of patients	Eff	ect	
Number of		Risk of	Inconsiste	Indirectne	Imprecisio			Relative	Absolute	
studies	Design	bias	ncy	SS	n	2 months	3 months	(95% CI)	(95% CI)	Quality
Response to treat	ment - culture sta	tus (assessed wit	th: number of sme	ar-negative patier	nts with all initial c	ultures negative to	be culture-negat	ive at the end of t	reatment)	
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{5,6,7}	very serious ^{8,9}	161/161 (100%)	161/161 (100%)	OR 1.00 (0.02 to 50.71) ¹⁰	-	VERY LOW
Relapse (follow-up relapse ¹¹)	60 months after tr	eatment initiation;	assessed with: nu	umber of smear-ne	egative patients w	ith all initial culture	es negative to exp	erience bacteriolo	ogical, radiograph	c or clinical
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	17/161 (10.6%)	11/161 (6.8%)	OR 1.61 (0.73 to 3.55) ¹⁰	4 more per 100 (from 2 fewer to 14 more)	VERY LOW
Bacteriological rel relapse ¹¹)	apse (follow-up 60) months after trea	atment initiation; a	ssessed with: nun	nber of smear-neg	ative patients wit	n all initial cultures	s negative to expe	rience bacteriolog	ically confirmed
1 ¹	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious ⁸	10/161 (6.2%)	5/161 (3.1%)	OR 2.07 (0.69 to 6.19) ¹⁰	3 more per 100 (from 1 fewer to 13 more)	VERY LOW

		Quality asso	essment			Number o	of patients	E	ffect	
Number of		Risk of	Inconsiste	Indirectne	Imprecisio			Relative	Absolute	
studies	Design	bias	ncy	SS	n	2 months	3 months	(95% CI)	(95% CI)	Quality
 ¹ Hong Kong Chest S ² Method of randomi. ³ Allocation concealm ⁴ Blinding unclear ⁵ Population does no ⁶ Intervention does no ⁷ Outcome is a subst ⁸ GRADE rule of thui ⁹ Wide confidence in ¹⁰ Odds ratio and 950 ¹¹ See evidence table ¹² Follow-up began fin Abbreviations: CI, construction 	sation unclear nent unclear t exactly match th ot exactly match t itute for an outcor mb: <300 events tervals % confidence inte e for the full defini rom treatment initi	le population of in the intervention of me of interest rvals calculated b tion tion; therefore, a	terest: may includ f interest: did not c y reviewer	ie some children (ontain all of or jus	(inclusion criteria = st the 4 standard r	: 15-75 years) ecommended dru	-			

MIXED POPULATIONS

<6 vs 6 months

Age: mix

HIV status: not specified – negative?

Disease status: various

Site of disease: pulmonary

Drug sensitivity: susceptible / unclear (pooled)

		Quality asse	essment			Number	of patients	Ef	fect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	<6 months	6 months	(95% CI)	(95% CI)	Quality
Response to treatme	ent - culture stat	us (assessed with	n: number of patie	nts to be culture-r	negative the end o	of treatment)				
2 ^{1,2}	randomised trials	very serious ^{3,4,5,6}	very serious7,8	very serious ^{9,10,11,12}	serious ¹³	1558/1558 (100%)	260/260 (100%)	OR 5.98 (0.12 to 302.19) ¹⁴	-	VERY LOW
 Research Committe Hong Kong Chest S Method of randomis Allocation concealm Blinding unclear Analysis did not follo Research Committe Unclear if loss to follo 	ervice / Tuberculo ation unclear ent unclear ow intent-to-treat J e of the Tuberculo	osis Research Ce principle osis Association c	ntre, Madras / Brii of India, 1984: con							

			Quality asse	essment			Number o	of patients	Eff	ect	
									Relative	Absolute	
Num	ber of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	<6 months	6 months	(95% CI)	(95% CI)	Quality

⁹ Research Committee of the Tuberculosis Association of India, 1984: intervention does not exactly match the intervention of interest: did not contain all of or just the 4 standard recommended drugs, and doses used are inconsistent with those recommended in the British National Formulary

¹⁰ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: intervention does not exactly match the intervention of interest: did not contain all of the 4 standard recommended drugs

¹¹ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: population does not exactly match the population of interest: includes some children (inclusion criteria = 15 to 75 years), and some cases were possibly 'inactive'

¹² Outcome is a substitute for an outcome of interest

¹³ Wide confidence intervals

¹⁴ Pooled odds ratio and 95% confidence intervals calculated by reviewer

¹⁵ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹⁶ GRADE rule of thumb: <300 events

¹⁷ Research Committee of the Tuberculosis Association of India, 1984: population does not exactly match the population of interest: includes some children (inclusion criteria = 15 to 45 years) Abbreviations: CI, confidence interval; OR, odds ratio

4 vs 6 months

Age: mix

HIV status: not specified – negative?

Disease status: various

Site of disease: pulmonary

Drug sensitivity: susceptible/unclear

		Quality ass	essment			Numbe	r of patients	Ef	ffect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Relapse (follow-up 5	•	treatment initiatio	n: assessed with: r	umber of patient		elapse)		(*****)	(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
31,2,3	randomised trials	very serious ^{4,5,6,7}	very serious ^{8,9,10,17}	very serious ^{11,12,13}	very serious ^{14,15}	27/515 (5.2%)	11/369 (3%)	OR 1.90 (0.11 to 32.97) ^{16,18}	3 more per 100 (from 3 fewer to 47 more)	VERY LOV
Allocation concealn Blinding unclear Analysis is not inter Follow-up began fro Teo et al, 2002: cor ⁹ Hong Kong Chest	nt-to-treat om treatment ini nparability of pa	tients at baseline u	ınclear				· ·	British Medical Rese	earch Council (19	79/86): numb
of patients lost to fo I Intervention does r	ollow-up in each	group is unclear								,
¹² Unclear if population ¹³ Teo et al, 2002: int whereas the 4-mor	tervention does	not exactly match i			y more than durat	tion – the continu	lation phase of the	e 6-month regimen	was intermittent (3 times week
¹⁴ Wide confidence ir ¹⁵ GRADE rule of thu	ntervals									
⁶ Pooled odds ratio a	and 95% confid	ence intervals calc								
¹⁷ Point estimates va ¹⁸ Forest plot (relansi		o overlap of the co	infidence intervals							

¹⁸ Forest plot (relapse):

Abbreviations: CI, confidence interval; OR, odds ratio

3 vs 4 or 4.5 months

Age: mix

HIV status: not specified - negative?

Disease status: various

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asse	essment			Number o	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4 or 4.5 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Response to treatm	ent - culture stat	us (assessed with	n: number of patie	nts to be culture-r	negative at the en	d of treatment)				
2 ^{1,2}	randomised trials	serious ^{3,4,5}	serious ^{6,7}	very serious ^{8,9,10,15}	serious ¹¹	850/850 (100%)	448/448 (100%)	OR 1.90 (0.04 to 95.74) ¹²	-	VERY LOW
Relapse (follow-up 1	year after treatme	ent completion to	5 years after treat	ment initiation; as	sessed with: num	ber of patients to	experience relaps	e)		
2 ^{1,2}	randomised trials	serious ^{3,4,5}	very serious ^{6,7,13}	very serious ^{8,9,15}	serious ¹⁴	49/850 (5.8%)	13/448 (2.9%)	OR 1.88 (1 to 3.53) ^{12,16}	2 more per 100 (from 0 more to 7 more)	VERY LOW
¹ Hong Kong Chest S	Service / Tuberculo	osis Research Ce	ntre, Madras / Brit	ish Medical Rese	arch Council, 198	9			· · ·	

² Mehotra et al, 1982

³ Method of randomisation unclear

⁴ Allocation concealment unclear

⁵ Blinding unclear

⁶ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: unclear if loss to follow-up was similar in the 2 groups

⁷ Mehotra et al, 1982: although not statistically significant, there was a higher number who did not complete treatment and for whom data was not available amongst the 3-month group (36%) than the 4.5-month group (24%)

⁸ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: population does not exactly match the population of interest: may include some children (inclusion criteria = 15-75 years), and some cases were possibly 'inactive'

⁹ Intervention does not exactly match the intervention of interest: did not contain all of or just the 4 standard recommended drugs

¹⁰ Outcome is a substitute for an outcome of interest

¹¹ Wide confidence intervals

¹² Pooled odds ratio and 95% confidence intervals calculated by reviewer

¹³ Hong Kong Chest Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989: follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹⁴ GRADE rule of thumb: <300 events

¹⁵ Mehotra et al, 1982: population does not exactly match the population of interest: may include some children (inclusion criteria: aged 12 years or more)

¹⁶ Forest plot (relapse):

Abbreviations: CI, confidence interval; OR, odds ratio

6 vs >6 months

Age: mix

HIV status: not specified - negative?

Disease status: various

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality asse	essment			Number o	of patients	Eff	ect	
Number of studies	Docian	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	>6 months	Relative (95% CI)	Absolute (95% CI)	Quality
	-				Imprecision	0 11011015				Quanty
Treatment failure (a	ssessed with: nun		experience treati	ment failure)						
2 ^{1,2}	randomised trials	serious ^{3,4,5,6,7}	no serious inconsistency	very serious ^{8,9,10,18}	very serious ^{11,12}	1/307 (0.33%)	1/324 (0.31%)	OR 1.08 (0.11 to 10.44) ^{13,18}	0 more per 100 (from 0 fewer to 3 more)	VERY LOW
Relapse (follow-up 1	2 months after tre	atment completio	n to 54 months aff	ter treatment initia	tion; assessed wit	th: number of pati	ents to experience	e relapse)		
4 ^{1,2,20,21}	randomised trials	very serious ^{3,4,5,6,7}	very serious ^{14,15,16,17}	very serious ^{8,9,10,18}	very serious ^{11,12}	21/691 (3%)	7/577 (1.2%)	OR 2.26 (0.61 to 8.39) ^{13,19}	1 more per 100 (from 0 fewer to 8 more)	VERY LOW
¹ British Thoracic Soc	ciety, 1975/80									

² Ziaullah et al, 2004

³ Method of randomisation unclear

⁴ British Thoracic Society, 1975/80: allocation concealment possible - "random allocations of treatment were made centrally by coordinators"

⁵ British Thoracic Society, 1975/80: radiographer blinded to treatment allocation, but unclear if to prognostic factors or if other investigators were blinded

⁶ Ziaullah et al (2004), British Thoracic Society (1981/2/4) and Nayar et al (1988): allocation concealment unclear

⁷ Ziaullah et al (2004), British Thoracic Society (1981/2/4) and Nayar et al (1988): blinding unclear

⁸ British Thoracic Society (1975/80 and 1981/2/4) and Nayar et al (1988): intervention does not exactly match the intervention of interest: does not contain all of or just the 4 standard recommended drugs

⁹ British Thoracic Society, 1975/80: population does not exactly match the population of interest: 3.4% drug resistance at baseline

¹⁰ Ziaullah et al, 2004: population does not exactly match the population of interest: includes children (33% aged 5 to 14 years, 33% aged 15 to 29 years)

¹¹ GRADE rule of thumb: <300 events

¹² Wide confidence intervals

¹³ Pooled odds ratio and 95% confidence intervals calculated by reviewer

¹⁴ Follow-up varies considerably between studies and between groups

¹⁵ British Thoracic Society, 1981/2/4: unclear if groups received the same care except for the intervention

¹⁶ British Thoracic Society, 1981/2/4: unclear if the groups were comparable for treatment completion

¹⁷ British Thoracic Society, 1981/2/4: high attrition rate with regards to the number of participants for whom data is available

¹⁸ Forest plot (treatment failure):

¹⁹ Forest plot (relapse):

²⁰ Nayar et al, 1988
 ²¹ British Thoracic Society, 1981/2/4
 Abbreviations: CI, confidence interval; OR, odds ratio

6 vs 9 months

Age: mix

HIV status: unspecified - negative?

Disease status: various

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality ass	essment			Numbe	r of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% CI)	Quality
Relapse (follow-up a	•									quanty
2 ^{1,2}	randomised trials	very serious ^{3,4,5,6}	serious ^{7,8,9}	very serious ^{10,11}	very serious ^{12,13}	11/380 (2.9%)	2/264 (0.76%)	OR 3.34 (0.45 to 24.5) ^{14,15}	2 more per 100 (from 0 fewer to 15 more)	VERY LOW
³ Method of randomis	sation unclear									

HIV-POSITIVE

6 vs >6 months

Age: mix

HIV status: positive

Disease status: various

Site of disease: respiratory

Drug sensitivity: some DR-TB

		Quality ass	essment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	>6 months	Relative (95% CI)	Absolute (95% CI)	Quality
Relapse (follow-up 2	4 to 36 months a	fter treatment initi	ation; assessed w	ith: number of pat	tients with HIV to e	experience relaps	se)			
2 ^{1,11}	randomised trials	very serious ^{2,3,4,5}	very serious ^{6,7,12}	serious ^{8,13}	very serious ⁹	22/290 (7.6%)	17/284 (6.0%)	OR 0.61 (0.02 to 16.51) ^{10,14}	2 fewer per 100 (from 6 fewer to 45 more)	VERY LOW
 Perriens et al, 1995 Perriens et al, 1995 Perriens et al, 1995 Perriens et al, 1995 Swaminathan et al, Follow-up began frc Perriens et al, 1995 Swaminathan et al, Wide confidence int Pooled odds ratio at Swaminathan et al, Point estimates vai Swaminathan et al, Forest plot (relapse Abbreviations: Cl, co. 	: method of rando : allocation conce : patients blinded 2010: unblinded im treatment initia : groups were sta 2010: population ervals; GRADE r and 95% confider 2010 y widely, with no 2010: doses use b):	ealment unclear I, but investigators ation; therefore, a tistically compara does not exactly ule of thumb: <30 nce intervals calcu overlap of the co ed are inconsister	s and those admin s different duratior ible at baseline, bu match the populat 0 events ilated by reviewer nfidence intervals	as of treatment we ut the 12-month a ion of interest: so	ere used, follow-up rm has a higher C ome DR-TB, and th	D4 count at base	eline	on = 15 years and	above)	

6 vs 9 months

Age: mix

HIV status: positive

Disease status: smear-positive or radiographically active

Site of disease: respiratory (91% pulmonary, 9% pleural or lymph node)

Drug sensitivity: some DR-TB

		Quality asso	essment			Number o	of patients	Eff	iect	
								Relative	Absolute	1
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Mortality (all cause)	(follow-up 36 mo	nths after treatme	ent initiation; asses	ssed with: number	of patients with H	IV to die (all caus	e))			
1 ¹	randomised trials	serious ²	serious ³	serious ^{4,10}	serious⁵	33/167 (19.8%)	37/160 (23.1%)	OR 0.82 (0.48 to 1.38)	3 fewer per 100 (from 11 fewer to 6 more)	VERY LOW

		Quality ass	essment			Numbe	r of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Cure (assessed with	: number of patie	nts with HIV to ac	hieve a 'favourable	e response' by th	e end of treatmen	t ⁶)				
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ^{4,10}	serious⁵	138/167 (82.6%)	122/160 (76.3%)	OR 1.48 (0.86 to 2.55) ⁷	6 more per 100 (from 3 fewer to 13 more)	VERY LOW
Freatment failure (a	ssessed with: nu	mber of patients v	vith HIV to experie	nce treatment fai	ilure ⁶)					
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ^{4,10}	serious⁵	8/167 (4.8%)	11/160 (6.9%)	OR 0.68 (0.27 to 1.74) ⁷	2 fewer per 100 (from 5 fewer to 5 more)	VERY LOW
Bacteriological rela	pse (follow-up 36	6 months after trea	atment initiation; a	ssessed with: nu	mber of patients v	vith HIV to exper	ience bacteriologi	cally confirmed rela	pse ⁶)	
1 ¹	randomised trials	serious ²	serious ³	serious ^{4,10}	serious⁵	21/167 (12.6%)	8/160 (5.0%)	OR 2.73 (1.17 to 6.36) ⁷	8 more per 100 (from 1 more to 20 more)	VERY LOW
Adverse events (an	v) (assessed with	n: number of patie	nts with HIV to exp	perience any adv	erse event resulti	ng from drug tox	icity)		,	
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ^{4,10}	very serious ^{5,9}	1/167 (0.6%)	1/160 (0.63%)	OR 0.96 (0.06 to 15.45) ⁷	0 fewer per 100 (from 1 fewer to 8 more)	VERY LOW
Adherence - treatme	ent default (asse	essed with: numbe	er of patients with I	HIV to default trea	atment)					
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ^{4,10}	serious⁵	11/167 (6.6%)	16/160 (10%)	OR 0.63 (0.29 to 1.41) ⁷	3 fewer per 100 (from 7 fewer to 4 more)	VERY LOW
¹ Swaminathan et al, ² Unblinded	2010									

³ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

⁴ Population does not exactly match the population of interest: some DR-TB (12% at baseline), and there may be some children (inclusion = 15 years and above)

⁵ GRADE rule of thumb: <300 events

⁶ See evidence table for the full definition

⁷ Odds ratio and 95% confidence intervals calculated by reviewer ⁸ Analysis did not follow intent-to-treat principle

⁹ Wide confidence intervals

¹⁰ Doses used are inconsistent with those listed in the British National Formulary

Abbreviations: CI, confidence interval; OR, odds ratio

Age: mix

HIV status: positive

Disease status: smear- or culture-positive or radiographically active

Site of disease: respiratory (91% pulmonary, 9% pleural or lymph node)

Drug sensitivity: susceptible only

Mortality (follow-up 36 months after treatment initiation: assessed with: number of drug susceptible patients with HIV to die (all cause)) OR 0.27 (0.07 to 1.01) ⁹ Fewer per 100 (from 10 frewer to 0 more) 11 randomised trials very serious ^{2.3} serious ⁴ serious ^{5.11} very serious ^{6.7} 3/100 (10.3%) 10/97 to 1.01) ⁹ OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 frewer to 0 more) Cure (assessed with: number of drug susceptible patients with HIV to achieve a 'favourable response' by the end of treatment ⁸) serious ^{5.11} serious ^{5.11} serious ⁶ 3/100 (10.3%) 10/97 to 1.01) ⁹ OR 0.27 (0.07 to 0.07 or prevent to 0 more) VERY freewer to 0 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ⁶ 3/100 (10.3%) 10/97 to 1.01) ⁹ OR 0.27 (0.07 to 0.07 or prevent to 0 more) VERY freewer to 0 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ⁶ 3/100 (10.3%) 10/97 to 1.01) ⁹ OR 0.40 (0.1 freewer to 0 more) fewer to 4 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ^{6.11} serious ^{6.11} (3%) OR 0.40 (0.1 freewer to 4 more) fewer to 4 more)			Quality ass	essment			Numbe	er of patients	Ef	fect	
Mortality (follow-up 36 months after treatment initiation; assessed with: number of drug susceptible patients with HIV to die (all cause)) OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more) VERY 100 (from 10 fewer to 0 more) 11 randomised trials very serious ^{2.3} randomised trials serious ⁴ serious ^{5.11} serious ^{5.11} very serious ^{6.7} 3/100 (3%) 10/97 (10.3%) OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more) VERY 100 (from 10 fewer to 0 more) 11 randomised trials very serious ^{2.3} very serious ^{2.3} no serious no serious inconsistency serious ^{5.11} serious ⁵ serious ⁶ 3/100 (3%) 10/97 (10.3%) OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more) VERY 100 (from 10 fewer to 0 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ⁵ serious ⁶ 3/100 (3%) 10/97 (10.3%) OR 0.40 (0.1 to 1.58) ⁹ 4 fewer per 100 (from 6 fewer to 4 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ^{5.11} serious ^{6.7} (3%) 0/97 (1.2%) OR 0.40 (0.1 to 1.58) ⁹ 4 fewer per 100 (from 6 fewer to 4 more) VERY 100 (from 6 fewer to 4 more) 11 randomised trials very serious ^{2.3} no serious inconsistency serious ^{5.11} serious ^{6.11}											
11 randomised trials very serious ^{2,3} serious ⁴ serious ^{5,11} very serious ^{6,7} 3/100 10/97 OR 0.27 (0.07 7 fewer per 100 (from 10 fewer to 0 more) VERY Cure (assessed with: number of drug susceptible patients with HIV to achieve a 'favourable response' by the end of treatment ⁹) Tewer per 100 (from 10 fewer to 0 more) VERY 11 randomised trials very serious ^{2,3} no serious inconsistency serious ^{5,11} serious ⁶ 3/100 (3%) (10.3%) OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more) VERY 11 randomised trials very serious ^{2,3} no serious no serious inconsistency serious ^{5,11} serious ⁶ 3/100 (3%) (10.3%) OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more) VERY 11 randomised trials very serious ^{2,3} no serious no serious inconsistency serious ^{5,11} serious ⁶ 3/100 (3%) (7.2%) OR 0.40 (0.1 to 1.58) ⁹ 4 fewer per 100 (from 6 fewer to 4 more) VERY 11 randomised trials very serious ^{2,3} no serious no serious serious ^{5,11} very serious ^{6,7} 1/100 (1%) 0/97 (0%) OR 2.93 (0.12 to 73.05) ⁹ - VERY Adverse						•			(95% CI)	(95% CI)	Quality
trialstrialstrialstrialstrialstrialstrialsto 1.01) ⁹ 100 (from 10 fewer to 0 more)Cure (assessed with: number of drug susceptible patients with HIV to achieve a 'favourable response' by the end of treatment*)10/97 (10.3%)0R 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more)VERY 100 (from 10 fewer to 0 more)11randomised trialsvery serious ^{2.3} inconsistencyno serious inconsistencyserious*11 serious*11serious* serious*3/100 (10.3%)10/97 (10.3%)OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more)VERY 100 (from 10 fewer to 0 more)VERY 100 (from 10 fewer to 0 more)VERY 100 (from 10 fewer to 0 more)VERY 100 (from 10 fewer to 0 more)0R 0.40 (0.1 to 1.58) ⁹ 4 fewer per 100 (from 6 fewer to 4 more)VERY 100 (from 6 fewer to 4 more)11randomised trialsvery serious*3no serious inconsistencyserious*5.11 serious*5.11serious*6 (3%)3/100 (7.2%)7/97 to 1.58) ⁹ OR 0.40 (0.1 to 1.58) ⁹ 4 fewer per to 1.00 (from 6 fewer to 4 more)11randomised trialsvery serious*3no serious inconsistencyserious*5.11 serious*5.11very serious*3.1 (1%)1/100 (1%)0/97 (0%)OR 2.93 (0.12 to 7.305) ⁹ -VERY to 4.70511randomised trialsvery serious*3.1 no serious inconsistencyserious*5.11 serious*5.111/100 (1%)0/97 (0%)	2 \ 1	36 months after 1						(all cause))			
11randomised trialsvery serious ^{2,3} no serious inconsistencyserious serious $3/100$ (3%) $10/97$ (10.3%)OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more)VERY VERYTreatment failure (assessed with: number of drug susceptible patients with HIV to experience treatment failure trialsvery serious ^{2,3} no serious inconsistencyno serious seriousserious serious $3/100$ (3%) $10/97$ (10.3%)OR 0.27 (0.07 to 1.01) ⁹ 7 fewer per 100 (from 10 fewer to 0 more)VERY very11randomised trialsvery serious very seriousno serious inconsistencyserious serious $3/100$ (3%) $7/97$ (7.2%)OR 0.40 (0.1 to 1.58) ⁹ 4 fewer per 100 (from 6 fewer to 4 more)VERY to 1.58) ⁹ VERY 100 (from 6 fewer to 4 more)Adverse events trials(assessed with: number of drug susceptible patients with HIV to experience any adverse event resulting inconsistencyfrom drug toxicity11randomised trialsvery serious very seriousno serious inconsistencyserious serious $1/100$ (1%) $0/97$ (0%)OR 2.93 (0.12 to 73.05) ⁹ -VERY to 73.05) ⁹ Adherence - treatment default (assessed with: number of drug susceptible patients with HIV to default treatment) $1/100$ (0%) $0/97$ (0%)OR 1.22 (0.32 to 4.7) ⁹ 1 more per 100 (from 3VERY to 4.7) ⁹		trials	,				(3%)	(10.3%)	· ·	100 (from 10 fewer to 0	VERY LOV
trialsinconsistency	Cure (assessed with	number of drug	susceptible patier	nts with HIV to ach	ieve a 'favourabl	e response' by the	end of treatme	nt ⁸)			
trialsinconsistencyinconsistency(3%)(7.2%)to 1.58)9100 (from 6 fewer to 4 more)Adverse events (any)(assessed with: number of drug susceptible patients with HIV to experience any adverse event resulting from drug toxicity)11randomised trialsvery serious ^{2,3} 	1 ¹		very serious ^{2,3}		serious ^{5,11}	serious ⁶				100 (from 10 fewer to 0	VERY LOV
trialsinconsistencyinconsistency (3%) (7.2%) to $1.58)^9$ 100 (from 6 fewer to 4 more)Adverse events (any)(assessed with: number of drug susceptible patients with HIV to experience any adverse event resulting from drug toxicity) $Very serious^{2.3}$ no serious inconsistencyserious 5,11 very serious 6,7 $1/100$ 	Freatment failure (a	ssessed with: nu	umber of drug susc	eptible patients wi	th HIV to experie	ence treatment fail	ure ⁸)				
trials inconsistency (1%) (0%) to 73.05) ⁶ Adherence - treatment default (assessed with: number of drug susceptible patients with HIV to default treatment) 1 ¹ randomised trials very serious ^{2,3} no serious serious ^{5,11} serious ⁶ 5/100 4/97 OR 1.22 (0.32) 1 more per 100 (from 3)	1 ¹		very serious ^{2,3}		serious ^{5,11}	serious ⁶				100 (from 6 fewer to 4	VERY LOV
trials inconsistency inconsistency (1%) (0%) to 73.05) ⁹ Adherence - treatment default (assessed with: number of drug susceptible patients with HIV to default treatment) (1%) (0%) to 73.05) ⁹ 1 ¹ randomised trials very serious ^{2.3} no serious serious ^{5.11} serious ⁶ 5/100 4/97 OR 1.22 (0.32 1 more per to 100 (from 3)	Adverse events (an	y) (assessed wit	h: number of drug	susceptible patien	ts with HIV to ex	perience any adve	rse event result	ting from drug tox	icity)		
$ \begin{array}{c} 1^{1} \\ \text{trials} \end{array} \begin{array}{c} \text{very serious}^{2.3} \\ \text{inconsistency} \end{array} \begin{array}{c} \text{serious}^{5.11} \\ \text{serious}^{6} \end{array} \begin{array}{c} 5/100 \\ (5\%) \end{array} \begin{array}{c} 4/97 \\ (4.1\%) \end{array} \begin{array}{c} \text{OR } 1.22 \\ (0.32 \\ to 4.7)^{9} \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} \text{VERY} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 100 \\ (\text{from } 3 \end{array} \begin{array}{c} 1 \\ \text{more per} \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	1 ¹		very serious ^{2,3}		serious ^{5,11}	very serious6,7				-	VERY LOV
trials inconsistency (5%) (4.1%) to 4.7) ⁹ 100 (from 3	Adherence - treatmo	ent default (ass	essed with: numbe	r of drug susceptil	ole patients with	HIV to default trea	tment)				
more)	1 ¹		very serious ^{2,3}		serious ^{5,11}	serious ⁶				100 (from 3 fewer to 13	VERY LOV

⁶ GRADE rule of thumb: <300 events

⁷ Wide confidence intervals

⁸ See evidence table for the full definition

⁹ Odds ratio and 95% confidence intervals calculated by reviewer
 ¹⁰ Population does not exactly match the population of interest: some extrapulmonary TB
 ¹¹ Doses used are inconsistent with those listed in the British National Formulary

Abbreviations: CI, confidence interval; OR, odds ratio

Age: mix

HIV status: positive

Disease status: culture-positive

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality asso	essment			Number	of patients	Efi	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Cure (assessed with	: number of cultur	e-positive patients	s with HIV to achie	eve a 'favourable i	response' by the e	end of treatment ¹)			,	
12	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	serious ⁶	96/117 (82.1%)	81/110 (73.6%)	OR 1.64 (0.87 to 3.09) ⁷	8 more per 100 (from 3 fewer to 16 more)	VERY LOW
Treatment failure (a	ssessed with: nur	nber of culture-po	sitive patients with	n HIV to experiend	ce treatment failur	e ¹)				
1 ²	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	serious ⁶	8/117 (6.8%)	11/110 (10%)	OR 0.66 (0.26 to 1.71) ⁷	3 fewer per 100 (from 7 fewer to 6 more)	VERY LOW
Adverse events (an	y) (assessed with	: number of cultur	e-positive patients	with HIV to expe	rience any advers	e event resulting	from drug toxicity)		
1 ²	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious6,8	1/117 (0.85%)	0/110 (0%)	OR 2.85 (0.11 to 70.6) ⁷	-	VERY LOW
 ¹ See evidence table ² Swaminathan et al, ³ Unblinded ⁴ Analysis did not foll ⁵ Population does no ⁶ GRADE rule of thur ⁷ Odds ratio and 95% ⁸ Wide confidence into ⁹ Doses used are inco Abbreviations: CI, co 	2010 low intent-to-treat t exactly match th nb: <300 events 6 confidence inten tervals consistent with tho	principle e population of in vals calculated by se listed in the Br.	reviewer		v be some childrer	n (inclusion = 15 y				

6 vs 12 months

Age: adults only (?)

HIV status: positive

Disease status: smear- and culture-positive

Site of disease: pulmonary

Drug sensitivity: unclear

		Quality asse	essment			Number o	of patients	Eff	ect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	12 months	(95% CI)	(95% CI)	Quality
Mortality (follow-up 2	24 months after tre	eatment initiation;	assessed with: nu	umber of smear- a	and culture-positiv	e patients with HI	V to die from tube	rculosis)		
1 ¹	randomised trials	very serious ^{2,3,4}	serious ^{5,6}	no serious indirectness	very serious7,8	1/123 (0.81%)	0/124 (0%)	OR 3.05 (0.12 to 75.58) ⁹	-	VERY LOW
Relapse (follow-up 24	4 months after tre	atment initiation;	assessed with: nu	mber of smear- a	nd culture-positive	patients with HIV	to experience re	lapse)		
1 ¹	randomised	very	serious ^{5,6}	no serious	serious ⁷	1/123	9/124	OR 0.10 (0.01	6 fewer per	VERY LOW

		Quality ass	essment			Number o	of patients	Ef	fect	
Number of stu	lies Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	12 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
	trials	serious ^{2,3,4}		indirectness		(0.81%)	(7.3%)	to 0.84) ⁹	100 (from 1 fewer to 7 fewer)	

¹ Perriens et al, 1995

² Method of randomisation unclear

³ Allocation concealment unclear

⁴ Patients blinded, but investigators and those administering care were not

⁵ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

⁶ Groups were statistically comparable at baseline, but the 12-month arm has a higher CD4 count at baseline

⁷ GRADE rule of thumb: <300 events

⁸ Wide confidence intervals

⁹ Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence interval; OR, odds ratio

HIV-POSITIVE, CULTURE-NEGATIVE

6 vs 9 months

Age: mix

HIV status: positive

Disease status: culture-negative

Site of disease: pulmonary

Drug sensitivity: some DR-TB

		Quality asse	essment			Number of	of patients	Eff	ect	
	_							Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Cure (assessed with	: number of cultur	e-negative patient	ts with HIV to achi	ieve a 'favourable	response' by the	end of treatment ¹				
12	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	serious ⁶	28/34 (82.4%)	31/38 (81.6%)	OR 1.05 (0.32 to 3.51) ⁷	1 more per 100 (from 23 fewer to 12 more)	VERY LOW
Treatment failure (a	ssessed with: nur	nber of culture-ne	gative patients wi	th HIV to experier	nce treatment failu	re ¹)				
1 ²	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious6,8	0/34 (0%)	0/38 (0%)	OR 1.12 (0.02 to 57.77) ⁷	-	VERY LOW
Adverse events (an	y) (assessed with	: number of cultur	e-negative patient	ts with HIV to exp	erience any adver	se event resulting	from drug toxicity	()		
1 ²	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious ^{6,8}	0/34 (0%)	1/38 (2.6%)	OR 0.36 (0.01 to 9.2) ⁷	2 fewer per 100 (from 3 fewer to 17 more)	VERY LOW

		Quality ass	essment		Number o	of patients		Effect					
								Relative	Absolute				
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality			
¹ See evidence table	for the full defi	inition											
² Swaminathan et al,	2010												
³ Unblinded													
⁴ Analysis did not follo	ow intent-to-tre	eat principle											
⁵ Population does not	exactly match	n the population of in	terest: some DR-	TB, and there may	y be some childrer	n (inclusion = 15 y	ears and above)						
⁶ GRADE rule of thun	nb: <300 even	ts											
7 Odds ratio and 95%	confidence in	tervals calculated by	/ reviewer										
8 Wide confidence inte	ervals												
⁹ Doses used are inco	onsistent with t	those listed in the Br	ritish National Forr	nulary									
Abbreviations: CI, cor	ofidence interv	val: OP adds ratio		•									

A.8 RQ M

A.8.1 Duration of treatment in children with respiratory tuberculosis

Intervention: 9 months

Comparator: 12 months

		Quality asse	essment			Number o	of patients	Eff	ect				
								Relative	Absolute				
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	(95% CI)	(95% CI)	Quality			
Recurrence (number	r to experience cli	nical or radiologic	al recurrence in th	ne 12 months after	r treatment compl	etion; follow-up 12	2 months after trea	atment completior	1)				
1 ¹	randomised trials	serious ^{2,3,4}	serious ⁶	very serious ^{7,12,13}	very serious ^{8,9}	0/18 (0%)	0/18 (0%)	OR 1.00 (0.02 to 53.12) ¹⁰	-	VERY LOW			
Adverse events - hepatotoxicity (number to experience elevated levels of serum aspartate aminotransferase and alanine aminotransferase)													
1 ¹	randomised trials	very serious ^{2,3,4,11}	serious ⁶	very serious ^{7,13}	very serious ^{8,9}	0/18 (0%)	1/18 (5.6%)	OR 0.32 (0.01 to 8.27) ¹⁰	4 fewer per 100 (from 5 fewer to 27 more)	VERY LOW			
Adherence (number	excluded due to '	'poor compliance"	')										
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	very serious ^{7,13}	serious ⁸	0/18 (0%)	3/18 (16.7%)	OR 0.12 (0.01 to 2.5) ¹⁰	14 fewer per 100 (from 16 fewer to 17 more)	VERY LOW			
¹ Kansoy et al, 1998													

² Method of randomisation unclear

³ Allocation concealment unclear

⁴ Blinding unclear

⁵ Outcome definition not provided

⁶ Loss to follow-up varied between the two arms: 3 of 18 patients were excluded from the 9-month group for "poor compliance", none were excluded from the 12-month group

⁷ Intervention is not the same as the intervention of interest: combination was not the 4 drugs in the standard recommended regimen, and intervention and comparator varied by more than duration

alone

⁸ GRADE rule of thumb event number <300

		Quality asse	essment			Number of	of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	Relative (95% Cl)	Absolute (95% Cl)	Quality		
⁹ Wide confidence intervals												
¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer												
¹¹ Outcome not clearl	y defined - thre	esholds for 'elevated'	' aspartate aminot	ransferase and a	lanine aminotrans	ferase not given						
¹² Substitute for outco	ome of interest	(relapse)										
¹³ Prescribed doses o	f isoniazid and	streptomycin are ab	ove that recomme	ended by the Briti	ish National Form	ulary						
Abbreviations: CI, col	nfidence interv	al; OR, odds ratio				•						

A.9 RQs N and Q

A.9.1 Use of adjunctive corticosteroids in people with active tuberculosis

PULMONARY TUBERCULOSIS

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance
Mortality	(follow-up 1	to 3 years; as	sessed with: nur	nber of deaths)								
2 ^{1,2}	randomised trials	serious ^{3,4}	very serious ^{5,6}	serious ⁷	serious ⁸	none	17/184 (9.2%)	14/181 (7.7%)	OR 1.28 (0.59 to 2.77) ^{9,20}	2 more per 100 (from 3 fewer to 11 more)	⊙OOO VERY LOW	
Respons	e to treatmen	nt – sputum co	onversion at 1 mo	onth (assessed	with: number	of patients to have	e a sputum culture	negative for M. tube	erculosis af	ter 1 month	of treatm	ent)
2 ^{2,10}	randomised trials	serious ^{11,12}	very serious ^{6,13}	very serious ^{14,15}	serious ⁸	none	139/354 (39.3%)	115/363 (31.7%)	OR 1.67 (0.65 to 4.31) ^{9,21}	12 more per 100 (from 9 fewer to 35 more)	⊙OOO VERY LOW	
Respons	e to treatmen	nt – sputum co	onversion at 2 mo	onths (assessed	l with: number	of patients to ha	ve a sputum cultur	e negative for M. tul	perculosis a	after 2 mont	hs of treat	ment)
2 ^{2,10}	randomised trials	serious ^{11,12}	very serious ^{6,13}	very serious ^{14,15}	serious ⁸	none	247/354 (69.8%)	247/363 (68%)	OR 1.08 (0.78 to 1.5) ^{9,22}	2 more per 100 (from 6 fewer to 8 more)	⊙OOO VERY LOW	
	e to treatmen	nt – sputum co	onversion at 3 mo	onths (assessed	d with: number	of patients to ha	ve a sputum cultur	e negative for M. tul	perculosis a	after 3 mont	hs of treat	ment)
1 ¹⁰	randomised trials	serious ^{11,12}	serious ¹³	very serious ^{14,15}	serious ⁸	none	187/261 (71.6%)	183/269 (68%)	OR 1.19 (0.82 to 1.72) ⁹	4 more per 100 (from 4 fewer to	⊙OOO VERY LOW	

			Quality asse	ssment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
					·					11 more)		
treatmer	•	symptoms - d	isappearance of	cavitation (asse	essed with: nu	mber of patients i	n whom cavitation	was present on adr	nission but	disappeare	d by the e	nd of
1 ¹⁰	randomised	serious ^{11,12}	serious ¹³	very	serious ⁸	none	103/245	88/250	OR 1.34	7 more	0000	
	trials			serious ^{14,15}			(42%)	(35.2%)	(0.93 to 1.92) ⁹	per 100 (from 2 fewer to 16 more)	VERY LOW	
		symptoms - r	adiographic impr	ovement (asses	ssed with: num	nber of patients to	achieve moderate	or greater radiogra	phic improv	ement after	r 2 months	s of
treatmen	randomised	a a mi a u a 11 12	serious ¹³		serious ⁸		130/261	107/269	OR 1.50	10	0000	
1.5	trials	senous	senous.	very serious ^{14,15}	senous	none	(49.8%)	(39.8%)	(1.06 to 2.12) ⁹	10 more per 100 (from 1 more to 19 more)	VERY LOW	
Change treatmer	nt) _		essening of cavit	ation (assessed	I with: number	of patients in wh	om the cavitation th	nat was present on	admission	had lessene	d by the e	end of
1 ¹⁰	randomised trials	serious ^{11,12}	serious ¹³	very serious ^{14,15}	serious ⁸	none	97/245 (39.6%)	111/250 (44.4%)	OR 0.82 (0.57 to 1.17) ⁹	5 fewer per 100 (from 13 fewer to 4 more)	⊙OOO VERY LOW	
			endobronchial les	sions (assessed	d with: number	of endobronchia	lesions identified	using bronchoscop	y before tre	atment to h	ave impro	oved after 2
	of treatment ¹⁶			i .								
1 ¹⁷	randomised trials		serious ¹⁸	no serious indirectness	serious ⁸	none	24/35 (68.6%)	22/30 (73.3%)	OR 0.79 (0.27 to 2.33) ⁹	5 fewer per 100 (from 31 fewer to 13 more)	⊙OOO VERY LOW	
								efore treatment to I	· · · · ·			treatment ¹⁶)
1 ¹⁷	randomised trials		serious ¹⁸	no serious indirectness	serious ⁸	none	22/35 (62.9%)	23/30 (76.7%)	OR 0.68 (0.19 to 2.48) ⁹	8 fewer per 100 (from 38 fewer to 12 more)	⊙OOO VERY LOW	
					-		lapse during follow					
2 ^{1,10}	randomised trials	very serious ^{3,4,11,} 12	serious ^{5,13}	serious ⁷	very serious ^{8,19}	none	5/352 (1.4%)	6/356 (1.7%)	OR 0.86 (0.26 to 2.84) ^{9,23}	0 fewer per 100 (from 1 fewer to 3 more)	⊙OOO VERY LOW	

² Mayanja-Kizza et al, 2005
 ³ Bilaçeroglu et al, 1999: method of randomisation and use of allocation concealment is unclear
 ⁴ Bilaçeroglu et al, 1999: only laboratory staff and those reading chest scans were blinded
 ⁵ Bilaçeroglu et al, 1999: follow-up period was appropriate (1 to 3 years), although it is unclear if it was the same in each group

	Quality assessment						No of p	atients	Eff	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	plus	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)		Importance

⁶ Mayanja-Kizza et al, 2005: fever and night sweats were present at baseline in significantly more patients who went on to receive prednisolone than amongst those that went on to receive placebo

⁷ Bilaçeroglu et al, 1999: antituberculosis regimens do not use all of or just the 4 standard recommended drugs

⁸ GRADE rule of thumb: <300 events

⁹ Odds ratio and 95% confidence interval calculated by reviewer

¹⁰ Tuberculosis Research Centre (Madras), 1983

¹¹ Tuberculosis Research Centre (Madras) (1983) and Park et al (1997): method of randomisation and use of allocation concealment and blinding is unclear

¹² Unclear if the analysis follows the intent-to-treat principle

¹³ Tuberculosis Research Centre (Madras), 1983: unclear if the groups were comparable for treatment completion and availability of outcome data

- ¹⁴ Outcome is a substitute for an outcome of interest
- ¹⁵ Tuberculosis Research Centre (Madras), 1983: antituberculosis regimens do not use all of or just the 4 standard recommended drugs; in particular, rifampicin is not used throughout
- ¹⁶ See evidence table for full definition

¹⁷ Park et al, 1997

¹⁸ Follow-up not for the full treatment period

¹⁹ Wide confidence interval

²⁰ Forest plot (mortality):

²¹ Forest plot (response to treatment – sputum conversion at 1 month):

²² Forest plot (response to treatment – sputum conversion at 2 month):

²³ Forest plot (relapse):

Prednisolone vs antituberculosis chemotherapy alone or plus placebo in people with HIV

		Quality asses	ssment			No of p	atients	Ef	fect		
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
(HIV-positive) (follow-up 1	to 3 years; asses	ssed with: num	ber of deaths)							
randomised trials	no serious risk of bias	serious ²	no serious indirectness	serious ³	none	17/93 (18.3%)	14/94 (14.9%)	OR 1.28 (0.59 to 2.77) ⁴	3 more per 100 (from 6 fewer to 18 more)	©©OO LOW	
ee survival (H	IV-positive) (f	follow-up 1 to 3 y	ears; assessed	with: number	of patients to surv	vive to 36 months v	vithout significant a	dverse eve	nt)		
randomised trials	no serious risk of bias	serious ²	serious ⁵	serious ³	none	36/93 (38.7%)	40/94 (42.6%)	OR 0.85 (0.48 to 1.53) ⁴	4 fewer per 100 (from 16 fewer to 11 more)	⊙OOO VERY LOW	
	(HIV-positive randomised trials ee survival (H randomised	Design bias (HIV-positive) (follow-up 1 randomised no serious trials risk of bias	Risk of biasInconsistency(HIV-positive) (follow-up 1 to 3 years; asser randomised trialsno serious risk of biasee survival (HIV-positive) (follow-up 1 to 3 y randomised no seriousserious²	DesignbiasInconsistencyIndirectness(HIV-positive)(follow-up 1to 3 years; assessed with: num randomised risk of biasno serious serious²no serious indirectnessee survival (HIV-positive)(follow-up 1 to 3 years; assessed serious²serious²serious²randomised randomisedno seriousserious²serious²	Risk of biasInconsistencyIndirectnessImprecision(HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) randomised trialsno serious risk of biasserious²no serious indirectnessserious³ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number randomised no seriousfollow-up 1 to 3 years; assessed with: number serious³	Risk of biasInconsistencyIndirectnessImprecisionOther considerations(HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) randomised trialsno serious reseriousserious2no serious indirectnessserious3noneee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survival randomised no seriousserious2serious3none	Risk of bias Inconsistency Indirectness Imprecision Other considerations Antituberculosis chemotherapy plus Design bias Inconsistency Indirectness Imprecision Other considerations Antituberculosis chemotherapy plus (HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) trials no serious risk of bias serious ² no serious indirectness serious ³ none 17/93 (18.3%) ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survive to 36 months w randomised no serious serious ⁵ serious ³ none 36/93	Risk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy plus prednisoloneAntituberculosis chemotherapy alone or plus placebo(HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) randomised trialsno serious serious²serious²no serious indirectnessserious³none17/93 (18.3%)14/94 (14.9%)ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survive to 36 months without significant a randomised no seriousserious²serious²serious³none36/9340/94	Risk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy plusAntituberculosis chemotherapy alone or plusRelative (95% CI)(HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) randomised trialsno serious risk of biasserious²no serious indirectnessserious³none17/93 (18.3%)14/94 (14.9%)OR 1.28 (0.59 to 2.77)4ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survive to 36 months without significant adverse ever randomised trialsno serious risk of biasserious²serious⁵ 	Risk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy plus prednisoloneAntituberculosis chemotherapy alone or plus placeboRelative (95% CI)Absolute (95% CI)(HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) randomised trialsno serious risk of biasserious²no serious indirectnessserious³none17/93 (18.3%)14/94 (14.9%)OR 1.28 (0.59 to 2.77)43 more per 100 (from 6 fewer to 18 more)ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survive to 36 months without significant adverse event)3 more per 100 (from 6 fewer to 18.3%)0R 0.85 (0.48 to 1.53)440/94 (12.6%)OR 0.85 (0.48 to per 100 (from 16 fewer to 1.53)4	Risk of bias Inconsistency Indirectness Imprecision Other considerations Antituberculosis chemotherapy plus prednisolone Antituberculosis chemotherapy alone or plus placebo Relative (95% CI) Absolute (95% CI) Quality (HIV-positive) (follow-up 1 to 3 years; assessed with: number of deaths) trials no serious risk of bias serious ² no serious indirectness serious ³ none 17/93 (18.3%) 14/94 (14.9%) OR 1.28 (0.59 to 2.77) ⁴ 3 more per 100 (from 6 fewer to 18 more) ©©OO LOW ee survival (HIV-positive) (follow-up 1 to 3 years; assessed with: number of patients to survive to 36 months without significant adverse event) 00 OO 18 more) 00 OO VERY (42.6%) OR 0.85 (0.48 to 1.53) ⁴ 4 fewer per 100 VERY LOW

			Quality asses	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
1 ¹	randomised trials	no serious risk of bias	serious ²	no serious indirectness	very serious ^{3,7}	none	1/93 (1.1%)	1/94 (1.1%)	OR 1.01 (0.06 to 16.41) ⁴	0 more per 100 (from 1 fewer to 14 more)	⊙OOO VERY LOW	onth of
treatmen		i – sputum co	onversion at 1 mc	onin (Hiv-positi	ve) (assessed	with: humber of p	atients to have a s	outum culture nega	live for IVI. L	uperculosis	s alter 1 m	onun oi
1 ¹	randomised trials	no serious risk of bias	serious ²	serious⁵	serious ³	none	58/93 (62.4%)	35/94 (37.2%)	OR 2.79 (1.54 to 5.05) ⁴	25 more per 100 (from 11 more to 38 more)	⊙OOO VERY LOW	
						rence within 2 yea	ars of initiating trea	tment ⁶)				
1 ¹	randomised trials	no serious risk of bias	serious ²	serious ⁵	serious ³	none	8/93 (8.6%)	11/94 (11.7%)	OR 0.71 (0.27 to 1.85) ⁴	3 fewer per 100 (from 8 fewer to 8 more)	⊙OOO VERY LOW	
				er of patients t	o experience a	ny adverse event)						
1 ¹	randomised trials	no serious risk of bias	serious ²	no serious indirectness	very serious ^{3,7}	none	87/93 (93.5%)	82/94 (87.2%)	OR 2.55 (0.86 to 7.54) ⁴	7 more per 100 (from 2 fewer to 11 more)	⊙OOO VERY LOW	
Respons treatmen		t – sputum co	onversion at 2 mo	onths (HIV-posi	tive) (assessed	d with: number of	patients to have a s	sputum culture neg	ative for M.	,	is after 2 n	nonths of
1 ¹	randomised trials	risk of bias	serious ²	serious⁵	serious ³	none	80/93 (86%)	80/94 (85.1%)	OR 1.08 (0.48 to 2.44) ⁴	1 more per 100 (from 12 fewer to 8 more)	⊙OOO VERY LOW	
				itive) (assessed		nts to experience		eatening adverse ev				
1 ¹	randomised trials	no serious risk of bias	serious ²	no serious indirectness	serious ³	none	22/93 (23.7%)	18/94 (19.1%)	OR 1.31 (0.65 to 2.64) ⁴	5 more per 100 (from 6 fewer to 19 more)	⊙⊙OO LOW	
¹ Mayanja	a-Kizza et al, 2	005								· · ·		

¹ Mayanja-Kizza et al, 2005
 ² Fever and night sweats were present at baseline in significantly more patients who went on to receive prednisolone than amongst those that went on to receive placebo
 ³ GRADE rule of thumb: <300 events
 ⁴ Odds ratio and 95% confidence interval calculated by reviewer
 ⁵ Outcome is a substitute for an outcome of interest
 ⁶ See evidence table for full definition

⁷ Wide confidence interval

Prednisolone vs antituberculosis chemotherapy alone or plus placebo in people without HIV

			Quality asses	ssment			No of p	oatients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importanc
/lortality	(HIV-negative	e) (follow-up	1 to 3 years; asse	essed with: nun	nber of deaths)						
¹	randomised trials	serious ^{2,3}	serious ⁴	serious⁵	very serious ^{6,7}	none	0/91 (0%)	0/87 (0%)	OR 0.96 (0.02 to 48.73) ⁸	-	⊙OOO VERY LOW	
Respons vas initi		t - decrease	in bacillary count	(HIV-negative)	(follow-up 50	days; assessed w	ith: number of to ex	perience a drop in l	/	ount 50 days		Inisolone
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	very serious ^{5,9}	very serious ^{6,7}	none	91/91 (100%)	81/87 (93.1%)	OR 14.60 (0.81 to 263.12) ⁸	6 more per 100 (from 1 fewer to 7 more)	⊙OOO VERY LOW	
	e to treatmen olone was initi		ecrease in bacilla	ry count (HIV-n	egative) (follov	w-up 50 days; ass	essed with: number	r of to experience a	marked dro	op in bacilla	ry count 5	0 days afte
1 ¹	randomised trials	,	serious ⁴	very serious ^{5,9}	serious ⁷	none	78/91 (85.7%)	54/87 (62.1%)	OR 3.67 (1.77 to 7.61) ⁸	24 more per 100 (from 12 more to 30 more)	⊙OOO VERY LOW	
hange i	in signs and s	ymptoms - fe	ever (HIV-negativ	e) (measured w	ith: change in	temperature within	n 72 hours; better i	ndicated by lower v	alues)			
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	serious⁵	serious ¹⁰	none	91	87	-	MD 1.4°C higher ¹¹	⊙OOO VERY LOW	
Change i	in signs and s	ymptoms - w	veight (HIV-negati	ive) (measured	with: weight c	hange during trea	tment; better indica	ted by lower values)			
1	randomised trials		serious ⁴	serious⁵	serious ¹⁰	none	91	87	-	MD 1.4kg higher ¹¹		
	in signs and s olone initiatior		narked radiograp	hic improvemer	nt (HIV-negativ	ve) (assessed with	: number of patient	s to experience mar	ked radiog	raphic impre	ovement 5	0 days afte
1 ¹	randomised trials		serious ⁴	serious ⁵	serious ⁷	none	15/91 (16.5%)	8/87 (9.2%)	OR 1.95 (0.78 to 4.86) ¹¹	7 more per 100 (from 2 fewer to 24 more)	⊙OOO VERY LOW	
	in signs and s after predniso			ovement (HIV-n	egative) (asse	ssed with: numbe	r of patients to exp	erience radiographi	c improven	,	d, modera	te or slight)
1	randomised trials		serious⁴	serious ⁵	very serious ^{6,7}	none	91/91 (100%)	83/87 (95.4%)	OR 9.86 (0.52 to 185.96) ¹	4 more per 100 (from 4 fewer to 5 more)	⊙OOO VERY LOW	

³ Bilaçeroglu et al, 1999: only laboratory staff and those reading chest scans were blinded
 ⁴ Bilaçeroglu et al, 1999: follow-up period was appropriate (1 to 3 years), although it is unclear if it was the same in each group
 ⁵ Bilaçeroglu et al (1999) and Tuberculosis Research Centre (Madras) (1983): antituberculosis regimens do not use all of or just the 4 standard recommended drugs

			Quality asses	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
⁶ Wide co	⁶ Wide confidence interval											
⁷ GRADE	rule of thumb	: <300 events										
⁸ Odds ra	tio and 95% c	onfidence inter	val calculated by i	reviewer								
⁹ Outcom	⁹ Outcome is a substitute for an outcome of interest											
¹⁰ Authors	s did not provid	de sufficient da	nta to calculate a c	onfidence interv	al							
		ulated bv revie										

¹² See evidence table for full definition

PLEURAL TUBERCULOSIS

Dexamethasone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment	-	· ·	No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Changes	in signs and	symptoms –	weight (follow-up	o unclear; meas	sured with: we	ight at the end of	follow-up; better ind	dicated by higher va	lues)			
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 1.6kg higher ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -		ollow-up uncle	ar; measured v	with: change in me	ean weight from bas	seline to the end of	follow-up; b	etter indica	ted by hig	her values)
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 0.5kg higher ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	cough (follow-up	unclear; meas	ured with: tim	e to relief of coug	h; better indicated k	oy lower values)				
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 12.1days lower ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	pleural effusion ((follow-up uncle	ear; measured	with: time taken f	or complete absorp	tion of pleural effus	ion; better	indicated by	y lower val	ues)
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 47.7 days lower ⁹	⊙OOO VERY LOW	
Changes values)	in signs and	symptoms –	large pleural effu	ision (follow-up	o unclear; mea	sured with: time ta	aken for complete a	bsorption of a large	pleural effu	usion; bette	r indicated	l by lower
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	9	4	-	MD 63.8 days lower ⁹	⊙OOO VERY LOW	
Changes lower val		symptoms –	medium pleural e	effusion (follow	-up unclear; m	neasured with: tim	e taken for complet	e absorption of a m	edium pleu	ral effusion	; better inc	licated by
1 ¹	non- randomised	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	16	12	-	MD 50.0 days	⊙OOO VERY	

			Quality asses	ssment			No of p	oatients	Ef	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
	trials									lower ⁹	LOW	
Changes values)	in signs and	symptoms –	small pleural eff	usion (follow-u	o unclear; mea	sured with: time t	aken for complete a	bsorption of a sma	ll pleural ef	fusion; bett	er indicate	d by lower
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	5	4	-	MD 30.0 days lower ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	chest pain (follow	w-up unclear; n	neasured with:	time to relief of c	hest pain; better in	dicated by lower val	ues)			
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 13.8 days lower ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	shortness of bre	ath (follow-up u	unclear; measu	ured with: time to	relief of shortness	of breath; better ind	icated by Ic	wer values		
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 12.6 days lower ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	temperature (foll	ow-up unclear;	measured wit	h: time to normali	sation of temperatu	re; better indicated	by lower va	alues)		
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ⁸	none	30	20	-	MD 19.8 days lower ⁹	⊙OOO VERY LOW	
Recurren	nce (follow-up	unclear; ass	essed with: num	ber of patients	to experience	recurrence)						
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious ⁷	serious ¹⁰	none	0/39 (0%)	4/20 (20%)	OR 0.06 (0 to 1.19) ¹¹	19 fewer per 100 (from 20 fewer to 3 more)	⊙OOO VERY LOW	
 ² No ranc ³ No alloc ⁴ No blind ⁵ Unclear ⁶ Unclear ⁷ Antitube ⁸ Authors ⁹ Mean d ¹⁰ GRAD 	if the groups w if the groups r erculosis regim did not provid ifference calcu E rule of thumb	nent vere compara received the sa ens do not us e sufficient da lated by review	e all of or just the ta to calculate a co wer	4 standard recor	nmended drugs	etails provided are s; of particular note		ot used, and that only	/ a 2-drug re	igimen was i	used	

¹¹ Odds ratio and 95% confidence intervals

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	oatients	Eff	fect	
No of studies	5 Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy plus	Antituberculosis chemotherapy alone or plus placebo	Relative	Absolute (95% Cl)	Importance

					Other	Antituberculosis chemotherapy	Antituberculosis chemotherapy				
cluding fever,				Imprecision	Other considerations	plus prednisolone	alone or plus placebo	Relative (95% CI)	Absolute (95% Cl)	Quality	Importanc
	, chest pain and dy	· · · · · · · · · · · · · · · · · · ·			s (follow-up uncle	ear; measured with:	time to disappeara	nce of clinio	cal signs an	d sympton	ns
		no serious	serious ⁶	r values) no serious	none	21	19		MD 6.8	0000	
trials	serious ^{2,3,4}	inconsistency ⁵	Sellous	imprecision	none	21	19	-	days lower (14.3 lower to 0.07 higher) ⁷	VERY LOW	
	s and symptoms - visualisation of the						usion (as defined b	y roentgend	ologic evide	nce of clea	aring of the
	nised very serious ^{2,3,4}	no serious inconsistency ⁵	serious ⁶	serious ⁸	none	21	19	-	MD 68.7 days lower ⁷	⊙OOO VERY LOW	
		- fever (follow-up	unclear; measu	red with: dura	tion of fever at 46	months; better ind	icated by lower valu	les)			
random trials	nised serious ²	no serious inconsistency ⁵	serious ⁶	serious ⁸	none	57	60	-	MD 0.83 days lower ⁷	⊙OOO VERY LOW	
anges in sign	s and symptoms -	- pleural adhesior	ns (follow-up ur	clear; assesse	ed with: number o	f patients to experi	ence pleural adhesi	ons)			
random trials	nised very serious ^{2,3,4}	no serious inconsistency⁵	serious ⁶	serious ¹⁰	none	1/21 (4.8%)	3/19 (15.8%)	OR 0.27 (0.03 to 2.82) ¹⁴	11 fewer per 100 (from 15 fewer to 19 more)	⊙OOO VERY LOW	

¹⁴ Odds ratio and 95% confidence interval calculated by reviewer

Prednisolone vs antituberculosis chemotherapy alone or plus placebo in people with HIV

			Quality asse				No of r	patients	Eff	t		
			Quality asse	ssment			•	1	EII	eci		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importanc
	· ·	<i>,</i> ,	with: mortality			r values)						
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	98	rate ratio 0.84 deaths/100 person years higher (0.53 to 1.32 higher)	-	⊙⊙⊙ HIGH	
Changes	in signs and	symptoms -	- anorexia (HIV-p	ositive) (asses	sed with: num	ber of patients to	be anorexic after 2	4 weeks of treatme	nt)			
1 ¹	randomised trials	risk of bias	no serious inconsistency	no serious indirectness	very serious ^{2,3}	none	12/99 (12.1%)	3/98 (3.1%)	OR 4.37 (1.19 to 16)⁴	9 more per 100 (from 1 more to 31 more)	©⊙OO LOW	
Changes	in signs and	symptoms -	- weight (HIV-po	sitive) (measur	ed with: weigh	t after 24 weeks o	f treatment; better i	indicated by higher	values)			
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious⁵	none	99	98	-	MD 3kg higher ⁶	0000 MODERATE	
Changes	in signs and	symptoms -	- cough (HIV-pos	sitive) (assesse	d with: numbe	or of patients with	a cough after 24 we	eks of treatment)				
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	26/99 (26.3%)	14/98 (14.3%)	OR 2.14 (1.04 to 4.4) ⁶	12 more per 100 (from 0 more to 28 more)	©⊙⊙O MODERATE	
Changes	in signs and	symptoms -	 pleural effusior 	n (HIV-positive)	(assessed wit	th: number of pati	ents with pleural ef		ks of treatme	nt)		
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	7/99 (7.1%)	17/98 (17.3%)	OR 0.36 (0.14 to 0.92) ⁴	10 fewer per 100 (from 1 fewer to 14 fewer)	©⊙⊙O MODERATE	
	nce (HIV-posit	ive) (measu	red with: recurre	nce rate; bette	r indicated by	lower values)						
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious ⁷	no serious imprecision	none	99	98	-	recurrenc e rate 2.3 higher (0.6 to 9 higher)	©⊙⊙ MODERATE	

No of Busion Risk of bias Inconsistency Inconsistency inconsistency indirectness Indirectness indirectness Antituber of pathsolone Antituber culousis predinisolone Antituber culousis plus Relative plus Absolut plus Absolut plus Adverse events - incidence of HV-related disease: no serious inconsistency blas no seri				Quality asse	ssment			No of p	oatients	Ef	fect		
placebolgrednisolone trials or construction		Design		Inconsistency	Indirectness	Imprecision		chemotherapy plus	chemotherapy alone or plus			Quality	Importance
11 randomised insist no serious inconsistency bias no serious inconsistency inconsistency serious indirectness serious ² serious ² none 9/99 (9.1%) 2/98 (2%) OR 4.80 (10 to 22.82) ⁴ 7 more inconsistency inconsistency 0 00 0 MODERATE inconsistency Advorse events - incidence of HIV-related disease: Kaposi sarcoma inconsistency no serious inconsistency very serious ² none 9/99 9/99 2/98 2/98 OR 4.80 (2%) OR 4.80 (10 to 22.82) ⁴ Or more inconsistency 00 0 0 00 0 0 41 randomised inconsistency no serious inconsistency no serious ² inconsistency none 9/99 9/99 2/98 2/98 OR 13.70 (2%) 20 more inconsistency 00 0 0 00 0 0 Advorse events - incidence of HIV-related disease: cryptococcal moningitis (HIV-positive) (assessed with: number of patients to experience cryptococcal moningitis) 10 0 0 00 0 0 00 0 0 0 00 0 0 0 0 0 0 0			•	nt discontinuatio	on (HIV-positive	e) (assessed w	ith: number of pat	tients to experience	an adverse event t	hat required	discontinua	tion of	
11 randomised trials no serious nisk of bias no serious inconsistency bias no serious inconsistency inconsistency bias no serious inconsistency inconsistency bias no serious inconsistency inconsistency inconsistency inconsistency serious ² inconsistency inconsistency no serious inconsistency inconsistency serious ² inconsistency no serious inconsistency serious ² inconsistency no ser	1 ¹	randomised trials	no serious risk of bias	inconsistency	indirectness			(9.1%)	(2%)	(1.01 to 22.82) ⁴	per 100 (from 0 more to 30 more)		
trials risk of bias inconsistency bias indirectness inconsistency trials serious inconsistency trials inconsistency inconsistency bias indirectness inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious inconsistency indirectness serious indirectness serious ² inconsistency indirectness no serious inconsistency indirectness serious ² inconsistency indirectness no serious indirectness serious ² inconsistency indirectness no serious indirectness no serious indirectness serious ² indirectness none 35/99 (35.4%) 23/98 (23.5%) OR 1.78 (0.6 to 23.32)* 12 more 0000 O (0.6 to 27.37)* MODERATE (0.6 to 27.37)* 11 randomised indirectness no serious indirectness no serious indirectness serious ² indirectness none 22/99 (22.2%) 19/98 (19.4%) OR 1.19 (0.6 to 2.3.37)* more indirectnes 000O (0.6 to 2.3.37)* 11 randomised indirectness no serious indirectness serious ² indirectness none 22/99 (22.2%)						· · ·					,		
11 randomised trials no serious bias no serious inconsistency no serious indirectness serious ² serious ² none 3/99 (3%) 5/98 (5.1%) OR 0.58 (14 to 2.5%) 2 fewer (0.14 to 2.5%) 0 @00 (14 to 2.5%) MODERATE (from 4 fewer to 7 MODERATE (from 4 fewer to 7 Adverse events - incidence of HIV-related disease: os serious inconsistency no serious indirectness serious ² serious ² none 35/99 (35.4%) 23/98 (23.5%) OR 1.78 (0.96 to 3.32) ⁴ 12 more per 100 (17m 1 fewer to 7 00000 mODERATE (from 1 fewer to 7 11 randomised trials no serious no serious indirectness no serious ² serious ² none 35/99 (35.4%) 23/98 (23.5%) OR 1.78 (0.96 to 3.32) ⁴ 12 more per 100 (0.6 to 2.7) ⁴ MODERATE per 100 (0.6 to 2.7) ⁴ 11 frandomised trials no serious indirectness no serious indirectness serious ² serious ² none 22/99 (22.2%) 19/98 (19.4%) OR 1.19 (0.6 to 2.3) ⁴ 3 more fewer to 0/000 MODERATE (from 7 fewer to 2.7) ⁴ 11 randomised trials no serious indirectness no serious indirectness serious ² serious ² none 22/99 (22.2%) 20/98 (20.4%) OR 1.11 (0.56 to 2.21) ⁴ 2 more fewer to 0/000 MODERATE fewer to </td <td></td> <td>trials</td> <td>risk of bias</td> <td>inconsistency</td> <td>indirectness</td> <td>serious^{2,3}</td> <td></td> <td>(9.1%)</td> <td>(2%)</td> <td>(0.76 to 246.52)⁴</td> <td>per 100 (from 0 fewer to 82 more)</td> <td>LOW</td> <td></td>		trials	risk of bias	inconsistency	indirectness	serious ^{2,3}		(9.1%)	(2%)	(0.76 to 246.52) ⁴	per 100 (from 0 fewer to 82 more)	LOW	
trials risk of blas inconsistency indirectness online (3%) (5.1%) (0.14 to 2.5) ⁴ per 100 (from 4 fewer to 7 more) MODERATE Adverse events - incidence of HIV-related disease: oesophageal candidiasis (HIV-positive) (assessed with: number of patients to experience oesophageal candidiasis trials no serious no serious <td></td> <td>events - incid</td> <td>lence of HIV</td> <td>-related disease:</td> <td>cryptococcal</td> <td>meningitis (HI</td> <td>V-positive) (asses</td> <td>sed with: number o</td> <td>f patients to experi</td> <td>ence cryptoo</td> <td>coccal menin</td> <td></td> <td></td>		events - incid	lence of HIV	-related disease:	cryptococcal	meningitis (HI	V-positive) (asses	sed with: number o	f patients to experi	ence cryptoo	coccal menin		
11 randomised trials no serious risk of bias no serious indirectness serious ² none 35/99 23/98 QR 1.78 12 more per 100 MODERATE Adverse events - incidence of HIV-related disease: herpes zoster (HIV-positive) (assessed with: number of patients to experience herpes zoster) Torre 33.21 ⁴ 3 more per 100 MODERATE 11 randomised trials no serious risk of bias no serious indirectness no serious ² none 22/99 19/98 QR 1.78 12 more per 100 MODERATE 11 randomised trials no serious risk of bias no serious indirectness no serious ² none 22/99 19/98 QR 1.18 3 more per 100 MODERATE Adverse events - incidence of HIV-related disease: no serious risk of bias no serious indirectness no serious ² none 22/99 (2.2%) QR 1.11 2 more per 100 MODERATE 11 randomised trials no serious risk of bias no serious indirectness no serious ² none 22/99 20/98 QR 1.11 2 more per 100 MODERATE 11 randomised trials no serious risk of bias no serious indirectness	1 ¹		risk of			serious ²	none			(0.14 to	per 100 (from 4 fewer to 7		
trials risk of bias inconsistency indirectness indirectness (35.4%) (23.5%) (0.96 to 3.32) ⁴ per 100 (from 1 fewer to 27 more) MODERATE Adverse events - incidence of HIV-related disease: herpes zoster (HIV-positive) (assessed with: number of patients to experience herpes zoster) MODERATE MODERATE 11 randomised bias no serious inconsistency no serious inconsistency no serious inconsistency no serious ² none 22/99 (22.2%) 19/98 (19.4%) OR 1.19 (0.6 to 2.37) ⁴ 3 more per 100 (from 7 fewer to 17 3 more per 100 (from 7 fewer to 17 0 @ O MODERATE 11 randomised trials no serious no serious inconsistency no serious inconsistency no serious ² inconsistency none 22/99 (22.2%) 20/98 (20.4%) OR 1.11 (0.56 to 2.21) ⁴ 2 more per 100 (from 7 fewer to 17 @ @ @ @ 11 randomised trials no serious inconsistency no serious ² inconsistency none 22/99 (22.2%) 20/98 (20.4%) OR 1.11 (0.56 to 2.21) ⁴ 2 more per 100 (from 8 fewer to 16 @ @ @ @ 11 randomised trials no serious risk of bias no serious inconsistency no serious ² indirectness none 31/99 (31.3%) 31/98 (31.6%) OR 1.43 (0.7	Adverse	events - incid	lence of HIV	-related disease:	oesophageal	candidiasis (H	IV-positive) (asses	ssed with: number of	of patients to exper	ience oesop	hageal cand	idiasis)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1 ¹		risk of			serious ²	none			(0.96 to	per 100 (from 1 fewer to		
trialsrisk of biasinconsistencyindirectnessindirectnessindirectness(22.2%)(19.4%)(0.6 to 2.37)4per 100 (from 7 fewer to 17 more)MODERATEAdverse events - incidence of HIV-related disease:oral or genital herpes simplex(HIV-positive) (assessed with: number of patients to experience oral or genital herpes simplexMODERATE11randomised trialsno serious inconsistencyno serious indirectnessserious ² none22/99 (22.2%)20/98 (20.4%)OR 1.11 (0.5 to 2.21)42 more per 100 (0.5 to per 100 (16 more) $\Theta \odot \odot$ MODERATEAdverse events - incidence of HIV-related disease:oral thrush (HIV-positive) (assessed with: number of patients to experience oral thrush (16 more)MODERATE $\Theta \odot \odot$ Adverse events - incidence of HIV-related disease:oral thrush (HIV-positive) (assessed with: number of patients to experience oral thrush (19.4%)0R 1.11 (0.5 to 2.21)42 more per 100 (16 more)11randomised trialsno serious no serious biasno serious inconsistencyno serious ² indirectnessnone31/99 (31.3%)31/98 (31.6%)OR 1.43 (0.79 to 2.56)48 more (from 5 fewer to 2.56)4 $\Theta \odot \odot$ MODERATE	Adverse	events - incid	lence of HIV	-related disease:	herpes zoster	(HIV-positive)	(assessed with: r	number of patients	o experience herpe	es zoster)			
1^{1} randomised trialsno serious no serious inconsistencyno serious indirectnessserious^2none $22/99$ (22.2%) $20/98$ $OR 1.11$ (0.56 to 2.21)4 2 more per 100 (from 8 fewer to 16 more) $\Theta \odot \odot O$ MODERATEAdverse events - incidence of HIV-related disease:oral thrush (HIV-positive) (assessed with: number of patients to experience oral thrush trialsoral serious no serious inconsistencyno serious serious^2none $31/98$ (31.3%) $OR 1.43$ (20.4%)8 more per 100 2.21)4 $\Theta \odot \odot O$ MODERATE 1^1 randomised trialsno serious piasno serious inconsistencyserious^2 indirectnessnone $31/99$ (31.3%) $31/98$ (31.6%) $OR 1.43$ (0.79 to 2.56)48 more per 100 (from 5 fewer to		randomised	no serious risk of	no serious	no serious			22/99	19/98	OR 1.19 (0.6 to	per 100 (from 7 fewer to		
trialsrisk of biasinconsistency biasindirectnessindirectnessindirectness(22.2%)(20.4%)(0.56 to $2.21)^4$ per 100 (from 8 fewer to 16 more)MODERATEAdverse events - incidence of HIV-related disease: oral thrush (HIV-positive) (assessed with: number of patients to experience oral thrushMODERATE11randomised trialsno serious no serious inconsistencyno serious indirectnessserious ² serious ² none31/99 (31.3%)31/98 (0.79 to 2.56)^4OR 1.43 (from 5 fewer to per 100 (from 5 fewer to8 more per 100 (from 5 fewer to	Adverse	events - incid	lence of HIV	-related disease:	oral or genital	herpes simple	ex (HIV-positive) (assessed with: nun	ber of patients to e	experience o	ral or genital	herpes simp	lex)
11randomised trialsno serious risk of biasno serious inconsistencyno serious indirectnessnone31/99 (31.3%)31/98 (31.3%)OR 1.43 (0.79 to 2.56)48 more per 100 (from 5 fewer to©⊙⊙ MODERATE	1 ¹		risk of			serious ²	none			(0.56 to	per 100 (from 8 fewer to		
trials risk of bias inconsistency indirectness (31.3%) (31.6%) (0.79 to per 100 (from 5 fewer to	Adverse	events - incid	lence of HIV	-related disease:	oral thrush (H	IV-positive) (as	ssessed with: nun	nber of patients to e	experience oral thru	ush)			
		trials	risk of bias	inconsistency	indirectness			(31.3%)	(31.6%)	(0.79 to 2.56) ⁴	per 100 (from 5 fewer to		
Adverse events - incidence of HIV-related disease: gastroenteritis (HIV-positive) (assessed with: number of patients to experience gastroenteritis)) (assessed with:						
11randomised trialsno serious risk ofno serious inconsistencyno serious indirectnessserious² serious²none34/99 (34.3%)28/98 (28.6%)OR 1.32 (0.72 to6 more per 100⊙⊙⊙O MODERATE	1 ¹					serious ²	none						

			Quality asse	ssment			No of p	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
		bias							2.39)4	(from 6 fewer to 20 more)		
 ² GRADE ³ Wide co ⁴ Odds rational ⁵ Authors ⁶ Mean data 	did not provid fference calcu	vals onfidence int le sufficient d lated by revie	erval calculated b ata to calculate a		val							

Prednisolone vs antituberculosis chemotherapy alone or plus placebo in people without HIV

			Quality asse	essment			No of J	patients	Ef	fect		
No of studies Changes	Design	Risk of bias symptoms -				Other considerations unclear; measure	Antituberculosis chemotherapy plus prednisolone d with: Index of rea	Antituberculosis chemotherapy alone or plus placebo bsorption of pleura	Relative (95% Cl) I hemithora	Absolute (95% CI) ax at 12 mon	Quality ths; bette	Importance r indicated
by lower	values)											
1 ¹⁰	randomised trials	serious ²	no serious inconsistency ⁴	serious ⁶	very serious ^{10,11}	none	57	60	-	MD 4% higher (18 lower to 26 higher) ⁹	⊙OOO VERY LOW	
	in signs and	symptoms -				ssessed with: nun	nber of patients wit	h residual pleural th	ickening, a	s assessed	using a cl	nest x-ray)
2 ^{1,10}	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	serious ¹⁰	none	18/91 (19.8%)	23/96 (24%)	OR 0.60 (0.13 to 2.67) ^{8,11}	8 fewer per 100 (from 20 fewer to 22 more)	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	 pleural thickeni 	ing on CT scan	(HIV-negative)) (assessed with: I	number of patients	with residual pleura	I thickenin	g, as assess	ed using	a CT scan)
1 ¹	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	serious ⁷	none	17/34 (50%)	21/36 (58.3%)	OR 0.71 (0.28 to 1.84) ⁸	8 fewer per 100 (from 30 fewer to 14 more)	⊙OOO VERY LOW	
Changes lower va	•	symptoms -	 pleural thickeni 	ing on x-ray (Hi	V-negative) (m	easured with: ple	ural thickening at 2	4 weeks, as assess	ed using a	chest x-ray;	better ind	icated by
1 ¹	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	no serious imprecision	none	34	36	-	MD 0.4mm lower (1.9 lower to 1.1	⊙OOO VERY LOW	

			Quality asse	essment			No of	patients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importanc
										higher) ⁹		
Changes	in signs and	symptoms	 pleural thicken 	ing on x-ray (H	V-negative) (m	neasured with: cha	ange in pleural thic	kening from baselin	e to 24 wee		ssed using	g a chest x-
ay; bette	er indicated b	y lower valu										
1 ¹	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	no serious imprecision	none	34	36	-	difference in change in means 0.6mm lower ⁹	⊙OOO VERY LOW	
hanges ower va		symptoms	 pleural thicken 	ing on CT scan	(HIV-negative)) (measured with:	pleural thickening	at 24 weeks, as asso	essed using	g a CT scan;	better inc	licated by
	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	no serious imprecision	none	34	36	-	MD 1.3mm lower (3.4 lower to 0.8 higher) ⁹	©000 VERY LOW	
1	randomised trials	serious ^{2,3}			imprecision	none e an adverse even		36	-	1.3mm lower (3.4 lower to 0.8	VERY	

⁴ Unclear if the groups received the same care apart from the intervention(s) studied; details provided are limited

⁵ Although not statistically significant (p = 0.06), more patients receiving placebo (44.4%) had pleuritis and pulmonary tuberculosis than amongst those receiving prednisolone (21.2)

⁶ Antituberculosis regimens do not use all of or just the 4 standard recommended drugs; of particular note is that Galarza et al (1995) used only a 2-drug antituberculosis regimen

⁷ GRADE rule of thumb: <300 events

⁸ Odds ratio and 95% confidence interval calculated by reviewer

⁹ Mean difference and confidence interval calculated by reviewer

¹⁰ Galarza et al, 1995

¹¹ Forest plot (changes in signs and symptoms – pleural thickening):

TUBERCULOSIS WITH SEVERE BRONCHIAL OBSTRUCTION

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asse	essment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy plus			Absolute (95% Cl)	Quality	Importance

Changes in signs and symptoms – normalisation of radiological status (prednisolone; children) (assessed with: number of patients whose radiological score normalised during

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
treatmen	t)											
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	very serious ^{6,7}	none	13/15 (86.7%)	9/14 (64.3%)	OR 6.61 (0.57 to 22.9) ⁸	28 more per 100 (from 14 fewer to 33 more)	⊙OOO VERY LOW	
Changes 1 month)		symptoms	 improvement ir 	n radiological s	tatus (predniso	olone; children) (a	ssessed with: num	ber of patients who	se radiolog	ical score in	nproved w	ithin
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	very serious ^{6,7}	none	7/15 (46.7%)	0/14 (0%)	OR 22.59 (1.29 to 506.48) ⁸	-	⊙OOO VERY LOW	
Changes treatmen			 deterioration in 	radiological st	tatus (predniso	olone; children) (a	ssessed with: numl	ber of patients who	se radiolog	ical score de	eteriorated	during
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁶	none	2/15 (13.3%)	5/14 (35.7%)	OR 0.58 (0.04 to 1.76) ⁸	11 fewer per 100 (from 34 fewer to 14 more)	⊙OOO VERY LOW	
	in signs and I by higher va		 bronchoscopy 	score (prednis	olone; childrer	n) (measured with:	change in broncho	oscopy score from I	paseline to	,	st-treatmer	nt ⁹ ; better
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	very serious ^{6,7}	none	15	14	-	MD 6.20 higher (1.83 to 10.57 higher) ¹⁰	⊙OOO VERY LOW	
						lren) (assessed wi		nts to require >2 br	onchoscop			
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	serious⁵	serious ⁶	none	1/15 (6.7%)	6/14 (42.9%)	OR 0.10 (0.01 to 0.94) ⁸	36 fewer per 100 (from 2 fewer to 42 fewer)	⊙OOO VERY LOW	

² Unclear if allocation concealment was used

 ³ 'Open' trial, although examination of bronchoscopy and radiographs blinded
 ⁴ Unclear if the groups received the same care apart from the intervention(s) studied: 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

⁵ Outcome is a surrogate for an outcome of interest ⁶ GRADE rule of thumb: <300 events

⁷ Wide confidence intervals

⁸ Odds ratio and 95% confidence interval calculated by reviewer

⁹ See evidence table for full definition

¹⁰ Mean difference and 95% confidence interval calculated by reviewer

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Dexamethasone vs antituberculosis chemotherapy alone or plus placebo

			Quality asse	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(dexamethas	one) (follow	-up 3 months to	5 years; assess	sed with: num	per of deaths)						
5 ^{1,2,3,4,5}	randomised trials	very serious ^{6,7,8}	very serious ^{9,10,11,12}	serious ¹³	no serious imprecision	none	216/486 (44.4%)	232/457 (50.8%)	OR 0.79 (0.61 to 1.02) ^{14,33}	6 fewer per 100 (from 12 fewer to 0 more)	⊙OOO VERY LOW	
	•	•						sessed with: numbe		·		
3 ^{2,4,5}	randomised trials	very serious ^{6,7}	very serious ^{10,11,12}	serious ¹³	no serious imprecision	none	138/330 (41.8%)	144/310 (46.5%)	OR 0.85 (0.62 to 1.16) ^{14,33}	4 fewer per 100 (from 11 fewer to 4 more	⊙OOO VERY LOW	
	(dexamethas	sone; non-rai			ssessed with:	number of deaths						
1 ¹⁵	non- randomised trials	very serious ^{16,17} , ¹⁸	serious ^{19,20}	serious ¹³	serious ²¹	none	39/66 (59.1%)	42/70 (60%)	OR 0.96 (0.49 to 1.91) ¹⁴	1 fewer per 100 (from 18 fewer to 14 more)	⊙OOO VERY LOW	
	se to treatmen	it - full or par	tial recovery (de	xamethasone)		n: number of patie	ents to achieve a ful	Il or partial recovery	()			
14	randomised trials	very serious ^{22,23}	no serious inconsistency	very serious ^{24,25}	serious ²¹	none	15/24 (62.5%)	13/23 (56.5%)	OR 1.28 (0.4 to 4.12) ¹⁴	6 more per 100 (from 22 fewer to 28 more)	⊙OOO VERY LOW	
Respons	se to treatmen	t - poor outc	ome (dexametha	isone) (assess	ed with: numbe	er of patients to e	xperience a poor ou	utcome (death or su	rvival with	major seque	elae (persiste	nt vegetative
,				derate-to-sever		npairment, severe		ty (totally depender				
14	randomised trials	serious ²²	no serious inconsistency	very serious ^{24,25}	serious ²¹	none	5/24 (20.8%)	8/23 (34.8%)	OR 0.49 (0.13 to 1.82) ¹⁴	14 fewer per 100 (from 28 fewer to 14 more)	⊙OOO VERY LOW	
							experience a good o ance)) or no seque	outcome (survival w lae))	ith minor (r	nild intellect	ual impairme	nt, mild-to-
1 ⁴	randomised trials	serious ²²	no serious inconsistency	very serious ^{24,25}	serious ²¹	none	15/24 (62.5%)	13/23 (56.5%)	OR 1.28 (0.4 to 4.12) ¹⁴	6 more per 100 (from 22 fewer to 28 more)	⊙OOO VERY LOW	
						· · · · ·	•	ng patients; better	indicated b			
1 ⁴	randomised trials	very serious ^{22,26}	no serious inconsistency	serious ²⁴	serious ²⁷	none	15	14	-	MD 2.7 days higher	⊙OOO VERY LOW	

			Quality asses	ssment			No of	patients	Ef	ffect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importanc
						to fever clearance	e (days from rando	misation to observa	tion of a m	aximal daily	temperature	of less than
2 ²	randomised trials	no serious	tive days); better no serious inconsistency	no serious indirectness	serious ²⁷	none	274	271	-	difference between	O O O O O O O O C O O C O O O O O O O O	
										the medians 2 days lower		
			coma (dexameth			to coma clearance	e (median, days fro	om randomization u	ntil observa	ation of a Gla	asgow coma	score of 15
l ²	randomised trials	no serious		no serious indirectness	serious ²⁷	none	274	271	-	difference between the	OOO MODERATE	
										medians 2 days lower		
	s in signs and	symptoms -	hemiparesis (de	xamethasone)		h: number of patie	ents with hemipares	sis at baseline to res	solve after	9 months of		
1 ²	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²¹	none	36/48 (75%)	30/37 (81.1%)	OR 0.70 (0.24 to 2) ¹⁴	6 fewer per 100 (from 30 fewer to 8 more)	©⊙⊙ MODERATE	
Changes reatmer	•	symptoms -	hemiparesis (de	xamethasone)	(assessed wit	h: number of patie	ents without hemipa	aresis at baseline to	be experie	encing hemip	aresis after 9	9 months of
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²¹	none	14/226 (6.2%)	11/234 (4.7%)	OR 1.34 (0.59 to 3.01) ¹⁴	1 more per 100 (from 2 fewer to 8 more)	0000 MODERATE	
hanges	in signs and	symptoms -	paraparesis (de)	(amethasone)	assessed with	: number of patie	nts with parapares	s at baseline to res	olve after 9	· · ·	reatment)	
2	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious ²¹	none	19/28 (67.9%)	9/11 (81.8%)	OR 0.47 (0.08 to 2.63) ¹⁴	14 fewer per 100 (from 55 fewer to 10 more)	©⊙⊙O MODERATE	
•	•	symptoms -	paraparesis (de)	(amethasone)	(assessed with	a: number of patie	nts without parapa	resis at baseline to	be experier	ncing parapa	resis after 9	months of
reatmer	randomised	no serious	no serious	no serious	serious ²¹	none	11/246	11/260	OR 1.06	0 more	0000	
	trials		inconsistency	indirectness		lione	(4.5%)	(4.2%)	(0.45 to 2.49) ¹⁴	per 100 (from 2 fewer to 6 more)	MODERATE	
				· · ·		8		a tuberculoma durir	-			
2	randomised trials		no serious inconsistency	no serious indirectness	serious ²¹	none	9/246 (3.7%)	5/260 (1.9%)	OR 1.81 (0.6 to 5.46) ¹⁴	2 more per 100 (from 1 fewer to 8 more)	©⊙⊙O MODERATE	

			Quality asse	ssment		No of J	Effect					
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance
Changes	-	symptoms -	hydrocephalus	(dexamethasor	ne) (assessed v	with: number of p	atients to experienc	e a hydrocephalus	during 9 m	onths of trea	atment)	
1 ²	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²¹	none	10/246 (4.1%)	7/260 (2.7%)	OR 1.43 (0.54 to 3.81) ¹⁴	1 more per 100 (from 1 fewer to 7 more)	©⊙ MODERATE	
	-		-				er of patients in a g	-				
2 ^{2,5}	randomised trials	serious ⁷	no serious inconsistency	no serious indirectness	serious ²¹	none	84/306 (27.5%)	65/287 (22.6%)	OR 1.36 (0.72 to 2.58) ^{14,34}	6 more per 100 (from 5 fewer to 20 more)	©⊙OO LOW	
	s in signs and domisation)	symptoms -	- intermediate or	severe disabil	ity status (dexa	amethasone) (ass	essed with: numbe	r of patients in an ir	ntermediate	or severe d	isability statu	is 5 years
2 ^{2,5}	randomised trials	serious ⁷	no serious inconsistency	no serious indirectness	serious ²¹	none	68/306 (22.2%)	58/287 (20.2%)	OR 1.12 (0.75 to 1.66) ^{14,36}	2 more per 100 (from 4 fewer to 9 more)	©©OO LOW	
Changes values)	in signs and	symptoms -	cognitive status	(dexamethaso	ne) (measured	I with: time to imp	provement in mini-m	ental score among	st surviving	g patients ²⁸ ;	better indica	ted by lower
1 ⁴	randomised trials	serious ²²	no serious inconsistency	serious ²⁴	serious ²⁷	none	15	14	-	MD 3.4 days higher	©OOO VERY LOW	
			neurological ab	normalities du	ring treatment	(dexamethasone)	(assessed with: nu	mber of patients to	develop ne	eurologic ab	normalities (f	undus,
1 ³	randomised trials	• •	no serious inconsistency	serious ¹³	serious ²¹	none	8/145 (5.5%)	15/135 (11.1%)	OR 0.47 (0.19 to 1.14) ¹⁴	6 fewer per 100 (from 9 fewer to 1 more)	⊙OOO VERY LOW	
•	in signs and hemiparesis			ogical abnorma	lities (dexame	thasone) (assesse	ed with: number of	patients to with per	manent res	idual neurol	ogic abnorm	alities
1 ³	randomised trials		no serious inconsistency	serious ¹³	serious ²¹	none	14/145 (9.7%)	27/135 (20%)	OR 0.43 (0.21 to 0.86) ¹⁴	10 fewer per 100 (from 2 fewer to 15 fewer)	0000 VERY LOW	
							of headache among		ts; better in	· · · · · ·		
1 ⁴	randomised trials	serious ²²	no serious inconsistency	serious ²⁴	serious ²⁷	none	15	14	-	MD 7.4 days higher	⊙OOO VERY LOW	
•	in signs and by lower val		activity of daily	living (dexame	thasone; child	ren) (measured w	ith: time to improve	ment in Barthel sco	ore amongs	t surviving p	patients ²⁸ ; be	tter
1 ⁴	randomised trials		no serious inconsistency	serious ²⁴	serious ²⁷	none	15	14	-	MD 5.3 days	⊙OOO VERY	

			Quality asse	ssment		No of patients		Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
						20.				higher	LOW	
1 ²	randomised trials	no serious risk of bias	inconsistency	no serious indirectness	serious ^{21,27}	none	41/274 (15%)	48/271 (17.7%)	OR 0.82 (0.52 to 1.29) ¹⁴	3 fewer per 100 (from 8 fewer to 4 more)	©⊙⊙O MODERATE	
		ar (dexameth						ith ocular complica				
1 ¹⁵	non- randomised trials	very serious ^{16,17}	serious ^{19,20}	serious ¹³	serious ²¹	none	2/66 (3%)	7/70 (10%)	OR 0.28 (0.06 to 1.41) ¹⁴	7 fewer per 100 (from 9 fewer to 4 more)	⊙OOO VERY LOW	
	events - seve /, or death))	re (dexamet	hasone) (assess	ed with: numbe	er of patients to	o experience a sev	vere event (any eve	nt causing or threat	ening to ca	ause prolong	jed hospital s	tay,
1 ²	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ^{21,27}	none	26/274 (9.5%)	45/271 (16.6%)	OR 0.53 (0.31 to 0.88) ¹⁴	7 fewer per 100 (from 2 fewer to 11 fewer)	©⊙⊙ MODERATE	
Adverse	events - hepa	atitis (dexam	ethasone; HIV-ne	egative) (asses	sed with: num	ber of patients to	experience clinical	or subclinical hepa	titis ²⁹)			
1 ⁵	randomised trials	very serious ^{30,31}	no serious inconsistency	no serious indirectness	serious ²¹	none	5/32 (15.6%)	4/16 (25%)	OR 0.56 (0.13 to 2.44) ¹⁴	9 fewer per 100 (from 21 fewer to 20 more)	⊙OOO VERY LOW	
Adverse	events - gast	rointestinal I	pleeding (dexam	ethasone; HIV-	negative) (asse	essed with: of pat	ients to experience	gastrointestinal ble	eding ²⁹)			
1 ⁵	randomised trials	very serious ^{30,31}	no serious inconsistency	no serious indirectness	very serious ^{21,32}	none	4/32 (12.5%)	0/16 (0%)	OR 5.21 (0.26 to 103) ¹⁴	-	⊙OOO VERY LOW	
	events - para	doxical tube	rculoma (dexam	ethasone; HIV-		essed with: numb	er of patients to exp	perience paradoxica	I tuberculo	oma ²⁹)		
1 ⁵	randomised trials	very serious ^{30,31}	no serious inconsistency	no serious indirectness	serious ²¹	none	2/32 (6.3%)	2/16 (12.5%)	OR 0.47 (0.06 to 3.66) ¹⁴	6 fewer per 100 (from 12 fewer to 22 more)	⊙OOO VERY LOW	
 ² Thwaite ³ Girgis e ⁴ Kumarv ⁵ Malhotr ⁶ Unclear ⁷ Malhotr 	a et al, 2009: L	owed the inte inclear if alloc	2011 nt-to-treat principl tation concealme	nt used, and blir								

⁸ Girgis et al, 1991: use of allocation concealment and blinding unclear
 ⁹ O'Toole et al, 1969: unclear if groups were comparable at baseline, or if they were comparable for treatment completion and availability of outcome data
 ¹⁰ Kumarvelu et al, 1994: follow-up only 3 months after treatment initiation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative	Absolute (95% Cl)	Quality	Importance

¹¹ Follow-up varied widely between groups

¹² Estimates of effect very widely across the studies

¹³ O'Toole et al (1969), Girgis et al (1983 and 1991), Kumarvelu et al (1994): antituberculosis regimens do not use all of or just the 4 standard recommended drugs; of particular not is the lack of rifampicin in O'Toole et al (1969) and Girgis et al (1983 and 1991)

¹⁴ Odds ratio and 95% confidence interval calculated by reviewer

¹⁵ Girgis et al, 1983

¹⁶ Non-randomised; patients were alternately assigned to receive antituberculosis chemotherapy plus dexamethasone or antituberculosis chemotherapy alone

¹⁷ No allocation concealment

¹⁸ Use of blinding unclear

¹⁹ 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

²⁰ Unclear if groups received the same care except for the intervention(s) studied; limited information available

²¹ GRADE rule of thumb: <300 events

²² Kumarvelu et al, 1994: use of allocation concealment and blinding is unclear

²³ Authors do not provide a definition

²⁴ Kumarvelu et a¹, 1994: antituberculosis regimens do not use all of or just the 4 standard recommended drugs

²⁵ Outcome is a surrogate for an outcome of interest

²⁶ 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

²⁷ Insufficient data to calculate confidence intervals

²⁸ For full definition, see evidence table

²⁹ For full definition, see evidence tables

³⁰ Malhotra et al, 2009: use of allocation concealment unclear

³¹ Malhotra et al, 2009: unblinded

³² Wide confidence intervals

³³ Forest plot (mortality):

³⁴ Forest plot (changes in signs and symptoms - good disability status):

³⁵ Forest plot (changes in signs and symptoms - intermediate or severe disability status):

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asse	ssment			No of j	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(prednisolon	e) (follow-up	3 to 18 months;	assessed with:	number of de	aths)				•		
2 ^{1,2}	randomised trials	very serious ^{3,4,5}	very serious ^{6,7}	serious ⁸	very serious ^{9,10}	none	9/99 (9.1%)	15/101 (14.9%)	OR 0.81 (0.08 to 8.31) ^{11,19}	2 fewer per 100 (from 13 fewer to 44 more)	⊙OOO VERY LOW	
						ative) (follow-up 1 ed lumbar punctu		d with: number of p	atients to r	equire ventr	icular shu	nting, as
1 ²	randomised trials	very serious ¹²	very serious ⁶	very serious ^{8,13}	very serious ^{9,10}	none	5/29 (17.2%)	4/30 (13.3%)	OR 1.35 (0.33 to 5.64) ¹¹	4 more per 100 (from 9 fewer to 33 more)	⊙OOO VERY LOW	
	in signs and	symptoms -				with: number of p	atients to be disabl	ed (severely or mild	lly) at 6 mo	,		
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	54/70 (77.1%)	49/71 (69%)	OR 1.52 (0.71 to 3.21) ¹¹	8 more per 100 (from 8 fewer to 19 more)	⊙OOO VERY LOW	
Change i during tr		symptoms - n	eurological abno	ormalities durin	g treatment (p	rednisolone; HIV-	negative) (assesse	d with: number of p	atients to d	evelop neur	ological a	bnormalities
1 ²	randomised trials	very serious ¹²	serious ⁶	serious ⁸	very serious ^{9,10}	none	2/29 (6.9%)	4/30 (13.3%)	OR 0.48 (0.08 to 2.86) ¹¹	6 fewer per 100 (from 12 fewer to 17 more)	⊙OOO VERY LOW	
	in signs and	symptoms -	hearing (prednis	olone; children) (assessed wi	ith: number of pat	ients with deterior	ation in their hearin	g (decrease	d hearing, t	hough not	deaf) at 6
months) 1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	3/70 (4.3%)	6/71 (8.5%)	OR 0.49 (0.12 to 2.02) ¹¹	4 fewer per 100 (from 7 fewer to 7 more)	⊙OOO VERY LOW	
	-	symptoms -				essed with: numb	per of patients to be	e severely disabled	at 6 months	5)		
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	14/70 (20%)	19/71 (26.8%)	OR 0.68 (0.31 to 1.5) ¹¹	7 fewer per 100 (from 17 fewer to 9 more)	⊙OOO VERY LOW	

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
	in signs and	symptoms -	tuberculoma (pr	ednisolone; chi	ldren) (assess	ed with: number of	of patients to devel	op tuberculomas in	the first m	onth of treat	ment)	
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	2/70 (2.9%)	9/71 (12.7%)	OR 0.20 (0.04 to 0.97) ¹¹	10 fewer per 100 (from 0 fewer to 12 fewer)	⊙OOO VERY LOW	
	s in signs and	symptoms -			essed with: n	umber of patients	to have an IQ of les	ss than 75 at 6 mon				
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	31/70 (44.3%)	36/71 (50.7%)	OR 0.77 (0.4 to 1.5) ¹¹	7 fewer per 100 (from 22 fewer to 10 more)	⊙OOO VERY LOW	
	-							experience hemiple				
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	24/70 (34.3%)	24/71 (33.8%)	OR 1.02 (0.51 to 2.05) ¹¹	0 more per 100 (from 13 fewer to 17 more)	⊙OOO VERY LOW	
0	•	symptoms -				h: number of patie		erioration (decreas		,		ns)
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	9/70 (12.9%)	7/71 (9.9%)	OR 1.35 (0.47 to 3.85) ¹¹	3 more per 100 (from 5 fewer to 20 more)	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	vision (predniso	lone; children)	(assessed witl	h: number of patie	ents to be blind at 6	months)				
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	serious ⁹	none	3/70 (4.3%)	3/71 (4.2%)	OR 1.01 (0.2 to 5.21) ¹¹	0 more per 100 (from 3 fewer to 14 more)	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	hearing (prednis	olone; children) (assessed w	ith: number of pat	tients to be deaf at	6 months)				
1 ¹	randomised trials	very serious ^{3,5,14}	serious ¹⁵	serious ¹⁶	very serious ^{9,17}	none	0/70 (0%)	0/71 (0%)	1.01 (0.02 to 51.82) ¹¹	-	⊙OOO VERY LOW	
	in signs and s gical abnorma			ormalities after	treatment (pre	dnisolone; HIV-ne	egative) (follow-up	18 months; assesse	ed with: nur	nber of patie	ents to dev	velop
1 ²	randomised trials	serious ¹²	serious ⁶	serious ⁸	very serious ^{9,10}	none	4/29 (13.8%)	2/30 (6.7%)	OR 2.24 (0.38 to 13.3) ¹¹	7 more per 100 (from 4 fewer to 42 more)	⊙OOO VERY LOW	
-	-							f headache; better i	ndicated by			
1 ²	randomised trials	very serious ¹²	serious ⁶	serious ⁸	serious ¹⁸	none	29	30	-	MD 2.6 days higher ¹¹	⊙OOO VERY LOW	

1 ² randomised trials very serious ¹² serious ⁶ serious ⁸ serious ¹⁸ none 29 30 - MD 3.7 days 0000 VERY lower ¹¹ Recurrence (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience recurrence of meningitis during follow-up) 1 ² randomised trials very serious ¹² serious ^{8,10} none 0/29 0/30 OR 1.03 - 00000 Adverse events - hyperglycaemia (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience hyperglycaemia) 1 ² randomised trials very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 1 ² randomised trials very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 Adverse events - gastrointestinal bleeding (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience gastrointestinal bleeding) 1 ² randomised trials serious ⁹ serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 1 ² randomised trials serious ^{9,10} serious ^{9,10} none 0/29 </th <th></th> <th></th> <th></th> <th>Quality asse</th> <th>ssment</th> <th></th> <th></th> <th>No of p</th> <th>patients</th> <th>Ef</th> <th>fect</th> <th></th> <th></th>				Quality asse	ssment			No of p	patients	Ef	fect		
1 ² randomised trials very serious ¹² serious ⁸ serious ¹⁸ none 29 30 - MD 3.7 days berow ¹¹ 0000 VERY bower ¹¹ Recurrence (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience recurrence of meningitis during follow-up) 1 ² randomised trials very serious ^{8,10} serious ^{8,10} overy serious ^{8,10} none 0/29 0/30 OR 1.03 - 0000 Adverse events - hyperglycaemia (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience hyperglycaemia) 1 ² randomised trials very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 1 ² randomised trials very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 VERY bower 1 ² randomised trials very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 VERY bower 1 ² randomised trials serious ⁹ very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 VERY bower 0000 0000 00		Design		Inconsistency	Indirectness	Imprecision		chemotherapy plus	chemotherapy alone or plus			Quality	Importance
1 ² randomised trials very serious ¹² serious ⁶ very serious ^{8,13} very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - OOOO VERY LOW Adverse events - hyperglycaemia (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience hyperglycaemia) 1 ² randomised trials very serious ⁶ serious ⁶ very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - OOOO VERY (0%) Adverse events - hyperglycaemia trials very serious ¹² serious ⁶ serious ⁶ very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0.02 to UCRY (0%) - OOOO Adverse events - gastrointestinal bleeding (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience gastrointestinal bleeding) 1 ² randomised trials very serious ¹² serious ⁸ very serious ^{8,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0.02 to UCRY (0%) very (0%) very (0%) Serious ^{8,10} UCW 1 ² chotomagkol et al, 1997 * * Chotomogkol et al, 1997 * OOOO ³ Method of randomisation and use of allocation concealment is	1 ²			serious ⁶	serious ⁸				30	-	days	⊙OOO VERY	
trials serious ¹² serious ^{8,13} serious ^{8,10} (0%) (0%) (0%) (0%) (0.2 to 53.83) ¹¹ VERY LOW Adverse events - hyperglycaemia (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience hyperglycaemia) 1 ² randomised very serious ¹² serious ⁶ very serious ^{8,10} none 0/29 0/30 OR 1.03 - 0000 Adverse events - gastrointestinal bleeding (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience gastrointestinal bleeding) VERY VERY 1 ² randomised very serious ⁹ none 0/29 0/30 OR 1.03 - 0000 1 ² randomised very serious ⁹ none 0/29 0/30 OR 1.03 - 0000 1 ² randomised very trials serious ⁹ very serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 1 ³ Schoeman et al, 1997 serious ^{9,10} none 0/29 0/30 OR 1.03 - 0000 ³ Method of randomisation and use of allocation concealment is unclear - - Schoeman et al,	Recurre	nce (prednisol	lone; HIV-neg	gative) (follow-up	18 months; as	sessed with: n	umber of patients	s to experience rec	urrence of meningi	tis during fo	ollow-up)		
1 ² randomised trials very serious ¹² serious ⁶ serious ⁸ very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - $\Theta O O O$ Adverse events - gastrointestinal bleeding (prednisolone; HIV-negative) (follow-up 18 months; assessed with: number of patients to experience gastrointestinal bleeding) 1 ² randomised trials very serious ¹² serious ⁶ serious ⁸ very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - $\Theta O O O$ 1 ² randomised trials very serious ¹² serious ⁶ serious ⁸ very serious ^{9,10} none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - $\Theta O O O$ 1 ² randomised trials very serious ¹² none 0/29 (0%) 0/30 (0%) OR 1.03 (0%) - $\Theta O O O$ 1 ³ Schoeman et al, 1997 Schoeman et al, 1996 Schoeman et al, 1996 Schoeman et al, 1997 Schoeman et al, 1997 Schoeman et al, 1997 Schoeman et al, 1997 Schoeman et al, 1996 Schoem	1 ²			serious ⁶			none			(0.02 to	-	VERY	
trials serious ¹² serious ^{9,10} (0%) (0%) (0%) (0.02 to 53.83) ¹¹ VERY LOW Adverse events - gastrointestinal bleeding (prednisolone; HIV-negative) (follow-up 18 months; assested with: number of patients to experience gastrointestinal bleeding) 1 ² randomised trials very serious ¹² serious ⁸ very serious ^{9,10} none 0/29 0/30 OR 1.03 - 00000 ¹ Schoeman et al, 1997 2 Chotmongkol et al, 1997 - 0/29 0/30 OR 1.03 - VERY LOW ³ Method of randomisation and use of allocation concealment is unclear - - VERY LOW - - - - - - - - - VERY LOW -				(prednisolone; H	V-negative) (fo	llow-up 18 moi	nths; assessed w	ith: number of patie	ents to experience h	nyperglycae	emia)		
1 ² randomised trials very serious ¹² serious ⁶ serious ⁸ very serious ^{9,10} none 0/29 0/30 OR 1.03 - ©OOO VERY LOW ¹ Schoeman et al, 1997 Chotmongkol et al, 1996 3 Method of randomisation and use of allocation concealment is unclear ³ Method of randomisation and use of allocation concealment is unclear 4 Schoeman et al, 1997: Dilided = clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function; unclear patients or other health professionals were blinded ⁵ Unclear if analysis followed the intent-to-treat principle 6 Chotmongkol et al, 1996; groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, althou statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients with less severe (stage 1) disease in the prednisolone weakness than in the placebo group, although again this was not statistically significant ⁷ Follow-up varied widely between groups 7	1 ²			serious ⁶	serious ⁸		none			(0.02 to	-	VERY	
trials serious ¹² serious ^{9,10} (0%) (0%) (0.2 to 53.83) ¹¹ VERY LOW ¹ Schoeman et al, 1997 ² Chotmongkol et al, 1996 ³ Method of randomisation and use of allocation concealment is unclear ⁴ Schoeman et al, 1997: 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 ⁵ Unclear if analysis followed the intent-to-treat principle ⁶ Chotmongkol et al, 1996: groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, althou 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, although again this was not statistically significant ⁷ Follow-up varied widely between groups		events - gast	rointestinal b	pleeding (prednis	olone; HIV-neg	ative) (follow-u	up 18 months; ass	sessed with: numbe	er of patients to exp	perience gas	strointestina	I bleeding)
 ² Chotmongkol et al, 1996 ³ Method of randomisation and use of allocation concealment is unclear ⁴ Schoeman et al, 1997: 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 ⁵ Unclear if analysis followed the intent-to-treat principle ⁶ Chotmongkol et al, 1996: groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, althou 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, although again this was not statistically significant ⁷ Follow-up varied widely between groups 	1 ²			serious ⁶	serious ⁸		none			(0.02 to	-	VERY	
 ⁸ Chotmongkol et al, 1996: antituberculosis regimens do not use all of or just the 4 standard recommended drugs ⁹ GRADE rule of thumb: <300 events ¹⁰ Wide confidence intervals ¹¹ Odds ratio and 95% confidence interval calculated by reviewer ¹² Chotmongkol et al, 1996: method of randomisation and use of allocation concealment is unclear ¹³ Outcome is a surrogate for an outcome of interest ¹⁴ Blinded = clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function; unclear if patients or other he professionals were blinded ¹⁵ Follow-up only 3 months after treatment initiation ¹⁶ Antituberculosis regimens do not use all of or just the 4 standard recommended drugs ¹⁷ Wide confidence interval ¹⁸ Authors did not provide sufficient data to calculate confidence interval ¹⁹ Forest plot (mortality): 	patient. ⁵ Unclear ⁶ Chotmo statistic weakne than in ⁷ Follow- ⁸ Chotmo ⁹ GRADE ¹⁰ Wide o ¹¹ Odds n ¹² Chotmo ¹³ Outcon ¹⁴ Blindee profess ¹⁵ Follow ¹⁶ Antitub ¹⁷ Wide o ¹⁸ Author	s or other healt r if analysis follo ongkol et al, 19- cally significant, ess than in the the placebo group varied widel ongkol et al, 19- confidence inter ratio and 95% congkol et al, 19- congkol et al, 19- congkol et al, 19- congkol et al, 19- me is a surroga d = clinical psyc sionals were bli -up only 3 mon perculosis regin confidence inter s did not provid	h professiona owed the inter 96: groups no more patient placebo group oup, although ly between gri 96: antitubero < <300 events rvals confidence int 296: method o the for an outo chologist asse nded ths after treat nens do not u rval de sufficient d	als were blinded nt-to-treat principle of comparable at b ts in the prednisole p (10%); additiona o again this was no oups culosis regimens d rerval calculated by of randomisation a come of interest essing intelligence tment initiation se all of or just the	e aseline - clinical one group (17%) Ily, there were n ot statistically sig o not use all of c v reviewer nd use of allocat , clinician testing e 4 standard reco	presentations a had motor wea hore patients wi nificant or just the 4 star tion concealmen hearing, ophth ommended drug	and staging were su kness than in the p th severe (stage 3) adard recommende nt is unclear almologist testing	imilar in the intervent blacebo group (3%), disease and fewer p od drugs	tion and comparator and more patients in patients with less sev	groups at ra the prednis vere (stage 1	ndomisation; olone group) disease in	however, ((17%) had the prednis	although not motor colone group

Methylprednisolone vs antituberculosis chemotherapy alone or plus placebo

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus methylprednisol one	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)		
Mortality	(methylpred)	nisolone; HIV	/-negative) (asse	ssed with: num	ber of deaths	after 6 months of	reatment)					
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	9/33 (27.3%)	7/16 (43.8%)	OR 0.48 (0.14 to 1.68) ⁵	17 fewer per 100 (from 34 fewer to 13 more)	⊙OOO VERY LOW	
Changes treatmen		symptoms -	 severe disability 	y (methylpredn	isolone; HIV-ne	egative) (assessed	with: number of pa	atients to experience	e severe di	isability afte	r 6 months o	of
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	6/33 (18.2%)	3/16 (18.8%)	OR 0.96 (0.21 to 4.47) ⁵	1 fewer per 100 (from 14 fewer to 32 more)	⊙OOO VERY LOW	
Changes of treatm		symptoms -	· intermediate dis	ability (methyl	prednisolone;	HIV-negative) (ass	essed with: numbe	r of patients to expe	erience inte	ermediate di	isability after	r 6 mon
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	0/33 (0%)	2/16 (12.5%)	OR 0.09 (0 to 1.92) ⁵	11 fewer per 100 (from 12 fewer to 9 more)	⊙OOO VERY LOW	
Changes treatmen	•	symptoms -	- good disability	status (methylp	prednisolone; ł	HV-negative) (ass	essed with: number	of patients to achie	eve a good	disability s	tatus after 6	month
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	15/33 (45.5%)	4/16 (25%)	OR 2.50 (0.67 to 9.39)⁵	20 more per 100 (from 7 fewer to 51 more)	⊙OOO VERY LOW	
Adverse	events - hepa	atitis (methyl	prednisolone; Hl	V-negative) (as	sessed with: n	umber of patients	to experience clinic	cal or subclinical he	patitis ⁶)			
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	7/33 (21.2%)	4/16 (25%)	OR 0.81 (0.2 to 3.3) ⁵	4 fewer per 100 (from 19 fewer to 27 more)	⊙OOO VERY LOW	
					5 / 1			experience gastroir		Ξ,		
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	very serious ^{4,7}	none	2/33 (6.1%)	1/16 (6.3%)	OR 0.97 (0.08 to 11.54)⁵	0 fewer per 100 (from 6 fewer to 37 more)	⊙OOO VERY LOW	
								experience parado			0000	
1 ¹	randomise d trials	very serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	2/33 (6.1%)	3/16 (18.8%)	OR 0.14 (0.01 to 1.42) ⁵	16 fewer per 100 (from 19 fewer to 6	⊙OOO VERY LOW	

			Quality asse	ssment			No of p	atients	Ef	fect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus methylprednisol one	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance	
	llocation conc	ealment uncle	ear										
³ Unblinde		· < 200 events											
	GRADE rule of thumb: <300 events Odds ratio and 95% confidence interval calculated by reviewer												
	definition, see												
⁷ Wide co	nfidence inter	val											

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo

			Quality asse	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importanc
Mortality	(follow-up 3 n	nonths to 5 y	ears; assessed v	with: number of	f deaths)							
7 ^{1,2,3,4,5,6,7}	randomise d trials	very serious ^{8,9,10} ,11	very serious ^{12,13,14,15,} 16	serious ¹⁷	no serious imprecision	none	234/618 (37.9%)	253/574 (44.1%)	OR 0.75 (0.56 to 0.99) ^{18,20}	7 fewer per 100 (from 13 fewer to 0 fewer)	⊙OOO VERY LOW	
			-up 3 to 10 mont					1				
3 ^{1,6,7}	randomise d trials	very serious ^{8,9,10} , ¹¹	very serious ^{14,15,16}	serious ¹⁷	serious ¹⁹	none	22/127 (17.3%)	35/126 (27.8%)	OR 0.52 (0.26 to 1.02) ^{18,21}	11 fewer per 100 (from 19 fewer to 0 more)	⊙OOO VERY LOW	
	(follow-up >1	year) (follow	-up 18 months to	o 5 years; asses	ssed with: nun	ber of deaths)						
3 ^{2,4,5}	randomise d trials	very serious ^{8,10}	very serious ^{12,15,16}	serious ¹⁷	no serious imprecision	none	198/448 (44.2%)	209/436 (47.9%)	OR 0.85 (0.6 to 1.21) ^{18,21}	4 fewer per 100 (from 12 fewer to 5 more)	⊙OOO VERY LOW	
Mortality	(rifampicin-co	ontaining ant	ituberculosis reg	jimens only) (fo	ollow-up 3 mor	ths to 5 years; as	sessed with: numb	er of deaths)				
5 ^{1,2,4,6,7}	randomise d trials	very serious ^{8,9,10} ,11	very serious ^{12,14,15,16}	serious ¹⁷	no serious imprecision	none	148/430 (34.4%)	165/427 (38.6%)	OR 0.76 (0.45 to 1.28) ^{18,22}	6 fewer per 100 (from 17 fewer to 6 more)	⊙OOO VERY LOW	
Change i	n signs and sy	vmptoms - ne	eurological abno	rmalities (follow	w-up 18 to 24 r	nonths: assessed	with: number of pa	tients to develop ne	urological	abnormaliti	es durina	treatment)
2 ^{2,5}	randomise d trials	serious ⁸	serious ¹²	serious ¹⁷	serious ¹⁹	none	10/174 (5.7%)	19/165 (11.5%)	OR 0.47 (0.21 to 1.04) ^{18,23}	6 fewer per 100 (from 9 fewer to 0 more)	©000 VERY LOW	
					picin-containi	ng antituberculosi	s regimens only) (f	ollow-up 18 months	; assessed	with: numb	er of patie	nts to
			during treatmen				0// /-				0000	
1 ²	randomise d trials	serious ⁸	serious ¹²	serious ¹⁷	serious ¹⁹	none	8/145 (5.5%)	15/135 (11.1%)	OR 0.47 (0.19 to 1.14) ¹⁴	6 fewer per 100 (from 9 fewer to 1 more)	⊙OOO VERY LOW	
 ² Chotmor ³ O'Toole ⁴ Thwaites ⁵ Girgis et ⁶ Kumarve 	an et al, 1997 ngkol et al, 199 et al, 1969 s et al, 2004/7 , al, 1991 elu et al, 1994		2011									

⁷ Malhotra et al, 2009

			Quality asses	ssment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy plus any		Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
⁹ Schoema	an et al, 1997:	blinded = clin					cealment is unclear hthalmologist testing	vision, and physical t	herapist tes	ting motor fu	inction; un	clear if

¹⁰ Unclear if analysis followed the intent-to-treat principle

¹¹ Malhotra et al. 2009: blinding not used

¹² Chotmongkol et al, 1996: groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, although not statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients with less severe (stage 1) disease in the prednisolone group than in the placebo group, although again this was not statistically significant

¹³ O'Toole et al, 1969: unclear if groups were comparable at baseline, or if they were comparable for treatment completion and availability of outcome data

¹⁴ Kumarvelu et al, 1994: follow-up only 3 months after treatment initiation

¹⁵ Follow-up varied widely between groups

¹⁶ Estimates of effect very widely across the studies

¹⁷ Chotmongkol et al (1996), O'Toole et al (1969), Girgis et al (1991), Kumarvelu et al (1994): antituberculosis regimens do not use all of or just the 4 standard recommended drugs

¹⁸ Odds ratio and 95% confidence interval calculated by reviewer

¹⁹ GRADE rule of thumb: <300 events

²⁰ Forest plot (mortality):

²¹ Forest plot (mortality; follow-up subgroups):

²² Forest plot (mortality; rifampicin-containing antituberculosis regimens only):

²³ Forest plot (change in signs and symptoms - neurological abnormalities):

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo in people without HIV

			Quality asses	sment			No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% CI)	Absolute (95% Cl)	Quality	Importance
Mortality	(HIV-negative)) (follow-up 1	8 months; asses	ssed with: num	ber of deaths)							
2 ^{1,2}	randomised trials	very serious ^{3,4,5}	serious ⁶	serious ⁷	serious ⁸	none	22/94 (23.4%)	15/62 (24.2%)	OR 1.04 (0.2 to 5.53) ^{9,14}	1 more per 100 (from 18 fewer to 40 more)	⊙OOO VERY LOW	
Response	e to treatment	- need for a	ditional interver	ntion (HIV-nega	tive) (follow-u	p 18 months; asse	essed with: number	r of deaths)				
1 ¹	randomised trials	very serious ³	very serious ⁶	very serious ^{7,10}	very serious ^{8,11}	none	5/29 (17.2%)	4/30 (13.3%)	OR 1.35 (0.33 to 5.64) ⁹	4 more per 100 (from 9 fewer to 33 more)	⊙OOO VERY LOW	

			Quality asses	ssment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance
		mptoms - n	eurological abno	rmalities durin	g treatment (H	IIV-negative) (ass	essed with: number	r of patients to deve	elop neurolo	ogical abnor	malities du	uring
treatment 1 ¹	randomised trials	very serious ³	serious ⁶	serious ⁷	very serious ^{8,11}	none	2/29 (6.9%)	4/30 (13.3%)	OR 0.48 (0.08 to 2.86) ⁹	6 fewer per 100 (from 12 fewer to 17 more)	⊙OOO VERY LOW	
	n signs and sy lities after trea		eurological abno	rmalities after	treatment (HI\	/-negative) (follow	-up 18 months; ass	essed with: numbe	r of patient	s to develop	neurologi	cal
1 ¹	randomised trials		serious ⁶	serious ⁷	very serious ^{8,11}	none	4/29 (13.8%)	2/30 (6.7%)	OR 2.24 (0.38 to 13.3) ⁹	7 more per 100 (from 4 fewer to 42 more)	⊙OOO VERY LOW	
-		mptoms - h	· · · ·			until disappearan		tter indicated by lo	wer values)			
1 ¹	randomised trials	very serious ³	serious ⁶	serious ⁷	serious ¹²	none	29	30	-	MD 2.6 days higher ⁹	⊙OOO VERY LOW	
Change i	n signs and sy	/mptoms - s	evere disability (HIV-negative) (assessed with	: number of patie	nts to experience s	evere disability afte	r 6 months		t ¹³)	
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	serious ⁸	none	11/65 (16.9%)	5/32 (15.6%)	OR 1.10 (0.35 to 3.49) ⁹	1 more per 100 (from 10 fewer to 24 more)	⊙OOO VERY LOW	
Change in	n signs and sy	/mptoms - ii	ntermediate disal	oility (HIV-nega	tive) (assesse	d with: number of	patients to experie	ence intermediate d	isability afte	er 6 months	of treatme	nt ¹³)
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	serious ⁸	none	3/65 (4.6%)	4/32 (12.5%)	OR 0.34 (0.07 to 1.62) ⁹	8 fewer per 100 (from 12 fewer to 6 more)	⊙OOO VERY LOW	
	n signs and sy	mptoms - n	o disability (HIV-	negative) (asse	essed with: nu	mber of patients v	with a good outcom	e after 6 months of	treatment ¹³	') '		
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	very serious ^{8,11}	none	30/65 (46.2%)	8/32 (25%)	OR 2.57 (1.01 to 6.56) ⁹	21 more per 100 (from 0 more to 44 more)	⊙OOO VERY LOW	
	n signs and sy	mptoms - fe				normalisation of	body temperature;	better indicated by	lower value			
1 ¹	randomised trials	very serious ³	serious ⁶	serious ⁷	serious ¹²	none	29	30	-	MD 3.7 days lower ⁹	⊙OOO VERY LOW	
Recurren	ce (HIV-negati	ve) (follow-	up 18 months; as	sessed with: n	umber of patie	ents to experience	e recurrence of men	ingitis during follo	w-up)			
1 ¹	randomised trials	very serious ³	serious ⁶	very serious ^{7,10}	very serious ^{8,11}	none	0/29 (0%)	0/30 (0%)	OR 1.03 (0.02 to 53.83) ⁹	-	⊙OOO VERY LOW	

			Quality asses	ssment			No of j	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
1 ¹	randomised trials	very serious ³	serious ⁶	serious ⁷	very serious ^{8,11}	none	0/29 (0%)	0/30 (0%)	OR 1.03 (0.02 to 53.83) ⁹	-	⊙OOO VERY LOW	
Adverse	events - hepat	itis (HIV-neg	ative) (assessed	with: number	of patients to	experience clinica	I or subclinical hep	atitis ¹³)				
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	serious ⁸	none	12/65 (18.5%)	8/32 (25%)	OR 0.68 (0.25 to 1.88) ⁹	7 fewer per 100 (from 17 fewer to 14 more)	⊙OOO VERY LOW	
Adverse	events - gastro	ointestinal b	leeding (HIV-neg	ative) (assesse	d with: numbe	er of patients to ex	kperience gastroint	estinal bleeding)				
2 ^{1,2}	randomised trials	very serious ^{3,4,5}	serious ⁶	serious ⁷	very serious ^{8,11}	none	6/94 (6.4%)	1/62 (1.6%)	OR 3.15 (0.36 to 27.37) ^{9,15}	3 more per 100 (from 1 fewer to 29 more)	⊙OOO VERY LOW	
	events - parad	oxical tuber	culoma (HIV-neg	ative) (assesse	d with: numbe	er of patients to ex	kperience paradoxi	cal tuberculoma ¹³)				
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	serious ⁸	none	3/65 (4.6%)	5/32 (15.6%)	OR 0.26 (0.06 to 1.17) ⁹	11 fewer per 100 (from 15 fewer to 2 more)	⊙OOO VERY LOW	

¹ Chotmongkol et al, 1996

² Malhotra et al, 2009

³ Chotmongkol et al, 1996: method of randomisation and use of allocation concealment is unclear

⁴ Malhotra et al, 2009: use of allocation concealment unclear

⁵ Malhotra et al, 2009: unblinded

⁶ Chotmongkol et al, 1996: groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, although not statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and 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

⁷ Chotmongkol et al, 1996: antituberculosis regimens do not use all of or just the 4 standard recommended drugs

⁸ GRADE rule of thumb: <300 events

⁹ Odds ratio and 95% confidence interval calculated by reviewer

¹⁰ Outcome is a surrogate for an outcome of interest

¹¹ Wide confidence intervals

¹² Authors did not provide sufficient data to calculate confidence interval

¹³ For full definition, see evidence tables

¹⁴ Forest plot (mortality):

¹⁵ Forest plot (adverse events - gastrointestinal bleeding):

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in children

			Quality asses	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or with placebo	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance
Mortality	(prednisolone	; children) (follow-up 3 mont	hs to 6 months	; assessed wit	h: number of dea	ths)					,
1 ¹	randomised trials	very serious ^{4,5,6}	no serious inconsistency	serious ⁸	serious ⁹	none	4/70 (5.7%)	13/71 (18.3%)	OR 0.27 (0.08 to 0.88) ¹⁰	-	⊙OOO VERY LOW	
Changes	in signs and s	symptoms - o	disability (predni	solone; childre	n) (assessed v	with: number of pa	atients to be disabl	ed (severely or mild	· ·	nths)		
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	54/70 (77.1%)	49/71 (69%)	OR 1.52 (0.71 to 3.21) ¹⁰	8 more per 100 (from 8 fewer to 19 more)	⊙OOO VERY LOW	
	in signs and s	symptoms - s	severe disability	(prednisolone;	children) (ass	essed with: numb	er of patients to be	e severely disabled		5)		
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	14/70 (20%)	19/71 (26.8%)	OR 0.68 (0.31 to 1.5) ¹⁰	7 fewer per 100 (from 17 fewer to 9 more)	⊙OOO VERY LOW	
Changes	in signs and s	symptoms - f	tuberculoma (pre	dnisolone; chi	ldren) (assess	ed with: number o	of patients to develo	op tuberculomas in	the first me	onth of treat	ment)	
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	2/70 (2.9%)	9/71 (12.7%)	OR 0.20 (0.04 to 0.97) ¹⁰	10 fewer per 100 (from 0 fewer to 12 fewer)	⊙OOO VERY LOW	
Changes	in signs and s	symptoms - I	Q (prednisolone)	; children) (ass	essed with: nu	imber of patients	to have an IQ of les	s than 75 at 6 mont	ths)			
1 ¹	trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	31/70 (44.3%)	36/71 (50.7%)	OR 0.77 (0.4 to 1.5) ¹⁰	7 fewer per 100 (from 22 fewer to 10 more)	⊙OOO VERY LOW	
	in signs and s	symptoms - I				ssed with: numbe		experience hemiple		riplegia at 6		
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	24/70 (34.3%)	24/71 (33.8%)	OR 1.02 (0.51 to 2.05) ¹⁰	0 more per 100 (from 13 fewer to 17 more)	⊙OOO VERY LOW	
Changes	in signs and s	symptoms -	vision (prednisol	one; children) (assessed with	: number of patie	nts with visual dete	erioration (decrease	d vision or	blindness)	at 6 month	s)
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	9/70 (12.9%)	7/71 (9.9%)	OR 1.35 (0.47 to 3.85) ¹⁰	3 more per 100 (from 5 fewer to 20 more)	⊙OOO VERY LOW	

			Quality asses	sment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or with placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Changes	in signs and s	symptoms - v	ision (prednisol	one; children) (assessed with	: number of patie	nts to be blind at 6	months)			,	
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	3/70 (4.3%)	3/71 (4.2%)	OR 1.01 (0.2 to 5.21) ¹⁰	0 more per 100 (from 3 fewer to 14 more)	⊙OOO VERY LOW	
Changes months)	in signs and s	symptoms - I	nearing (prednise	olone; children)	(assessed wi	th: number of pat	ients with deteriora	tion in their hearing	(decrease	d hearing, t	hough not	deaf) at 6
11	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	serious ⁹	none	3/70 (4.3%)	6/71 (8.5%)	OR 0.49 (0.12 to 2.02) ¹⁰	4 fewer per 100 (from 7 fewer to 7 more)	©OOO VERY LOW	
Changes	in signs and s	symptoms - I	nearing (prednise	olone; children)	(assessed wi	th: number of pat	ients to be deaf at (6 months)				
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹¹	serious ¹²	very serious ^{9,13}	none	0/70 (0%)	0/71 (0%)	OR 1.01 (0.02 to 51.82) ¹⁰	-	⊙OOO VERY LOW	
¹ Schoema	an et al, 1997											

⁴ Unclear if analysis followed the intent-to-treat principle

⁵ Schoeman et al. 1997: method of randomisation and use of allocation concealment is unclear

⁶ Schoeman et al, 1997: blinded = clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function; unclear if patients or other health professionals were blinded

⁹ GRADE rule of thumb: <300 events

¹⁰ Odds ratio and 95% confidence interval calculated by reviewer

¹¹ Follow-up only 3 months after treatment initiation ¹² Antituberculosis regimens do not use all of or just the 4 standard recommended drugs

¹³ Wide confidence interval

¹⁴ Insufficient data to calculate confidence intervals

¹⁵ Authors do not provide a definition

¹⁶ Outcome is a surrogate for an outcome of interest

¹⁷ For full definition, see evidence table

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in stage 1 CNS tuberculosis

			Quality asse	ssment			No of	patients	Ef	ffect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
				: survival rate		-		dmission; better in	dicated by	-		
1 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	86	-	difference in survival rates 0.14 higher (0.01 lower to 0.29 higher)	0000 MODERATE	
	(stage 1) (foll	ow-up 10 to			ber of deaths	amongst those cl	assified as stage 1	on admission)				
2 ^{3,4}	randomised trials	very serious ^{5,6,7}	serious ⁸	serious ⁹	very serious ^{10,11}	none	0/17 (0%)	1/13 (7.7%)	OR 0.15 (0.01 to 4.18) ^{12,15}	6 fewer per 100 (from 8 fewer to 18 more)	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	severe disability	status (stage 1) (follow-up 10) months; assess	ed with: number of	deaths amongst the	ose with st	age 1 CNS T	B on admissi	on)
1 ⁴	randomised trials	serious ¹³	no serious inconsistency	serious ¹⁴	very serious ^{10,11}	none	2/14 (14.3%)	1/7 (14.3%)	OR 1.00 (0.07 to 13.37) ¹²	0 fewer per 100 (from 13 fewer to 55 more)	⊙OOO VERY LOW	
 Analysis Chotmol Malhotra Chotmol Malhotra Chotmol Malhotra Chotmol Chotmol statistica than in ti placebo Chotmol GRADE Wide co Odds ra Malhotra 	a et al, 2009: us a et al, 2009: un ngkol et al, 199 ally significant, he placebo gro group, althoug group, althoug E rule of thumb. onfidence inter atio and 95% c ra et al, 2009: u	w intent-to-tre 26: method of se of allocation nblinded 26: groups no more patient oup (10%); ac gh again this 26: antituberco c <300 events vals onfidence into use of allocation	eat principle f randomisation ar on concealment un t comparable at b s in the prednisolo dditionally, there w was not statistical ulosis regimens d s erval calculated b ion concealment is	nclear aseline - clinical one group (17%) rere more patien ly significant o not use all of c y reviewer s unclear; blindir	presentations a had motor wea ts with severe (or just the 4 star	and staging were si akness than in the j istage 3) disease a ndard recommende	placebo group (3%), nd fewer patients wit	tion and comparator and more patients in th less severe (stage nded drugs	the prednis	solone group	(17%) had mo	tor weaknes

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in stage 2 CNS tuberculosis

very serious ^{5,6,7,8} mpicin-conta very serious ^{5,6,7,8}	very serious ^{9,10,11,12,13} ining antitubercu very serious ^{9,11,12,13}	serious ¹⁴ Iosis regimens serious ¹⁴	er of deaths ar serious ¹⁵ only) (follow-u serious ¹⁵	none up 6 to 18 months none	7/75	Antituberculosis chemotherapy alone or plus placebo admission) 14/82 (17.1%) mber of deaths amo 7/73 mission; better indi 125	OR 0.91 (0.28 to 2.99) ¹⁶	1 fewer per 100 (from 7 fewer to 14 more) gher values	⊙OOO VERY LOW	Importance admission)
very serious ^{5,6,7,8} mpicin-conta very serious ^{5,6,7,8} sone; stage 2)	very serious ^{9,10,11,12,13} ining antitubercu very serious ^{9,11,12,13} (measured with: no serious	serious ¹⁴ losis regimens serious ¹⁴ survival rate at no serious	serious ¹⁵ sonly) (follow-u serious ¹⁵ t 5 years amon no serious	none up 6 to 18 months; none gst those classifie	16/98 (16.3%) assessed with: nu 7/75	14/82 (17.1%) mber of deaths amo 7/73 mission; better indi	(0.28 to 1.77) ^{16,22} ongst those OR 0.91 (0.28 to 2.99) ¹⁶	per 100 (from 12 fewer to 10 more) with stage 1 fewer per 100 (from 7 fewer to 14 more) gher values	VERY LOW 2 CNS TB on ©OOO VERY LOW	admission
serious ^{5,6,7,8} mpicin-conta very serious ^{5,6,7,8} sone; stage 2)	serious ^{9,10,11,12,13} ining antitubercu very serious ^{9,11,12,13} (measured with: no serious	losis regimens serious ¹⁴ survival rate at no serious	serious ¹⁵ serious ¹⁵ t 5 years amon no serious	up 6 to 18 months none Igst those classifie	(16.3%) assessed with: nu 7/75 ed as stage 2 on ad	(17.1%) mber of deaths amo 7/73 mission; better indi	(0.28 to 1.77) ^{16,22} ongst those OR 0.91 (0.28 to 2.99) ¹⁶	per 100 (from 12 fewer to 10 more) with stage 1 fewer per 100 (from 7 fewer to 14 more) gher values	VERY LOW 2 CNS TB on ©OOO VERY LOW	admission
very serious ^{5.6,7,8}	very serious ^{9,11,12,13} (measured with: no serious	serious ¹⁴ survival rate at no serious	serious ¹⁵ t 5 years amon no serious	none gst those classifie	7/75 ed as stage 2 on ad	7/73 mission; better indi	OR 0.91 (0.28 to 2.99) ¹⁶	1 fewer per 100 (from 7 fewer to 14 more) gher values	⊙OOO VERY LOW	admission)
serious ^{5,6,7,8} sone; stage 2)	serious ^{9,11,12,13} (measured with: no serious	survival rate and no serious	t 5 years amon no serious	gst those classifi	ed as stage 2 on ad	mission; better indi	(0.28 to 2.99) ¹⁶	per 100 (from 7 fewer to 14 more) gher values	VERY LOW	
	no serious	no serious	no serious	-	-		cated by hi	-	;)	
serious ¹⁸				none	122	125	-	-1:00	1	
			adista aat					differenc e in survival rates 0.02 lower (0.15 lower to 0.11 higher)	0000 MODERATE	
						-	1			
serious ^{6,7,19}			serious ^{15,21}		(3.5%)	(1.8%)	(0.19 to 13.49) ^{16,2} 3	per 100 (from 1 fewer to 18 more)	VERY LOW	
										n)
	no serious inconsistency	serious ²⁰	serious ¹⁵	none	6/35 (17.1%)	3/18 (16.7%)	OR 1.03 (0.23 to 4.73) ¹⁶	0 more per 100 (from 12 fewer to 32 more)	⊙OOO VERY LOW	
	very serious ^{6,7,19}	very serious ^{9,12} serious ^{6,7,19} symptoms - severe disability serious ⁸ no serious inconsistency	very serious6.7.19very serious9.12serious20symptoms - severe disability status (stage 2 serious8no serious seriousserious20	very serious6:7,19very serious9,12serious20very serious15,21symptoms - severe disability status (stage 2)(follow-up 10 serious8no serious inconsistencyserious20serious15	very serious6.7.19very serious9.12serious20very serious15.21nonesymptoms - severe disability status (stage 2)(follow-up 10 months; assessed serious8noneno serious inconsistencyserious20serious15none	very serious6.7.19very serious9.12serious20very serious15.21none2/57 (3.5%)symptoms - severe disability status (stage 2)(follow-up 10 months; assessed with: number of deserious8no serious serious20serious15none6/35 (17.1%)	very serious67.19very serious9.12serious20very serious15.21none2/57 (3.5%)1/56 (1.8%)symptoms - severe disability status (stage 2)(follow-up 10 months; assessed with: number of deaths amongst those serious8none6/35 (17.1%)3/18 (16.7%)	seriousseriousseriousserious (3.5%) (1.8%) (0.19 to) symptoms - severe disability status (stage 2)(follow-up 10 months; assessed with: number of deaths amongst those with stage serious (3.5%) (1.8%) (0.19 to) seriousno serious inconsistencyseriousserious $(5/35)$ $3/18$ OR 1.03 (0.23 to) (16.7%) (16.7%) (16.7%) $(1.3\%)^{16}$	e; stage 2) (follow-up 6 to 18 months; assessed with: number of deaths amore st those classified as stage 2 on admission very serious ^{9,12} serious ²⁰ very serious ^{15,21} none 2/57 1/56 OR 1.61 1 more (0.19 to per 100 13.49) ^{16,2} (from 1 fewer to 18 more) serious ^{15,21} none 2/57 (3.5%) (1.8%) 0R 1.61 1 more vert to 18 more) symptoms - severe disability status (stage 2) (follow-up 10 months; assessed with: number of deaths amongst those vert as amongst those vert as amongst those of 0.13 more) serious ⁸ no serious serious ²⁰ serious ¹⁵ none 6/35 (17.1%) 0R 1.67%) OR 1.03 0 more fewer to 32 more)	e; stage 2) (follow-up 6 to 18 months; assessed with: number of deaths amongst those classified as stage 2 on admission) very serious ^{9,12} very serious ^{9,12} serious ²⁰ very serious ^{15,21} none 2/57 (3.5%) (1.8%) OR 1.61 (0.19 to 13.49) ^{16,2} 3 (1.8%) OR 1.61 (1.8%) OR 1.6

⁵ Schoeman et al (1997) and Chotmongkol et al (1996): method of randomisation and use of allocation concealment is unclear

⁶ Schoeman et al, 1997: blinded = clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function; unclear if patients or other health professionals were blinded

⁷ Unclear if analysis followed the intent-to-treat principle

⁸ Malhotra et al, 2009: use of allocation concealment is unclear; blinding not used

⁹ Chotmongkol et al, 1996: groups not comparable at baseline - clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, although not statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness

			Quality asses	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
			ditionally, there we was not statistically		with severe (st	age 3) disease and	d fewer patients with	less severe (stage 1,) disease in	the prednisc	olone group t	han in the
^{10'} O'Tool	e et al, 1969: I	unclear if grou	ps were comparabl	e at baseline, or		mparable for treatn	nent completion and	availability of outcom	ie data			
		ely between a	nly 3 months after ti roups	reatment initiatio	n							
			oss the studies									
				et al (1991), Ku	marvelu et al (1	994): antituberculo	sis regimens do not	use all of or just the 4	4 standard r	ecommende	d drugs	
		b: <300 events										
			erval calculated by	reviewer								
		/7 / Török et al, low intent-to-tr										
			of allocation concea	lment is unclear								
						all of or just the 4	standard recommend	ded drugs				
	onfidence inte		()	U U				U				
²² Forest	plot (mortality)):										
²³ Forest	plot (mortality	; prednisolone,):									

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in stage 3 CNS tuberculosis

			Quality asses	ssment			No of p	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(stage 3) (fol	llow-up 6 to 1	8 months; assess	ed with: numbe	er of deaths am	ongst those with	stage 3 CNS TB on	admission)				
4 ^{1,2,3,4}	randomised trials	very serious ^{5,6,7,8}	very serious ^{9,10,11,12,13}	serious ¹⁴	serious ¹⁵	none	13/49 (26.5%)	21/49 (42.9%)	OR 0.42 (0.14 to 1.27) ^{16,24}	19 fewer per 100 (from 33 fewer to 6 more)	⊙OOO VERY LOW	
Mortality	/ (stage 3; rifa	mpicin-conta	ining antitubercu	losis regimens	only) (follow-u	p 6 to 18 months;	assessed with: nu	nber of deaths amo	ongst those	with stage	3 CNS TB on	admission)
3 ^{1,2,4}	randomised trials		very serious ^{9,11,12,13}	serious ¹⁴	serious ¹⁵	none	10/45 (22.2%)	17/45 (37.8%)	OR 0.53 (0.12 to 2.27) ¹⁶	13 fewer per 100 (from 31 fewer to 20 more)	©OOO VERY LOW	

			Quality asses	ssment			No of p	patients	Ef	fect		
No of studies		Risk of bias	Inconsistency		Imprecision	Other considerations		Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)		Quality	Importance
							ed as stage 3 on ad		cated by hi			
1 ¹⁷	randomised trials	serious ¹⁸	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	60	-	difference in survival rates 0.02 lower (0.2 lower to 0.15 higher)	©⊙⊙ MODERATE	
		, ,,					igst those classified			45 6	0000	
2 ^{1,2}	trials	very serious ^{6,7,19}	very serious ^{9,12}	serious ²⁰	serious ¹⁵	none	7/39 (17.9%)	14/39 (35.9%)	OR 0.47 (0.05 to 4.44) ^{16,25}	15 fewer per 100 (from 33 fewer to 35 more)	⊙OOO VERY LOW	
-			severe disability		(follow-up 10	months; assessed	d with: number of d	eaths amongst those	se with stag	je 3 CNS TB		on)
14	randomised trials	serious ²¹	no serious inconsistency	serious ²²	very serious ^{15,23}	none	3/12 (25%)	1/5 (20%)	OR 1.22 (0.1 to 17.1) ¹⁶	3 more per 100 (from 18 fewer to 61 more)	©OOO VERY LOW	
Schoem Schoem or other Unclear Malhotra Chotmo statistic than in : placebc ⁰ ° O'Toole ¹ Kuman ² Follow- ³ Estimat ⁴ Chotmo ⁵ GRADE ⁶ Odds ra	nan et al, 1997. r health profes. if analysis folk a et al, 2009: b ngkol et al, 19 ally significant, the placebo gr o group, althou e et al, 1969: u velu et al, 1994. up varied wide tes of effect ve ongkol et al (19 E rule of thumb	: blinded = clir sionals were b owed the inter blinding not us 96: groups not oup (10%); ac gh again this unclear if group 4: follow-up on ely between gr ery widely acro 996), O'Toole 5: <300 events confidence inte	nical psychologist a blinded nt-to-treat principle ed t comparable at ba s in the prednisolo Iditionally, there we was not statistically os were comparab ly 3 months after t oups iss the studies et al (1969), Girgis s	assessing intellig nseline - clinical µ ne group (17%) ere more patient v significant le at baseline, or reatment initiation s et al (1991), Ku	rence, clinician t presentations ar had motor weak s with severe (s r if they were co on	testing hearing, oph and staging were sin kness than in the pl tage 3) disease an mparable for treatn	ncealment is unclear nthalmologist testing nilar in the interventio lacebo group (3%), a d fewer patients with nent completion and psis regimens do not i	on and comparator g nd more patients in t less severe (stage 1 availability of outcon	roups at rand he predniso) disease in ne data	domisation; h lone group (1 the prednisc	nowever, altho 17%) had mot lone group th	ough not or weakness
⁸ Analysi ⁹ Method ⁰ Chotmo ¹ Malhoti	is does not foll I of randomisat ongkol et al, 19 ra et al, 2009:	ow intent-to-tr tion and use o 996: antitubero use of allocati	eat principle f allocation concea culosis regimens d on concealment is	o not use all of c unclear; blinding	r just the 4 stan g not used	dard recommended	d drugs standard recommend	ded druas				

			Quality asses	ssment			No of p	atients	Eff	ect		
	Design onfidence inter plot (mortality)		Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative	Absolute (95% Cl)	Quality	Importance
²⁵ Forest	plot (mortality;	prednisolone):									

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in culture-positive CNS tuberculosis

			Quality asses	sment			No of p	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(dexamethas	sone; culture-p	ositive) (follow-u	up 2 years; ass	essed with: nu	mber of deaths a	mongst those class	ified as culture-pos	sitive on a	dmission)	,	
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ³	serious ⁴	none	32/75 (42.7%)	50/85 (58.8%)	OR 0.52 (0.28 to 0.98) ⁵	16 fewer per 100 (from 0 fewer to 30 fewer)	⊙OO O VERY LOW	
								low-up ; assessed v		er of patien	ts to deve	Іор
1 ¹	randomised trials		no serious inconsistency	serious	serious ⁴	none	4/75 (5.3%)	re-positive on admi 10/85 (11.8%)	OR 0.42 (0.13 to 1.41) ⁵	6 fewer per 100 (from 10 fewer to 4 more)	⊙OO O VERY LOW	
						asone; culture-po is culture-positive		vith: number of pati	ents to wit	,	t residual	neurologic
1 ¹	randomised trials	· · · · · · · · · · · · · · · · · · ·	no serious inconsistency	serious	serious ⁴	none	6/75 (8%)	13/85 (15.3%)	OR 0.48 (0.17 to 1.34) ⁵	7 fewer per 100 (from 12 fewer to 4 more)	⊙OO O VERY LOW	
					ositive) (meas	ured with: time to	become afebrile (c	lefined as a temper	ature of <3	/	gst those	classified as
1 ¹	randomised trials	serious ²	r indicated by lo no serious inconsistency	serious	no serious imprecision	none	75	85 9 fully alert amongs	-	MD 3.0 days lower (6.9 lower to 0.9 higher) ⁶	©©O O LOW	

			Quality asses	sment			No of p	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ³	serious ⁸	none	75	85	-	MD 4 days higher (4.9 lower to 12.9 higher) ⁶	⊙OO O VERY LOW	

Adverse events - ocular (dexamethasone; culture-positive; non-randomised) (follow-up unclear; assessed with: number of patients with ocular complications amongst those classified as culture-positive on admission)

1 ⁹	non- very randomised serious trials	5 Serious ^{13,14} Dus ^{10,11,12}		very serious ^{4,8}	none	2/30 (6.7%)	4/34 (11.8%)	OR 2.46 (0.42 to 14.52) ⁵	13 more per 100 (from 6 fewer to 54 more)	©OO O VERY LOW
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¹ Girgis et al, 1991

² Girgis et al, 1991: use of allocation concealment and blinding unclear

³ Girgis et al (1983 and 1991): antituberculosis regimens do not use all of or just the 4 standard recommended drugs; of particular note is the lack of rifampicin

⁴ GRADE rule of thumb: <300 events

⁵ Odds ratio and 95% confidence interval calculated by reviewer

⁶ Mean difference and 95% confidence interval calculated by reviewer

⁷ For full definition, see evidence table

⁸ Wide confidence interval

⁹ Girgis et al, 1983

¹⁰ Non-randomised; patients were alternately assigned to receive antituberculosis chemotherapy plus dexamethasone or antituberculosis chemotherapy alone

¹¹ No allocation concealment

¹² Use of blinding unclear

¹³ 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

¹⁴ Unclear if groups received the same care except for the intervention(s) studied; limited information available

Corticosteroids vs antituberculosis chemotherapy alone or plus placebo in culture-negative CNS tuberculosis

			Quality asse	essment			No of p	oatients	Ef	fect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance		
Mortality	lortality (dexamethasone; culture-negative) (follow-up 2 years; assessed with: number of deaths amongst those classified as culture-negative on admission)													
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ³	serious ⁴	none	40/70 (57.1%)	29/50 (58%)	OR 0.97 (0.46 to 2.01) ⁵	1 fewer per 100 (from 19 fewer to 16 more)	⊙OOO VERY LOW			

Changes in signs and symptoms - neurological abnormalities during treatment (dexamethasone; culture-negative) (follow-up; assessed with: number of patients to develop

			Quality asse	essment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
neurolog	gic abnormalit	ies (fundus	s, hemiparesis oi	r hydrocephalu	s) during treat	ment amongst the	ose classified as cu	lture-negative on ad	mission)			
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ³	serious ⁴	none	4/70 (5.7%)	5/50 (10%)	OR 0.67 (0.17 to 2.6) ⁵	3 fewer per 100 (from 8 fewer to 12 more)	⊙OOO VERY LOW	
								d with: number of pa	atients to w	ith permane	ent residua	l neurologic
abnorma						•	ative on admission)			47.6	0000	
1'	randomised trials	serious ²	no serious inconsistency	serious ³	serious ⁴	none	8/70 (11.4%)	14/50 (28%)	OR 0.33 (0.13 to 0.87)⁵	17 fewer per 100 (from 3 fewer to 23 fewer)	⊙OOO VERY LOW	

¹ Girgis et al, 1991
 ² Use of allocation concealment and blinding unclear
 ³ Antituberculosis regimens do not use all of or just the 4 standard recommended drugs; of particular note is the lack of rifampicin
 ⁴ GRADE rule of thumb: <300 events
 ⁵ Odds ratio and 95% confidence interval calculated by reviewer

BONE & JOINT, INCLUDING SPINAL, TUBERCULOSIS

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality ass	essment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Respons	e to treatmen	it – need fo	r additional surg	ical interventio	n (assessed w	ith: number of pa	tients requiring sur	gery due to insuffic	cient shrink	age of the s	wollen joir	nt)
1 ¹	randomised trials	serious ²	serious ^{3,4}	very serious ^{5,6,7,8}	very serious ^{9,10}	none	9/10 (90%)	5/6 (83.3%)	OR 1.80 (0.09 to 35.43) ¹¹	67 more per 1000 (from 523 fewer to 161 more)	⊙OOO VERY LOW	
Changes	in signs and	symptoms	– weight (asses	sed with: numb	per of patients	that failed to gain	weight)					
1 ¹	randomised trials	serious ²	serious ^{3,4}	very serious ^{5,6,7}	very serious ^{9,10}	none	1/10 (10%)	1/6 (16.7%)	OR 0.56 (0.03 to 10.93) ¹¹	66 fewer per 1000 (from 161 fewer to 519 more)	⊙OOO VERY LOW	

¹ Cathro, 1958

² Method of randomisation, and use of allocation concealment and blinding, is unclear

³ 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

⁴ It is unclear if the groups received the same care apart from the intervention(s) studied as authors provided only limited information

⁵ Only limited details of the study population available; therefore the directness of the study population cannot be confirmed

⁶ Antituberculosis regimens do not use all of or just the 4 standard recommended drugs; of particular note was the lack of rifampicin

⁷ Only 2 antituberculosis drugs used

⁸ Outcome is a surrogate for the outcomes of interest

⁹ GRADE rule of thumb: <300 events

¹⁰ Wide confidence interval

¹¹ Odds ratio and 95% confidence interval calculated by reviewer

PERICARDIAL TUBERCULOSIS

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(follow-up 1	to 10 years; a	ssessed with: nu	umber of deaths	s)							
4 ^{1,2,3,4}	randomised trials	very serious ^{5,6,7,8}	very serious ^{9,10,11}	serious ¹²	serious ¹³	none	47/224 (21%)	64/249 (25.7%)	OR 0.70 (0.45 to 1.08) ^{14,17}	6 fewer per 100 (from 12 fewer to 1 more)	⊙OOO VERY LOW	
Respons	e to treatmen	t - favourable	e (assessed with:	number of pati	ients to be cor	sidered in a favo	urable status after 2	24 months of follow	-up)			
2 ^{3,4}	randomised	very	serious ¹⁰	very	serious ¹³	none	141/187	140/196	OR 1.23	4 more	0000	

			Quality asse	ssment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
	trials	serious ^{7,8}		serious ^{12,15}			(75.4%)	(71.4%)	(0.78 to 1.93) ^{14,18}	per 100 (from 5 fewer to 11 more)	VERY LOW	
Respons 3 ^{1,3,4}	se to treatmer randomised	nt - need for s very	urgical intervent serious ¹⁰	ion (assessed v very	vith: number c	of patients to requinone	iire surgical interve 31/220	ntion (pericardector 29/220	my)) OR 1.12	1 more		
·	trials	serious ^{5,7,8}		serious ^{12,15}			(14.1%)	(13.2%)	(0.6 to 2.09) ^{14,19}	per 100 (from 5 fewer to 11 more)		
	s in signs and	symptoms -				number of patien	ts with unrestricted	I physical activity a	fter 10 year	,	.(qu	
2 ^{3,4}	randomised trials	serious ^{7,8}	serious ¹⁰	serious ¹²	serious ¹³	none	30/187 (16%)	60/196 (30.6%)	OR 0.43 (0.26 to 0.71) ^{14,20}	15 fewer per 100 (from 7 fewer to 20 fewer)	⊙OOO VERY LOW	
	s in signs and follow-up)	symptoms -	'out and about' b	out restricted ph	nysical activity	(assessed with:	number of patients	to be 'out and abou	it' but with	restricted p	hysical act	tivity after 10
2 ^{3,4}	randomised trials	very serious ^{7,8}	serious ¹⁰	serious ¹²	serious ¹³	none	94/187 (50.3%)	78/196 (39.8%)	OR 1.53 (1.02 to 2.3) ^{14,21}	10 more per 100 (from 0 more to 21 more)	⊙OOO VERY LOW	
							- 8	ed to home or hosp		17		
2 ^{3,4}	randomised trials	very serious ^{7,8}	serious ¹⁰	serious ¹²	very serious ^{13,16}	none	96/187 (51.3%)	140/196 (71.4%)	OR 0.21 (0 to 9.34) ^{14,22}	37 fewer per 100 (from 71 fewer to 24 more)	⊙OOO VERY LOW	
 ² Hakim (³ Strang ⁴ Strang ⁵ Reuter intraper ⁶ Hakim (⁷ Analysi ⁸ Strang ⁹ Hakim (¹⁰ Strang ¹¹ Follow ¹² Strang ¹³ GRAD ¹⁴ Odds n ¹⁵ Outcol 	icardial steroid et al, 2000: use s does not folk et al (1987/200 et al, 2000: unn et al, 1988/20 -up periods va. et al (1987/20 E rule of thumh atio and 95% o	04 Indomisation of Is/placebo was of allocation by the intent-t 04 and 1988/2 clear if the gro 04: unclear if ti ried widely 04 and 1988/2 0: <300 events confidence intention of the time of the time the for an outcome of the time of the time time of the time of the time of the time of the time of the time time of the time of	s unblinded concealment uncl o-treat principle 004): quasi-rando ups were compara the groups were c 2004): antitubercu	ear mised able in terms of t omparable at the losis regimens d	reatment comp baseline	letion and availabi	or the study subjects lity of outcome data ard recommended dr	until completion of th	ne study; ho	,	cian admin	istering the

	Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy		Absolute (95% Cl)		Importance
¹⁷ Forest	plot (mortality)											

¹⁸ Forest plot (response to treatment – favourable):

¹⁹ Forest plot (response to treatment – need for surgical intervention):

²⁰ Forest plot (changes in signs and symptoms - unrestricted physical activity):

²¹ Forest plot (changes in signs and symptoms - 'out and about' but restricted physical activity):

²² Forest plot (changes in signs and symptoms - confined, restricted physical activity):

Prednisolone vs antituberculosis chemotherapy alone or plus placebo for effusive pericardial tuberculosis

			Quality asses	ssment			No of p	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency		•	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% CI)	Absolute (95% Cl)	Quality	Importance
	. ,	(follow-up 1	to 10 years; asse			;)						
3 ^{1,2,3}	randomised trials	very serious ^{4,5,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	31/154 (20.1%)	43/176 (24.4%)	OR 0.69 (0.4 to 1.17) ^{13,15}	6 fewer per 100 (from 13 fewer to 3 more)	⊙OOO VERY LOW	
	e to treatmen	t - favourable	e (effusive TB) (fo	ollow-up 10 yea	rs; assessed v	with: number of pa	atients to be consid	ered in a favourable	e status aft	er 24 month	s of follow	/-up)
1 ³	randomised trials	very serious ^{6,7}	serious ⁹	serious ¹¹	serious ¹²	none	91/117 (77.8%)	88/123 (71.5%)	OR 1.39 (0.77 to 2.5) ¹³	6 more per 100 (from 6 fewer to 15 more)	⊙OOO VERY LOW	
Respons	e to treatmen	t - need for s	urgical intervent	ion (effusive TE	B) (follow-up 1	to 10 years; asse	ssed with: number	of patients to requir	e surgical	intervention	(pericard	ectomy))
2 ^{1,3}	randomised trials	very serious ^{4,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	12/125 (9.6%)	7/147 (4.8%)	OR 1.98 (0.77 to 5.09) ^{13,16}	4 more per 100 (from 1 fewer to 16 more)	©OOO VERY LOW	
	in signs and follow-up)	symptoms -	unrestricted phy	sical activity (e	ffusive TB) (fo	llow-up 10 years;	assessed with: nur	nber of patients to v	vith unrest	ricted physic	cal activity	y after 10
1 ³	randomised trials	very serious ^{6,7}	serious ⁹	serious ¹¹	serious ¹²	none	21/116 (18.1%)	20/123 (16.3%)	OR 0.68 (0.36 to 1.27) ¹³	5 fewer per 100 (from 10 fewer to 4	©OOO VERY LOW	

			Quality asse	ssment			No of j	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Changes	in signs and	symptoms -	'out and about' h	ut restricted n	hysical activity	(effusive TB) (fol	low-up 10 years: as	sessed with: numb	er of natier	more)	t and abou	it' but with
			years of follow-u		iysical activity		iow-up to years, as	Sessea with. humb				
1 ³	randomised trials	serious ^{6,7}	serious ⁹	serious ¹¹	serious ¹²	none	57/117 (48.7%)	46/123 (37.4%)	OR 1.59 (0.95 to 2.66) ¹³	11 more per 100 (from 1 fewer to 24 more)	⊙OOO VERY LOW	
	s in signs and follow-up)	symptoms -	confined, restric	ted physical ac	tivity (effusive	TB) (follow-up 10) years; assessed w	vith: number of pation	ents to con	fined to hon	ne or hosp	oital after 10
1 ³	randomised trials	very serious ^{6,7}	serious ⁹	serious ¹¹	serious ¹²	none	8/117 (6.8%)	7/123 (5.7%)	OR 1.22 (0.43 to 3.47) ¹³	1 more per 100 (from 3 fewer to 12 more)	⊙OOO VERY LOW	
			-	1			1	perience reduced le				w-up)
1 ¹	randomised trials	serious⁴	no serious inconsistency	no serious indirectness	very serious ^{12,14}	none	1/8 (12.5%)	3/24 (12.5%)	OR 1.00 (0.09 to 11.24) ¹³	0 fewer per 100 (from 11 fewer to 49 more)	⊙OOO VERY LOW	
 ² Hakim e ³ Strang e ⁴ Reuter e ⁵ Hakim e ⁶ Analysis ⁷ Strang e ⁸ Hakim e ⁹ Strang e ¹⁰ Follow- ¹¹ Strang ¹² GRADI ¹³ Odds r. ¹⁴ Wide c 	ricardial steroic et al, 2000: use s does not follo et al, 1988/200 et al, 2000: unc et al, 1988/200 -up periods vai et al, 1988/20 E rule of thumk	ndomisation c ds/placebo wa of allocation w the intent-to 4: quasi-rand clear if the gro 04: unclear if th ried widely 04: antituberc 05: <300 events confidence intervals	is unblinded concealment uncl o-treat principle omised ups were compara he groups were co ulosis regimens do	ear able in terms of t omparable at the o not use all of o	treatment comp baseline	-	lity of outcome data	until completion of t	he study; ho	wever, physi	ician admir	istering the
¹⁶ Forest	plot (response	to treatment	- need for surgical	intervention):								

Prednisolone vs antituberculosis chemotherapy alone or plus placebo for constrictive tuberculous pericarditis

Quality assessment	No of patients	Effect	Quality	Importance	

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)		
Mortality	(constrictive	tuberculous	pericarditis) (fol	low-up 10 years	s; assessed wi	th: number of dea	iths)					
1 ¹	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ⁴	serious ⁵	none	16/70 (22.9%)	21/73 (28.8%)	OR 0.73 (0.35 to 1.56) ⁶	6 fewer per 100 (from 16 fewer to 10 more)	⊙OOO VERY LOW	
							of patients to be c					ollow-up)
1 ¹	randomised trials	very serious ^{2,3}	no serious inconsistency	very serious ^{4,7}	serious⁵	none	50/70 (71.4%)	52/73 (71.2%)	OR 1.01 (0.49 to 2.08) ⁶	0 more per 100 (from 16 fewer to 13 more)	⊙OOO VERY LOW	
•		t - need for s	urgical intervent	ion (constrictiv	e tuberculous	pericarditis) (Cop	y) (assessed with:	number of patients	to require s	surgical inte	rvention	
(pericard 1 ¹	ectomy))						40/70	00/70		4 6	0000	
	randomised trials	very serious ^{2,3}	no serious inconsistency	very serious ^{4,7}	serious⁵	none	18/70 (25.7%)	22/73 (30.1%)	OR 0.80 (0.39 to 1.67) ⁶	4 fewer per 100 (from 16 fewer to 12 more)	VERY LOW	
				sical activity (c	onstrictive tub	erculous pericaro	litis) (follow-up 10 y	ears; assessed wit	h: number	of patients t	o with unr	estricted
physical 1 ¹	activity after			4	5		0/70	4.4/70		0.6	0000	
1.	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ⁴	serious⁵	none	9/70 (12.9%)	14/73 (19.2%)	OR 0.62 (0.22 to 1.55) ⁶	6 fewer per 100 (from 14 fewer to 8 more)	⊙OOO VERY LOW	
						(constrictive tub	erculous pericarditi	s) (follow-up 10 yea	irs; assess	ed with: nun	nber of pat	ients to be
fout and			physical activity				07/70	00/70	00444	0	0000	
1.	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ⁴	serious⁵	none	37/70 (52.9%)	32/73 (43.8%)	OR 1.44 (0.74 to 2.78) ⁶	9 more per 100 (from 7 fewer to 25 more)	⊙OOO VERY LOW	
	in signs and hospital after			ted physical ac	tivity (constric	tive tuberculous	pericarditis) (follow	-up 10 years; asses	sed with: n	umber of pa	tients to c	onfined to
1 ¹	randomised	verv	no serious	serious ⁴	very	none	5/70	2/73	OR 2.73	4 more	0000	
	trials	serious ^{2,3}	inconsistency	3011003	serious ^{5,8}	none	(7.1%)	(2.7%)	(0.51 to 14.56) ⁶	per 100 (from 1 fewer to 26 more)	VERY LOW	
² Analysis ³ Quasi-ra ⁴ Antitube ⁵ GRADE ⁵ Odds ra	andomised rculosis regim rule of thumb tio and 95% co	w the intent-t ens do not us : <300 events onfidence inte	o-treat principle are all of or just the prvals calculated b pome of interest		mmended drug	s						

	Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo		Absolute (95% Cl)		Importance
8 Mida a	anfidance inter											

⁸ Wide confidence interval

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo

			Quality asse	essment			No of j	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
	(follow-up 1	to 10 years; a	assessed with: n		,							
4 ^{1,2,3,4}	randomised trials	very serious ^{5,6,7,8}	very serious ^{9,10,11}	serious ¹²	serious ¹³	none	47/249 (18.9%)	64/249 (25.7%)	OR 0.67 (0.44 to 1.03) ^{14,16}	6 fewer per 100 (from 12 fewer to 1 more)	⊙OOO VERY LOW	
	se to treatmer	nt - need for s	urgical intervent			ssessed with: nur	mber of patients to	require surgical int	ervention (pericardecte	omy))	
3 ^{1,3,4}	randomised trials	very serious ^{5,7,8}	very serious ^{10,11}	serious ¹²	serious ¹³	none	31/220 (14.1%)	29/220 (13.2%)	OR 1.12 (0.6 to 2.09) ^{14.17}	1 more per 100 (from 5 fewer to 11 more)	⊙OOO VERY LOW	
			-		up 1 years; ass	essed with: numb		perience reduced le				v-up)
1 ¹	randomised trials	serious⁵	no serious inconsistency	no serious indirectness	very serious ^{13,15}	none	4/33 (12.1%)	3/24 (12.5%)	OR 0.97 (0.20 to 4.78) ¹⁴	12 fewer per 100 (from 10 fewer to 28 more)	⊙OOO VERY LOW	
 ² Hakim e ³ Strang e ⁴ Strang e ⁵ Reuter e ⁶ Hakim e ⁷ Analysis ⁸ Strang e ⁹ Hakim e ¹⁰ Strang ¹¹ Follow- ¹² Strang ¹³ GRADI ¹⁴ Odds r. ¹⁵ Wide c 	ricardial stéroid et al, 2000: use s does not follo et al (1987/200 et al, 2000: unn et al, 1988/200 et al (1987/20 E rule of thumil atio and 95% o confidence inte	04 andomisation of ds/placebo wa e of allocation bw the intent-t 04 and 1988/2 clear if the gro 04: unclear if ried widely 04 and 1988/2 04 and 1988/2 04 and 1988/2 confidence inter rvals	s unblinded concealment unc o-treat principle 004): quasi-rando ups were compar the groups were c 2004): antitubercu	lear mised able in terms of comparable at th losis regimens o	treatment comp e baseline	letion and availabili		until completion of th	ne study; ho	wever, physi	cian admin	istering the
	plot (mortality) plot (response		- need for surgica	l intervention):								

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo for effusive pericardial tuberculosis

Quality assessment No of patients Effect Quality Importance				
	Quality assessment	No of patients	Effect	

¹⁴ Forest plot (mortality):

¹⁵ Forest plot (response to treatment - need for surgical intervention):

Prednisolone vs triamcinalone

	Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus triamcinalone		Absolute (95% Cl)	Quality	Importance
Mortality	(effusive TB)) (follow-up 1	years; assessed	with: number of	of deaths)							
1 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	very serious ^{3,4}	none	0/8 (0%)	0/17 (0%)	2.06 (0.04 to 112.94)⁵	-	⊙OOO VERY LOW	

	Quality assessment						No of p	atients	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus triamcinalone	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Respons	se to treatmer	nt – need for a	additional interve	ntion (effusive	TB) (follow-up	1 years; assessed	with: number of pa	atients to require su	urgery)			
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ⁶	very serious ^{3,4}	none	1/8 (12.5%)	0/17 (0%)	OR 6.18 (0.23 to 168.11) ⁵	-	0000 VERY LOW	
Changes	s in signs and	symptoms -	activity levels (e	ffusive TB) (fol	low-up 1 years	; assessed with: n	umber of patients t	o experience reduc	ed levels o	f activity at	1-year of f	ollow-up)
1 ¹	randomised trials		no serious inconsistency	no serious indirectness	very serious ^{3,4}	none	1/8 (12.5%)	2/17 (11.8%)	OR 1.07 (0.08 to 13.9)⁵	1 more per 100 (from 11 fewer to 53 more)	©OOO VERY LOW	

² 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

³ GRADE rule of thumb: <300 events

⁴ Wide confidence intervals

⁵ Odds ratio and 95% confidence intervals calculated by reviewer
 ⁶ Outcome is a surrogate for an outcome of interest

Prednisolone vs antituberculosis chemotherapy alone or plus placebo for effusive pericardial tuberculosis in people with HIV

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	/ (HIV-positive	e; effusive TB) (follow-up 18 m	onths; assesse	d with: numbe	er of deaths)						
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	serious⁵	none	5/29 (17.2%)	10/29 (34.5%)	OR 0.40 (0.12 to 1.36) ⁶	17 fewer per 100 (from 29 fewer to 7 more)	⊙OOO VERY LOW	
Changes	s in signs and	symptoms -	constrictive perio	carditis (HIV-po	sitive; effusive	e TB) (follow-up 18	months; assessed	with: number of pa	tients to ex	perience co	onstrictive	pericarditis)
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	very serious ^{5,7}	none	2/29 (6.9%)	2/29 (6.9%)	OR 1.00 (0.13 to 7.62) ⁶	0 fewer per 100 (from 6 fewer to 29 more)	⊙OOO VERY LOW	

No of											
studies Desig	Risk of ign bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Adherence (HI)	IV-positive; effusive T	B) (follow-up 18	months; assess	sed with: num	ber of pill counts s	showing that >90% of tablets had been consumed))		
1 ¹ rando trials		serious ⁴	serious ⁸	no serious imprecision	none	169/230 (73.5%)	119/182 (65.4%)	OR 1.47 (0.96 to 2.24) ⁶	8 more per 100 (from 1 fewer to 15 more)	⊙OOO VERY LOW	

³ Unclear if analysis follows the intent-to-treat principle
 ⁴ Unclear if the groups were comparable in terms of treatment completion and availability of outcome data
 ⁵ GRADE rule of thumb: <300 events

⁶ Odds ratio and 95% confidence intervals calculated by reviewer

⁷ Wide confidence intervals

⁸ Outcome is a surrogate for an outcome of interest

TB-ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
Mortality	(follow-up 12	2 weeks; asse	essed with: numb	er of deaths)								
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	very serious ^{5,6}	none	3/55 (5.5%)	2/55 (3.6%)	OR 1.53 (0.25 to 9.52) ⁷	2 more per 100 (from 3 fewer to 23 more)	⊙OOO VERY LOW	
Change	in signs and s	symptoms – i	mprovement (ass	essed with: nu	mber of patien	ts in whom sympt	oms improved or w	vere resolved after	4 weeks⁴)			
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	serious⁵	none	44/55 (80%)	31/55 (56.4%)	OR 1.81 (0.72 to 4.5) ⁷	14 more per 100 (from 8 fewer to 29 more)	⊙OOO VERY LOW	

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
		2 .		sessed with: nu		ts in whom sympt	oms deteriorated a	· · · ·				
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	serious⁵	none	7/55 (12.7%)	9/55 (16.4%)	OR 0.75 (0.26 to 2.17) ⁷	4 fewer per 100 (from 12 fewer to 13 more)	⊙OOO VERY LOW	
Change	in signs and s	symptoms –	improvement of c	hest radiograp	h (assessed wi	ith: number of pat	ients whose chest i	adiographs improv	ed or were	resolved af	ter 4 week	S⁴)
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	very serious ^{5,6}	none	40/55 (72.7%)	25/55 (45.5%)	OR 3.20 (1.44 to 7.09) ⁷	27 more per 100 (from 9 more to 40 more)	⊙OOO VERY LOW	
Change	in signs and s	symptoms –	deterioration of c	hest radiograph	n (assessed wi	th: number of pati	ents whose chest r	adiographs deterio	rated after	4 weeks⁴)		
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	serious⁵	none	4/55 (7.3%)	18/55 (32.7%)	OR 0.16 (0.05 to 0.52) ⁷	26 fewer per 100 (from 13 fewer to 30 fewer)	⊙OOO VERY LOW	
Adverse	events - drug	reactions (a	assessed with: nu	mber of patient	ts to experienc	e adverse drug re	actions)					
1 ¹	randomised trials		serious ³	no serious indirectness	very serious ^{5,6}	none	8/55 (14.5%)	3/55 (5.5%)	OR 2.95 (0.74 to 11.78) ⁷	9 more per 100 (from 1 fewer to 35 more)	⊙OOO VERY LOW	
Adverse	events - infe	ctions (asses	ssed with: numbe	r of patients to	experience inf	ections)						
1 ¹	randomised trials	serious ²	serious ³	no serious indirectness	serious⁵	none	27/55 (49.1%)	17/55 (30.9%)	OR 2.16 (0.99 to 4.7) ⁷	18 more per 100 (from 0 fewer to 37 more)	⊙OOO VERY LOW	

¹ Meintjes et al, 2010 ² Unclear if allocation concealment was used ³ Groups were not comparable at baseline: there was a longer period (p = 0.02) between taking antituberculosis chemotherapy and initiating ART amongst patients in the prednisolone arm (66 days) than the placebo arm (43.5 days) ⁴ For full definition, see evidence table ⁵ GRADE rule of thumb: <300 events

⁶ Wide confidence intervals

⁷ Odds ratio and 95% confidence intervals calculated by reviewer

A.10 RQ P

CENTRAL NERVOUS SYSTEM TB

6 MONTHS vs 9 MONTHS

Mortality

		Quality as	sessment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (childr	en only; antitube	rculosis chemot	herapy + corticos	teroids) (number	of deaths during	treatment)				
1 ¹	non- randomised trials/observati onal studies	very serious ^{2,3,4,6}	serious ^{5,6}	very serious ^{7,8,11}	serious ⁹	7/45 (15.6%)	2/4 (50%)	OR 0.18 (0.02 to 1.53) ¹⁰	35 fewer per 100 (from 48 fewer to 10 more)	VERY LOW
 ⁶ Unclear if the gr ⁷ Regimens do no ⁸ All patients receive ⁹ GRADE rule of ¹⁰ Odds ratio and ¹¹ Doses used and 	ealment unclear oups were compa roups were followe ot contain all of/jus vived corticosteroid thumb: <300 even 95% confidence ii	d up for the same t the 4 standard r ds ts ntervals calculate those recommen	ecommended drug d by reviewer ded in the British I		Ŷ					

Change in signs and symptoms

		Quality as	sessment			Number o	of patients	Eff	ect			
Number of								Relative	Absolute			
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality		
Change in signs and symptoms – neurological sequelae (children only; antituberculosis chemotherapy + corticosteroids) (number of patients to experience neurological sequelae												
(hydrocephalus, cerebral palsy with mental retardation, hemiparesis, long-term seizures, or behavioural changes))												
1 ¹	non- randomised trials/observati onal studies	very serious ^{2,3,4,6}	serious ^{5,6}	very serious ^{7,8,11}	serious ⁹	11/45 (24.4%)	2/4 (50%)	OR 0.32 (0.04 to 2.58) ¹⁰	26 fewer per 100 (from 46 fewer to 22 more)	VERY LOW		
¹ Jacobs et al, 1992 ² No randomisation or blinding ³ Allocation concealment unclear ⁴ No blinding												

		Quality as	sessment			Number of patients		Effect			
Number of								Relative	Absolute		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality	
⁵ Unclear if the groups were comparable at baseline											
⁶ Unclear if the groups were followed up for the same length of time, or if follow-up was for an appropriate length of time											
⁷ Regimens do i	not contain all of/ju	ist the 4 standard r	ecommended drug	IS		-					
8 All patients red	eived corticostero	ids									
⁹ GRADE rule of	f thumb: <300 eve	nts									
¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer											
¹¹ Doses used are inconsistent with those recommended in the British National Formulary											
Abbreviations: C	CI, confidence inter	rval; OR, odds ratio)		-						

Number of patients

12 to 16

Effect

Absolute

Relative

8 MONTHS vs 12 to 16 MONTHS

Quality assessment

Change in signs and symptoms

Number of

studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	8 months	months	(95% CI)	(95% CI)	Quality
(median months	and symptoms – ne (IQR)) = 13 (4–36); as or hearing loss))									
1 ¹	non-randomised trials/observational studies	serious ^{2,3,4}	very serious ^{2,5,6,7}	serious ⁸	serious ⁹	8/37 (21.6%)	10/35 (28.6%)	OR 0.69 (0.24 to 2.02) ¹⁰	7 fewer per 100 (from 20 fewer to 16 more)	VERY LOW
 ³ Unclear if attern ⁴ No randomisati ⁵ Retreatment an ⁶ Differences bet ⁷ Wide variations ⁸ Intervention doe ⁹ GRADE rule of ¹⁰ Odds ratio and 	pased upon the centre pts were made within on, and blinding uncle d default cases exclu ween groups in the co in duration of follow-u es not exactly match t thumb: <300 events 95% confidence interval;	the study design ar ded from 8-month orticosteroid regim up he intervention of rvals calculated b	or analysis to bala group but not the ens used interest: does not	ance potential col	nfounders group				han duration alone	9
Relapse										
		Quality asse	essment			Number	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	8 months	12 to 16 months	Relative (95% Cl)	Absolute (95% Cl)	Quality

	U									
B I (C II	• • • • • •				/ P		00)			
Relanse (follow-	up: 8-month group (m	nedian months (IC.	$(6-24)^{\circ}$	12-to-16-month ar	oup (median mon	(1(1)R) = 13(4)	-36) assessed w	ith' number of r	atients to experie	nce relanse)
Itelapoo (Ionom	ap. o monai group (n		((0, -1))	i i to i i o i o i i o i i o i i o i i o i i o i i o i i o i i o i o i i o i i o i i o i i o i i o i i o o i o o i o	oup (moulan mon		, accessa	ian. nambol ol p		noo rolapoo)
- 1		. 224			. 0.12	0// 00	0//00	00 4 00 40 00		
1'	non-randomised	serious ^{2,3,4}	verv	serious [®]	verv serious ^{9,12}	0/100	0/100	OR 1.00 (0.02	_	VERY LOW
1	non-randomised	3011003	very	3011003	very serious	0/100	0/100	011 1.00 (0.02		

		Quality ass	essment			Numbe	r of patients	I	Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	8 months	12 to 16 months	Relative (95% CI)	Absolute (95% Cl)	Quality
	trials/observational studies		serious ^{2,5,6,7,11}			(0%) ¹³	(0%) ¹³	to 50.89) ¹⁰		
 ³ Unclear if atter ⁴ Blinding unclear ⁵ Retreatment at ⁶ Differences be ⁷ Wide variation: ⁸ Intervention do ⁹ GRADE rule on ¹⁰ Odds ratio and ¹¹ Unclear if the ¹² Wide confider ¹³ It is unclear hor rate in each g 	nd default cases exclu tween groups in the co s in duration of follow-u es not exactly match t f thumb: <300 events d 95% confidence inter 2 arms were comparal foce intervals fow many patients in ea	the study design ded from 8-mont pricosteroid regin p he intervention o rvals calculated b ble for the availa ach group had rea	n or analysis to bal h group but not the mens used f interest: does not by reviewer bility of outcome da	ance potential co 12-to-16-month contain all of or j ata	nfounders group iust the 4 standar	d recommendeo	l drugs, and the 2	2 arms vary by more		

Adverse events

		Quality asse	essment			Number of patients		Eff		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	8 months	12 to 16 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Adverse events	(any) (assessed with:	number of patier	nts to experience a	any adverse event	t)					
1 ¹	non-randomised trials/observational studies	serious ^{2,3,4}	very serious ^{2,5,6}	serious ⁸	serious ⁹	6/37 (16.2%)	8/35 (22.9%)	OR 0.65 (0.20 to 2.12) ¹⁰	7 fewer per 100 (from 17 fewer to 16 more)	VERY LOW

¹ Doğanay et al, 1995

² Allocation was based upon the centre attended by the patient - potential systematic differences between clinics (for example, differences in delivery of care)

³ Unclear if attempts were made within the study design or analysis to balance potential confounders

^₄ Blinding unclear

⁵ Retreatment and default cases excluded from 8-month group but not the 12-to-16-month group

⁶ Differences between groups in the corticosteroid regimens used

⁷ Wide variations in duration of follow-up

⁸ Intervention does not exactly match the intervention of interest: does not contain all of or just the 4 standard recommended drugs, and the 2 arms vary by more than duration alone

⁹ GRADE rule of thumb: <300 events

¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence interval; OR, odds ratio

SPINAL TB

6 MONTHS vs 9 MONTHS

Mortality

Quality assessment							Number of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (antituberculosis chemotherapy + surgery) (follow-up 60 months; number of deaths associated with spinal tuberculosis)										
1 ¹	randomised trials	very serious ^{2,3,4}	serious ¹⁰	very serious ^{5,6}	very serious7,8	0/24 (0%)	0/26 (0%)	OR 1.08 (0.02 to 56.64) ⁹	-	VERY LOW
_ *	alment unclear ot follow the inten	t-to-treat principle								

⁵ Intervention does not exactly match the intervention of interest: regimens do not contain all of/just the 4 standard recommended drugs, and all patients underwent surgery in addition to receiving antituberculosis chemotherapy

⁶ Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance

⁷ GRADE rule of thumb: <300 events

⁸ Wide confidence intervals

⁹ Odds ratio and 95% confidence intervals calculated by reviewer

¹⁰ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

Abbreviations: CI, confidence interval; OR, odds ratio

Change in signs and symptoms

	Quality assessment							Effect				
Number of								Relative	Absolute			
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality		
Change in signs and symptoms - complete bony fusion (antituberculosis chemotherapy + surgery) (follow-up 36 months; number of patients with complete bony fusion ¹)												
1 ¹¹	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious9,13	25/25 (100%)	26/26 (100%)	OR 0.96 (0.02 to 50.35) ¹⁰	-	VERY LOW		
	Change in signs and symptoms – kyphosis (antituberculosis chemotherapy + surgery) (follow-up minimum 10 years; mean increase in the angle of kyphosis from baseline to end of follow- up; better indicated by lower values)											
1 ²¹	randomised trials	serious ^{4,5,6}	no serious inconsistency	very serious ^{8,12}	no serious imprecision ¹⁶	25	26	-	MD 0.7 lower (5.31 lower to 3.91 higher) ²²	VERY LOW		
	Change in signs and symptoms – kyphosis (antituberculosis chemotherapy + surgery) (follow-up 60 months; increase in the mean angle of kyphosis from baseline to end of follow-up ¹⁹ ; better indicated by lower values)											
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	no serious imprecision ¹⁶	14	14	-	MD 14.1 higher ^{17,18,20}	VERY LOW		
Change in signs baseline to 60 mm	and symptoms - onths)	- kyphosis (antitu	uberculosis chem	notherapy + surg	ery) (number of pa	atients with improv	ement in their ang	le of kyphosis (red	duction of 11° or n	nore) from		
1 ²³	randomised	very serious5,6,7	serious ²⁴	very serious ^{8,12}	very serious9,13	0/14	1/14	OR 0.31 (0.01	5 fewer per	VERY LOW		

Quality assessment							Number of patients		Effect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
	trials					(0%)	(7.1%)	to 8.29) ¹⁰	100 (7 fewer to 32 more)	
Change in sign 60 months)	s and symptoms ·	– kyphosis (antitu	uberculosis chen	notherapy + surg	ery) (number of p	atients with no	change in their angle	e of kyphosis (withi	n $\pm 10^{\circ}$) from base	line to
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious ^{9,13}	5/14 (35.7%)	11/14 (78.6%)	OR 0.15 (0.03 to 0.81) ¹⁰	43 fewer per 100 (4 fewer to 69 fewer)	VERY LOW
Change in sign baseline to 60 m		– kyphosis (antitu	uberculosis chen	notherapy + surg	ery) (number of p	atients with dete	erioration in their ang	gle of kyphosis (inc	rease of 11° or mo	ore) from
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious ^{9,13}	9/14 (64.3%)	2/14 (14.3%)	OR 10.80 (1.69 to 68.94) ¹⁰	50 more per 100 (from 8 more to 78 more)	VERY LOW
	s and symptoms in 0.24 vertebrae))		antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; i	number of patients w	ith no change in th	eir vertebral loss (an increase or
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	serious ⁹	13/24 (54.2%)	14/25 (56%)	OR 0.93 (0.30 to 2.86) ^{10,20}	2 fewer per 100 (from 28 fewer to 22 more)	VERY LOW
	s and symptoms n 0.25 vertebrae))	– vertebral loss (antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; ı	number of patients w	ith improvement in	their vertebral los	s (reduction in
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	serious ⁹	2/24 (8.3%)	5/25 (20%)	OR 0.36 (0.06 to 2.09) ¹⁰	12 fewer per 100 (from 19 fewer to 14 more)	VERY LOW
	s and symptoms n 0.25 vertebrae))	– vertebral loss (antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; i	number of patients w	ith deterioration in	,	s (increase in
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	serious ⁹	6/24 (25%)	9/25 (37.5%)	OR 0.59 (0.17 to 2.03) ¹⁰	11 fewer per 100 (from 27 fewer to 17 more)	VERY LOW
	s and symptoms			chemotherapy +	surgery) (mean	vertebral loss fr	om treatment initiatio	on to 60 months)		
1 ²³	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	no serious imprecision ¹⁶	24	25	-	MD 0.06 higher ^{17,18,20}	VERY LOW
	s and symptoms /ed during follow-up		berculosis chem			months; numbe	er of patients with sin	us and/or clinically	evident abscesse	s on admission
1 ¹¹	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious9,13	4/5 (80%)	2/2 (100%)	OR 0.60 (0.02 to 20.98) ¹⁰	-	VERY LOW
Change in sign resolved during		– sinuses (antitu	berculosis chem	otherapy + surge	ery) (follow-up 36	months; numbe	er of patients with new	w sinus and/or clini	cally evident abso	esses that
1 ¹¹	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious ^{9,13}	1/1 (100%)	2/3 (66.7%)	OR 1.80 (0.04 to 79.43) ¹⁰	12 more per 100 (from 59 fewer to 33 more)	VERY LOW
	s and symptoms - had resolved during		n involvement (ar	ntituberculosis c	hemotherapy + s	urgery) (follow-	-up 36 months; numb	per of patients with	nervous system i	nvolvement on
1 ¹¹	randomised	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious9,13	1/1	2/2	OR 0.60 (0.01	-	VERY LOW

		Quality as	ssessment	Numbe	er of patients		Effect			
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
	trials					(100%)	(100%)	to 49.45) ¹⁰		
For full definit	tion, see evidenc	e tables in the appen	dices							
Method of rar	ndomisation uncle	ear								
[;] Allocation col	ncealment unclea	ar								
Blinding uncle	ear									
		tent-to-treat principle								
		match the intervention	n of interest: regime	ens do not contain	all of/just the 4 s	tandard recomm	nended drugs, and	all patients under	went surgery in a	ddition to receiv
	sis chemotherap									
	of thumb: <300 e									
		ce intervals calculate								
		orking Party on Tube								<u> </u>
		natch the population					istance (Medical F	Research Council	Working Party on	I uberculosis of
		nd Darbyshire (1999))), or some patients	s also nad respira	tory TB (Upadnya	ay et al (1986))				
³ Wide confide		Courseil Marking Do	du an Tukana daala	of the Onine (Onit		· · · · · · · · · · · · · · · · · · ·	ann in addition ta r			
		Council Working Par	ty on Tuberculosis	or the Spine (Gri	tiths et al) (1986)	underwent surg	ery in addition to r	eceiving antituber	culosis chemothe	rapy
	int estimates var	y widely I deviations or standa	rd arrara of the ma	ono: roviowor oou	ld not oppop im	radician				
		deviations or standa					ntervals			
	nce calculated by			ans, reviewer cou			nei vais			
	y the reviewer	y icvicwci								
		ferences in the chang	e from baseline to	36 months are un	likely to be due to	o the different du	rations of treatme	nt because they o	courred mainly in	the first 6 month
that is when	there was no dif	ference between the	reaimens of the tw	o arouns						
¹ Upadhyay et				- <u>g</u> , p						
		nfidence intervals cal	culated by reviewe	r						
²³ Darbyshire,										
		ant initiation: therefor		tions of treatment	ware wood falle	www.www.fordiffe	arout longtha			

²⁴ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio

Response to treatment

Quality assessment							Number of patients		Effect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Response to tre	atment – favoura	ble response (an	tituberculosis ch	emotherapy + su	irgery) (follow-up	60 months; numbe	er of patients who	had a 'favourable'	response to treatr	nent ¹²)
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹²	very serious ^{7,8,13}	very serious ^{9,10}	23/24 (95.8%)	25/26 (96.2%)	OR 0.92 (0.05 to 15.58) ¹¹	0 fewer per 100 (from 41 fewer to 4 more)	VERY LOW
	atment – unfavou nd/or surgery durin			chemotherapy +	surgery) (numbe	r of patients who h	ad an unfavourab	le response to trea	atment that require	ed additional
1 ¹	randomised trials	very serious ^{4,5,6}	serious ¹²	very serious ^{7,8,13}	very serious ^{9,10}	1/24 (4.2%)	1/26 (3.8%)	OR 1.09 (0.06 to 18.40) ¹¹	0 more per 100 (from 4 fewer to 39 more)	VERY LOW
Darbyshire, 199	99									

⁴ Allocation concealment unclear

	Quality assessment							Number of patients		Effect	
Nur	mber of								Relative	Absolute	
stu	dies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality

⁵ Blinding unclear

⁶ Analysis does not follow the intent-to-treat principle

⁷ Intervention does not exactly match the intervention of interest: regimens do not contain all of/just the 4 standard recommended drugs, and all patients underwent surgery in addition to receiving antituberculosis chemotherapy

⁸ Substitute for outcome of interest

⁹ GRADE rule of thumb: <300 events

¹⁰ Wide confidence intervals

¹¹ Odds ratio and 95% confidence intervals calculated by reviewer

¹² Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths

¹³ Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance

Abbreviations: CI, confidence interval; OR, odds ratio

Relapse

		Quality as	sessment			Number of	of patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Recurrence (ant	ituberculosis che	motherapy + su	rgery) (follow-up n	ninimum 10 years;	number of patien	ts to experience re	ecurrence or react	ivation of tubercule	osis during follow-	up)
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency ¹²	very serious ^{6,10,13}	very serious ^{8,11}	0/25 (0%)	0/26 (0%)	OR 1.04 (0.02 to 54.38) ⁹	-	VERY LOW
 ⁶ Intervention doe antituberculosis ⁷ Substitute for ou ⁸ GRADE rule of ⁹ Odds ratio and ¹⁰ Population doe ¹¹ Wide confidence ¹² Unclear if follow ¹³ Substitute for ou 	omisation unclear ealment unclear ot follow the intent es not exactly matc chemotherapy itcome of interest thumb: <300 event 95% confidence im s not exactly matcl	th the intervention ts tervals calculated h the population o h in each group (relapse)	by reviewer f interest: some pa		·	andard recommer	nded drugs, and al	l patients underwe	nt surgery in addi	tion to receiving

Adverse events

		Quality as	sessment			Number o	of patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
	leading to treatm		(antituberculosis	s chemotherapy	+ surgery) (follow	-up for the full trea	tment period; num	ber of patients to	experience advers	e events that
led to modificatio	n of the allocated r	regimen)								
1 ¹	randomised trials	serious ^{3,4}	no serious inconsistency	very serious6,11	very serious7,8	2/31 (6.5%)	0/29 (0%)	OR 5.00 (0.23 to 108.68) ⁹	-	VERY LOW
Adverse events	- any (antituberco	ulosis chemothe	rapy + surgery) (f	ollow-up minimum	10 years; numbe	r of patients to exp	perience an advers	se event)		
1 ¹³	randomised trials	serious ^{2,3,4}	no serious inconsistency	very serious ^{6,11}	very serious ^{7,8}	6/25 (24%)	5/26 (19.2%)	OR 1.33 (0.35 to 5.06) ^{9,14}	5 more per 100 (from 12 fewer to 35 more)	VERY LOW
	ch Council Workin omisation unclear ealment unclear	g Party on Tuberc	ulosis of the Spine	e (Griffiths et al), 1	986					

⁴ Blinding unclear

⁶ Intervention does not exactly match the intervention of interest: regimens do not contain all of/just the 4 standard recommended drugs, and all patients underwent surgery in addition to receiving antituberculosis chemotherapy

⁷ GRADE rule of thumb: <300 events

⁸ Wide confidence intervals

⁹ Odds ratio and 95% confidence intervals calculated by reviewer
 ¹¹ Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance (Medical Research Council Working Party on Tuberculosis of the Spine (Griffiths et al) (1986) and Darbyshire (1999)), or some patients also had respiratory TB (Upadhyay et al (1986))
 ¹³ Upadhyay et al, 1986

		Quality as	sessment			Number o	f patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design Risk of bias Inconsistency				Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
		ce of drug reaction val; OR, odds ratio		the duration of ch	nemotherapy beca	use most of the ac	lverse events wer	e observed in the	earlier period of d	rug therapy

LYMPH NODE TB

6 MONTHS vs 9 MONTHS

Treatment success or failure

		Quality as	sessment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Treatment succ	ess (number of pa	atients to be define	ed as a treatment	success after 5 ye	ars of follow-up (5	-year actuarial re	emission rate)1)			
1 ²	randomised trials	very serious ^{3,4,5,6}	no serious inconsistency	serious ^{7,11}	serious ⁸	39/43 (90.7%)	47/48 (97.9%)	OR 0.21 (0.02 to 1.93) ⁹	7 fewer per 100 (from 49 fewer to 1 more)	VERY LOW
Treatment failu	re (number of pati	ents to be defined	as a treatment fai	lure at the end of t	reatment ¹)					
1 ²	randomised trials	very serious ^{3,4,5,6}	no serious inconsistency	serious ⁷	very serious ^{8,10}	2/43 (4.7%)	1/48 (2.1%)	OR 2.29 (0.20 to 26.22) ⁹	3 more per 100 (from 2 fewer to 34 more)	VERY LOW
 ² Yuen et al, 199 ³ Method of rand ⁴ Allocation cond ⁵ Blinding uncleat ⁶ Analyses did n ⁷ Regimens does ⁸ GRADE rule of ⁹ Odds ratio and ¹⁰ Wide confident ¹¹ Doses not cord 	lomisation unclear cealment unclear ar ot follow the intent s not contain all of thumb: <300 even 95% confidence i	-to-treat principle or just the 4 stand nts ntervals calculated listed in the Britisi	lard recommended I by reviewer n National Formula	Ū						

Change in signs and symptoms

		Quality as	sessment			Numbe	er of patients	Ef	fect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Change in sign	s and symptoms	– residual nodes	(follow-up 30 mor	nths; number of pa	atients with residu	al nodes)	,			
1 ¹	randomised trials	very serious ^{2,3,4}	serious ¹⁰	serious⁵	serious ⁶	10/58 (17.2%)	16/107 (15%) ⁷	OR 1.18 (0.50 to 2.81) ⁸	2 more per 100 (from 7 fewer to 18 more)	VERY LOW
Change in sign	s and symptoms	- node enlargem	ent (follow-up 30	months; number o	of patients with no	des that had enl	arged in size)			
1 ¹	randomised trials	very serious ^{2,3,4}	serious ¹⁰	serious⁵	serious ⁶	4/58 (6.9%)	8/107 (7.5%) ⁷	OR 0.81 (0.24 to 2.77) ⁸	1 fewer per 100 (from 6 fewer to 11 more)	VERY LOW
change in sign	s and symptoms	- sinuses (follow	-up 30 months; nu	mber of patients v	with new sinuses)					
1	randomised trials	very serious ^{2,3,4}	serious ¹⁰	serious⁵	very serious ^{6,9}	2/58 (3.4%)	3/107 (2.8%) ⁷	OR 1.24 (0.20 to 7.63) ⁸	1 more per 100 (from 2 fewer to 15 more)	VERY LOW
Change in sign	s and symptoms	- glands (follow-u	up 30 months; nun	nber of patients wi	ith new glands)					
1 ¹	randomised trials	very serious ^{2,3,4}	serious ¹⁰	serious ⁵	serious ⁶	2/58 (3.4%)	7/107 (6.5%) ⁷	OR 0.51 (0.10 to 2.54) ⁸	3 fewer per 100 (from 6 fewer to 9 more)	VERY LOW
 Blinding uncleases Analyses did n Intervention do GRADE rule of Data for multip Odds ratio and Wide confidence Follow-up beg 	domisation unclea ar ot follow the inten bes not contain all f thumb: <300 eve le groups pooled l 95% confidence ce intervals uan from treatmen	t-to-treat principle of/contains drugs o ents	l by reviewer e, as different dura			v-up was for diff	erent lengths			

Relapse

		Quality as	ssessment			Number	of patients	Eff	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Relapse (numbe	er of patients to ex	perience relapse o	during follow-up ¹)							
2 ^{2,3}	randomised trials	very serious ^{4,5,6,7}	no serious inconsistency	very serious ^{8,9,12,13}	serious ¹⁰	14/158 (8.9%)	16/207 (7.7%)	OR 1.05 (0.49 to 2.26) ^{11,14}	0 more per 100 (from 4 fewer to 8 more)	VERY LOW
 ² Campbell et al, ³ Yuen et al, 199 ⁴ Method of rand 										

		Quality as	ssessment			Numbe	er of patients		Effect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
⁸ Intervention do ⁹ Different combination ¹⁰ GRADE rule of ¹¹ Odds ratio and	ot follow the intent es not contain all d inations of drugs ir f thumb: <300 eve d 95% confidence 97: doses not cons	of/contains drugs n each arm in Can ents intervals calculate	other than the 4 sta npbell et al (1993) d by reviewer listed in the British		Ū					

Abbreviations: CI, confidence interval; OR, odds ratio

Adverse events

		Quality as	sessment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Adverse events	leading to treatr	nent modificatior	(number of patie	nts to experience	adverse events th	at led to modifica	tion of the allocated	regimen)		
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ^{6,9}	serious ⁷	4/49 (8.2%)	13/64 (20.3%)	OR 0.35 (0.11 to 1.15) ⁸	12 fewer per 100 (from 18 fewer to 2 more)	VERY LOW
 ³ Allocation conc ⁴ Blinding unclear ⁵ Analyses did no 	lomisation unclear cealment unclear	-to-treat principle	other than the 4 st	andard recommen	nded drugs					

⁷ GRADE rule of thumb: <300 events
 ⁸ Odds ratio and 95% confidence intervals calculated by reviewer
 ⁹ Doses not consistent with those listed in the British National Formulary Abbreviations: CI, confidence interval; OR, odds ratio

Adherence and treatment default

		Quality as	sessment			Number of patients Effect			ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Treatment defai	ult (follow-up for th	ne full treatment pe	eriod; number of pa	atients to default t	reatment)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ^{6,10}	very serious ^{7,8}	2/49 (4.1%)	3/64 (4.7%)	OR 0.87 (0.14 to 5.39) ⁹	1 fewer per 100 (from 4 fewer to 16 more)	VERY LOW

¹ Yuen et al. 1997

² Method of randomisation unclear

³ Allocation concealment unclear

⁴ Blinding unclear

⁵ Analyses did not follow the intent-to-treat principle

		Quality as	ssessment			Number	of patients	Eff	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality	
 ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and ¹⁰ Doses not con 	thumb: <300 ever e intervals 95% confidence ir	nts ntervals calculated listed in the British	n National Formula		ded drugs						

9 months vs >9 months

Adverse events

		Quality as	sessment			Number of	of patients	Ef	iect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	>9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Adverse events	- hepatotoxicity	(number of patien	ts to experience h	epatotoxicity durin	g treatment)					
2 ^{1,2}	randomised trials	very serious ^{3,4,5,6}	no serious inconsistency	serious ⁷	serious ⁸	1/110 (0.91%)	3/109 (2.8%)	OR 0.33 (0.01 to 8.20) ^{9,10}	2 fewer per 100 (from 3 fewer to 16 more)	VERY LOW
⁴ Allocation conc. ⁵ Blinding unclea ⁶ Analysis in Can ⁷ Intervention dou ⁸ GRADE rule of ⁹ Odds ratio and ¹⁰ Forest plot (he	1985 omisation unclear r npell et al (1985) c es not contain all c thumb: <300 ever 95% confidence ir	lid not follow the in of/contains drugs o nts ntervals calculated	l by reviewer	iple andard recommen	ded drugs					

Abbreviations: CI, confidence interval; OR, odds ratio

9 MONTHS vs 12 MONTHS

Response to treatment

		Quality as	ssessment			Number o	of patients	Eff		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Response to tre	eatment - favoura	ble response (nu	mber of patients to	o achieve a favour	able outcome)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	very serious6,7,8	serious ⁹	30/34 (88.2%)	32/33 (97%)	OR 0.23 (0.02 to 2.22) ¹⁰	9 fewer per 100 (from 58	VERY LOW

		Quality as	ssessment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
									fewer to 2 more)	
 ³ Allocation conc ⁴ Blinding unclea ⁵ No clear definit ⁶ Intervention do ⁷ Different combination ⁸ Substitute for a ⁹ GRADE rule of ¹⁰ Odds ratio and 	omisation unclear ealment unclear r ion of the outcome	e of/contains drugs (n each arm rest nts intervals calculate		andard recommer	nded drugs					

Adverse events

		Quality as	sessment			Number of	of patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	(95% CI)	(95% CI)	Quality
Adverse events	 hepatotoxicity (nu 	umber of patients	o experience hepa	atotoxicity)						
1 ¹	randomised trials	very serious ^{2,3,4}	no serious inconsistency	serious ^{5,6}	very serious ^{7,8}	1/34 (2.9%)	2/33 (6.1%)	OR 0.47 (0.04 to 5.44) ⁹	3 fewer per 100 (from 6 fewer to 20 more)	VERY LOW
 ³ Allocation conc ⁴ Blinding unclea ⁵ Intervention do ⁶ Different combin ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and 	omisation unclear ealment unclear r es not contain all o nations of drugs ir thumb: <300 ever	of/contains drugs o n each arm nts ntervals calculatec		andard recommen	ded drugs					

9 MONTHS vs 18 MONTHS

Response to treatment

		Quality as	sessment			Number of	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	Relative (95% CI)	Absolute (95% CI)	Quality
Change in signs	s and symptoms	 residual nodes 	(number of patien	ts with residual no	des at the end of	treatment)				
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	7/56 (12.5%)	3/57 (5.3%)	OR 2.57 (0.63 to 10.50) ⁹	7 more per 100 (from 2 fewer to 32 more)	VERY LOW
Change in signs	s and symptoms	 residual nodes 	(follow-up 36 mor	ths; number of pa	tients with residua	al nodes during fol	low-up)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ⁶	very serious ⁷	2/56 (3.6%)	3/57 (5.3%)	OR 0.67 (0.11 to 4.15) ⁹	2 fewer per 100 (from 5 fewer to 13 more)	VERY LOW
Change in signs	s and symptoms	- fresh nodes (ni	umber of patients v	with fresh nodes d	uring treatment)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ⁶	serious ⁷	5/56 (8.9%)	8/57 (14%)	OR 0.60 (0.18 to 1.96) ⁹	5 fewer per 100 (from 11 fewer to 10 more)	VERY LOW
Change in signs	s and symptoms	- fresh nodes (fo	llow-up 36 months	; number of patier	nts with fresh node	es during follow-up))			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ⁶	very serious ^{7,8}	2/56 (3.6%)	0/57 (0%)	OR 5.28 (0.25 to 112.39) ⁹	-	VERY LOW
Change in signs	s and symptoms	 node enlargem 	ent (number of pa	tients with nodes	that had enlarged	in size during trea	tment)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	8/56 (14.3%)	5/57 (8.8%)	OR 1.73 (0.53 to 5.66) ⁹	5 more per 100 (from 4 fewer	VERY LOW

		Quality as	ssessment			Numbe	r of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
									to 26 more)	
Change in sign	s and symptoms	- node enlargem	ent (follow-up 36	months; number o	f patients with not	des that had enla	arged in size during	follow-up)		
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ⁶	very serious ^{7,8}	6/56 (10.7%)	4/57 (7%)	OR 1.59 (0.42 to 5.97) ⁹	4 more per 100 (from 4 fewer to 24 more)	VERY LOW
Change in sign	s and symptoms	- sinuses (numb	er of patients with	new sinuses durin	g treatment)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ⁶	serious ⁷	0/56 (0%)	3/57 (5.3%)	OR 0.14 (0.01 to 2.73) ⁹	4 fewer per 100 (from 5 fewer to 8 more)	VERY LOW
Change in sign	s and symptoms	- sinuses (follow	-up 36 months; nu	mber of patients v	vith new sinuses d	uring follow-up)				
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ⁶	very serious ^{7,8}	0/56 (0%)	0/57 (0%)	OR 1.02 (0.02 to 52.18) ⁹	-	VERY LOW
 ³ Allocation cond ⁴ Blinding uncleated ⁵ Analysis did not ⁶ Intervention do ⁷ GRADE rule of ⁸ Wide confident ⁹ Odds ratio and ¹⁰ Follow-up beg 	lomisation unclear cealment unclear ar of follow the intent- es not contain all of thumb: <300 even ce intervals 95% confidence in	to-treat principle of/contains drugs nts ntervals calculated initiation; therefor	e, as different dura		-	v-up was for diffe	erent lengths			

Response to treatment

Number of patients Effect **Quality assessment** Number of Relative Absolute **Risk of bias** Imprecision 9 months (95% CI) (95% CI) Quality studies Design Inconsistency Indirectness 18 months Response to treatment - need for surgical intervention (number of patients needing surgical intervention (e.g. aspiration of pus) during treatment) very serious6,7 **1**¹ randomised no serious serious⁸ 4/56 6/57 OR 0.65 (0.17 3 fewer per VERY LOW very serious^{2,3,4,5} trials inconsistency (7.1%) (10.5%) to 2.45)⁹ 100 (from 9 fewer to 12 more) Response to treatment - need for surgical intervention (follow-up 36 months; number of patients needing surgical intervention (e.g. aspiration of pus) during follow-up) **1**¹ serious¹¹ very serious6,7 very serious^{8,10} 4/56 6/57 OR 0.65 (0.17 VERY LOW randomised very 3 fewer per serious^{2,3,4,5} to 2.45)⁹ trials (7.1%) (10.5%) 100 (from 9 fewer to 12 more)

¹ Campbell et al, 1985

² Method of randomisation unclear

³ Allocation concealment unclear

⁴ Blinding unclear

⁵ Analysis did not follow the intent-to-treat principle

		Quality as	ssessment			Number	of patients		Effect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	(95% CI)	(95% CI)	Quality
⁶ Intervention do	es not contain all o	of/contains drugs of	other than the 4 sta	andard recommen	ded drugs					
⁷ Substitute for a	an outcome of inter	rest			-					
⁸ GRADE rule of	f thumb: <300 ever	nts								
⁹ Odds ratio and	95% confidence in	ntervals calculated	d by reviewer							
¹⁰ Wide confiden	nce intervals									
¹¹ Follow-up beg	an from treatment	initiation; therefor	e, as different dura	ations of treatment	t were used, follow	v-up was for diffe	rent lengths			
Abbreviations: C	I, confidence inter	val; OR, odds ratio	0				-			

Relapse

		Quality as	ssessment			Number of	of patients	Eff	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Relapse (follow-	up 5 years; numbe	er of patients to ex	perience clinical o	r microbiological r	elapse during follo	ow-up)				
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ⁶	very serious ^{7,8}	0/34 (0%)	0/39 (0%)	OR 1.14 (0.02 to 59.26) ⁹	-	VERY LOW
 ³ Allocation conc ⁴ Blinding unclea ⁵ Analysis did no ⁶ Intervention dou ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and ¹⁰ Follow-up bega 	omisation unclear ealment unclear t follow the intent- es not contain all o thumb: <300 ever e intervals 95% confidence ir an from treatment	to-treat principle of/contains drugs o nts ntervals calculated	e, as different dura		Ŭ	/-up was for differe	ent lengths			

Adverse events

		Quality as	sessment			Number	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Adverse events	- hepatotoxicity	(number of patien	ts to experience h	epatotoxicity durin	g treatment)					
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	0/76 (0%)	1/76 (1.3%)	OR 0.33 (0.01 to 8.20) ⁹	1 fewer per 100 (from 1 fewer to 9 more)	VERY LOW
 ³ Allocation cond ⁴ Blinding uncleat ⁵ Analysis did not ⁶ Intervention do 	lomisation unclear ealment unclear	to-treat principle of/contains drugs o	other than the 4 sta	andard recommen	ded drugs					

⁷ GRADE rule of thumb: <300 events

		Quality as	sessment			Number o	of patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	(95% CI)	(95% CI)	Quality
⁸ Wide confidence	Wide confidence intervals									

⁹ Odds ratio and 95% confidence intervals calculated by reviewer Abbreviations: CI, confidence interval; OR, odds ratio

GASTROINTESTINAL TB

6 months vs 9 months

Response to treatment

		Quality as	sessment			Number o	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Response to tre	eatment - complet	te response (follo	w-up 1 year after t	reatment complet	ion; number of pat	ients to achieve a	complete respons	e during follow-up	¹)	,
1 ²	randomised trials	serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious ^{6,7}	42/45 (93.3%)	41/45 (91.1%)	OR 1.37 (0.29 to 6.48) ⁸	2 more per 100 (from 16 fewer to 7 more)	VERY LOW
Response to tre	eatment - need fo	r additional treat	ment (follow-up fo	r the full treatment	period; number o	f patients to need	additional chemot	herapy due to inco	mplete response ¹)
1 ²	randomised trials	serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious6,7	1/45 (2.2%)	0/45 (0%)	OR 3.07 (0.12 to 77.33) ⁸	-	VERY LOW
Response to tre	eatment - need fo	r additional treat	ment (follow-up fo	r the full treatment	t period; number o	f patients to need	surgery due to inc	omplete response	¹)	
1 ²	randomised trials	serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious6,7	0/45 (0%)	0/45 (0%)	OR 1.00 (0.02 to 51.49) ⁸	-	VERY LOW
 ² Park et al, 2009 ³ Allocation cond ⁴ Investigators no ⁵ Substitute for a ⁶ GRADE rule of ⁷ Wide confidence ⁸ Odds ratio and ⁹ Doses not cons 	ealment unclear ot blinded, unclear n outcome of inter thumb: <300 ever	if others were blir est hts htervals calculated isted in the British	nded I by reviewer National Formular	у						

Relapse

		Quality as	sessment			Number of	of patients	Eff		
Number of								Relative	Absolute	1
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Recurrence (foll	ow-up 1 year after	treatment comple	tion; number of pa	atients to experien	ce recurrence dur	ing follow-up ¹)				
1 ²	randomised	serious ^{3,4}	no serious	very serious ^{8,9}	very serious5,6	1/45	0/45	OR 3.07 (0.12	-	VERY LOW
	trials		inconsistency			(2.2%)	(0%)	to 77.33) ⁷		
¹ For full definitio	ns. see evidence i	tables in the appe	ndices							

		Quality as	ssessment			Number o	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
² Park et al, 2009										
³ Allocation conc		: 6 - 41								
	thumb: <300 ever	r if others were blin ats	naea							
⁶ Wide confidence		113								
		ntervals calculated	d by reviewer							
⁸ Doses not cons	sistent with those I	isted in the British	National Formula	Ŷ						
	n outcome of inter									
Abbreviations: C	I, confidence inter	val; OR, odds rati	0							

Adverse events

		Quality as	sessment			Number	of patients	Eff	ect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Adverse events	leading to treat	ment discontinua	tion (follow-up up	to the full treatme	ent period; number	of patients to exp	erience adverse e	vents that led to tr	eatment discontine	uation)
1 ¹	randomised trials	serious ^{2,3}	no serious inconsistency	serious ⁶	serious ⁴	2/45 (4.4%)	4/45 (8.9%)	OR 0.48 (0.08 to 2.74) ⁵	4 fewer per 100 (from 8 fewer to 12 more)	VERY LOW

¹ Park et al, 2009

¹ Park et al, 2009
 ² Allocation concealment unclear
 ³ Investigators not blinded, unclear if others were blinded
 ⁴ GRADE rule of thumb: <300 events
 ⁵ Odds ratio and 95% confidence intervals calculated by reviewer
 ⁶ Doses not consistent with those listed in the British National Formulary Abbreviations: CI, confidence interval; OR, odds ratio

9 months vs 15 months

Response to treatment

		Quality as	ssessment			Number o	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	15 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Response to tre	eatment - comple	te response (follo	w-up 23-34 month	s; number of patie	ents to achieve a c	omplete response	during follow-up1			
1 ²	randomised trials	serious ^{3,4}	serious⁵	serious ^{6,11}	very serious7,8	22/22 (100%)	18/18 (100%)	OR 1.22 (0.02 to 64.31) ⁹	-	VERY LOW
Response to tre	eatment - comple	te response (follo	w-up 23-34 month	ns; mean interval (months) to comple	ete response ¹ ; bett	ter indicated by low	ver values)		
1 ²	randomised trials	serious ^{3,4}	serious⁵	serious ^{6,11}	very serious ⁸	22	18	-	MD 0.9 lower (2.6 lower to 0.80 higher) ¹⁰	VERY LOW
 ² Kim et al, 2003 ³ Allocation cond ⁴ Blinding of part ⁵ Follow-up not et ⁶ Substitute for of ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and ¹⁰ Mean difference ¹¹ Doses not confidence 	ealment unclear icipants and those equal utcome of interest thumb: <300 ever te intervals 95% confidence in the and 95% confidence in the and 95% confidence in the sistent with those	administering car nts ntervals calculated ence intervals cal listed in the Britisi	re unclear	ary						

Relapse

		Quality as	ssessment			Numbe	er of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	15 months	Relative (95% CI)	Absolute (95% Cl)	Quality
	•					9 monuis	15 11011015	(95% CI)	(95% CI)	Quality
· ·	•		tients to experienc		U 1 /					
1 ²	randomised trials	serious ^{3,4}	serious⁵	very serious9,10	very serious ^{6,7}	0/22 (0%)	0/18 (0%)	OR 0.82 (0.02 to 43.48) ⁸	-	VERY LOW
 Follow-up not e GRADE rule of Wide confidence Odds ratio and Doses not cons Substitute for a 	icipants and those qual thumb: <300 ever e intervals 95% confidence in istent with those l an outcome of inte	ntervals calculated isted in the British	d by reviewer National Formula	ry						

A.11 RQs O, R and X

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality assess	sment			No of j	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Mortality	(follow-up uncle	ear; assessed w	ith: number of de	aths)				,				
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10,11}	very serious ^{12,13}	serious ¹⁴	none	6/184 (3.3%)	3/48 (6.3%)	OR 0.51 (0.12 to 2.10) ¹⁵	3 fewer per 100 (from 5 fewer to 6 more)	VERY LOW	
Cure (foll	ow-up unclear; a	assessed with:	number of patient	s to be classified	l as a cure)					,		
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10,11}	very serious ^{12,13}	very serious ^{14,16}	none	175/184 (95.1%)	35/48 (72.9%)	OR 7.22 (2.87 to 18.20) ¹⁵	22 more per 100 (from 16 more to 25 more)	VERY LOW	
Treatmen	nt failure (follow	-up unclear; as	sessed with: num	ber of patients w	ho still had acti	ive tuberculosis)						
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10,11}	very serious ^{12,13}	very serious ^{14,16}	none	3/184 (1.6%)	10/48 (20.8%)	OR 0.06 (0.02 to 0.24) ¹⁵	19 fewer per 100 (from 15 fewer to 20 fewer)	VERY LOW	
Function	ality – return to	work (follow-u	ip unclear; assess	ed with: numbe	r of patients wh	o still had active tu	berculosis)					
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10,11}	very serious ^{12,13,17}	very serious ^{14,16}	none	3/184 (1.6%)	10/48 (20.8%)	OR 0.06 (0.02 to 0.24) ¹⁵	19 fewer per 100 (from 15 fewer to 20 fewer)	VERY LOW	
¹ Jaworsk	ki, 1972											

² retrospective

³ allocation based on qualification for surgery and subsequent agreement or refusal to undergo surgery by the patient ⁴ blinding unclear, though unlikely

			Quality assess	sment		No of J	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	s do not appear		ade to balance co	onfounders							

⁶ unclear of length of follow-up appropriate

⁷ unclear if precise and reliable definitions of outcome used (diagnostic criteria for †cure' and the number of patients to still have active tuberculosis not provided)

⁸ unclear if comparable at baseline

⁹ unclear if groups received the same â€~other' care

¹⁰ unclear if groups were followed for an equal period

¹¹ groups comparable for treatment completion and availability of outcome data

¹² some drug resistant cases were included

¹³ unclear which antituberculosis drugs were used, or if same regimens were used in the 2 groups

¹⁴ GRADE rule of thumb: <300 events

¹⁵ Odds ratio and 95% confidence intervals calculated by reviewer

¹⁶ Wide confidence intervals

¹⁷ substitute for outcome of interest

POST-OPERATIVE COMPLICATIONS

Jaworski, 1972

Pleural empyema with fistula = 6%

Exacerbations = 4.4%

Bleeding into the operated space requiring thoracotomy = 1.6%

Jaundice = 3.3%

Psychoses = 1.6%

Early death resulting from fibrinolytic shock = 1.1%

By type of surgery

Fewest complications were found after segmentectomies (20%), and the most after pneumonectomies (56.3%)

By duration of disease

The influence of duration of disease was not negligible, with complications found in 15.5% of patients ill for 1 to 5 years, and in 50% ill over 5 years

By susceptibility status

Complications were most frequent in in patients resistant to 3 or more drugs (81.1%), occurring in 22.7% of those resistant to 2 drugs and in 9% of those resistant to 1 drug

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality asses	ssment			No of J	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importanc
			mprovement in e reduced) or heale				itiation of treatment;	assessed with: numl	ber of patier	nts in whom	lesions we	re improved
1 ¹	observational studies ²	very serious ^{3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	none	41/41 (100%)	62/74 (83.8%)	OR 6.60 (0.97 to 288.09) ⁹	13 more per 100 (from 0 fewer to 16 more)	VERY LOW	
			eterioration in en had increased) at		esions (follow-u	p 9 months after in	itiation of treatment;	assessed with: numb	per of patier	its in whom I	esions had	l deteriorateo
1 ¹	observational studies ²	very serious ^{3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	none	0/41 (0%)	3/74 (4.1%)	OR 0.25 (0.01 to 4.88) ⁹	3 fewer per 100 (from 4 fewer to 13 more)	VERY LOW	
	s in signs and s of follow-up)	ymptoms - r	ecurrence of end	lobronchial les	ions (follow-up	9 months after initi	ation of treatment; as	ssessed with: numbe	r of patients	,	ions and r	ecurred afte
1 ¹	observational studies ²	very serious ^{3,4,5}	no serious inconsistency	serious ⁶	very serious ^{7,8}	none	0/41 (0%)	0/74 (0%)	OR 1.80 (0.04 to 92.15) ⁹	-	VERY LOW	
³ allocatio ⁴ blinding ⁵ attempt ⁶ may ha ⁷ GRADE	al controlled trial on was based up unclear, though s do not appear	oon the time a unlikely to have been rug resistant (<300 events	ve observational t which the patier made to balance cases were includ	confounders	s with disease re	esistant to a combi	nation of rifampicin, i	soniazid or ethambul	tol were exc	luded)		

⁹ Odds ratio and 95% confidence intervals calculated by reviewer

POST-OPERATIVE COMPLICATIONS

Jin et al, 2013

Laryngeal spasm = 1 (2.4%) Cough = 35 (85.4%) 5–10 ml bleeding = 5 (12.2%) Secondary pulmonary infection = 0 Esphagotrachea fistula = 0 Pneumothorax = 0 Trachea perforation = 0 Death = 0

.11.3 Adjunctive surgery in the treatment of active CHEST WALL tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality asses	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
Respons	e to treatment	- good outcom	ne (follow-up uncle	ar; assessed wi	th: number of pa	atients to have a go	od outcome)					
1 ¹	observational studies	very serious ^{2,3,4,5,6}	very serious ^{7,8,9,10}	very serious ^{11,12}	very serious ^{13,14}	none	6/6 (100%)	1/1 (100%)	OR 4.33 (0.06 to 320.42)	-	VERY LOW	
 ⁵ if unclea ⁶ definition ⁷ significa ⁸ groups n ⁹ unclear ¹⁰ groups ¹¹ antitube 	s do not appear ar length of follo n of 'good outco nt variation in a received differen if groups were f appear to be co	w-up was appro ome' not provide ge, size and loc nt combinations followed for an e omparable for tr ens did not use	ed cation of the chest of antituberculosi equal period eatment completic all of or just the 4	wall mass, radio s drugs for treat on and availabilit standard recomi	ment periods of y of outcome da mended drugs, a	different duration	ge involvement, and i and comparator arm	histological status ns varied by more th	an the prese	ence or abse	nce of sur	gery

¹³ GRADE rule of thumb: <300 events

¹⁴ wide confidence intervals

POST-OPERATIVE COMPLICATIONS

Hsu et al, 1995

No details provided

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality asses	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importanc
Changes	s in signs and s	ymptoms – boi	ny fusion (follow		s ¹ ; assessed v	vith: number of pa	tients to experience	e bony fusion/ankyl	osis)			
1 ²	observational studies ³	very serious ^{4,5,6,7,8}	very serious ^{9,10,11}	very serious ^{12,13}	very serious ^{14,15}	none	4/15 (26.7%)	0/15 (0%)	OR 12.13 (0.59 to 248.50) ¹⁶	-	⊙OOO VERY LOW	
		symptoms – boi med using CT o			onths ¹⁷ ; assess	sed with: number	of patients to exper	ience fusion of the	sacroiliac j	oint, as asse	essed usin	ıg plain
1 ¹⁸	observational studies ³	very serious ^{5,6,7,8,19}	very serious ^{10,20}	very serious ^{12,21}	very serious ^{14,15}	none	6/12 (50%)	0/4 (0%)	OR 9.00 (0.40 to 203.31) ¹⁶	-	⊙OOO VERY LOW	
Changes	in signs and s	ymptoms – hea	aling (follow-up r	nean 29.3 months	¹⁷ ; assessed v	vith: number of pa	tients to heal ²²)					
1 ¹⁸	observational studies ³	very serious ^{5,6,7,8,19}	very serious ^{10,20}	very serious ^{12,21}	serious ¹⁴	none	6/12 (50%)	4/4 (100%)	OR 0.11 (0.00 to 2.51) ¹⁶	-	⊙OOO VERY LOW	
Changes	in signs and s	ymptoms – hea	aling (follow-up r	nean 29.3 months	¹⁷ ; measured v	with: time to heali	ng ²² ; better indicate	d by lower values)	,			
1 ¹⁸	observational studies ³	very serious ^{5,6,7,8,19}	very serious ^{10,20}	very serious ^{12,21}	serious ¹⁴	none	12	4	-	MD 1.0 higher (0.9 lower to 2.9 higher) ²³	⊙OOO VERY LOW	
Recurren	nce (follow-up i	mean 15 years ¹	; assessed with:	number of patien	ts to experien	ce recurrence)						
1 ²	observational studies ³	very serious ^{4,5,6,7,8}	very serious ^{9,10,11}	very serious ^{12,13,24}	very serious ^{14,15}	none	4/15 (26.7%)	0/14 (0%)	OR 12.13 (0.59 to 248.50) ¹⁶	-	⊙OOO VERY LOW	

⁵ blinding unclear, though unlikely

⁶ attempts do not appear to have been made to balance confounders

⁷ length of follow-up was appropriate

			Quality asses	sment			No of p	atients	Ef	fect		
No of							Antituberculosis chemotherapy	Antituberculosis chemotherapy	Relative			
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	plus surgery	alone	(95% CI)	Absolute	Quality	Importance

⁸ outcome definitions were valid and precise

⁹ 50% of the surgical group were treated before the age of 20, whereas 80% of those treated conservatively were treated before the age of 20

¹⁰ groups appeared to receive the same care apart from the intervention(s) studied, although details were limited

¹¹ mean follow-up in the surgical group was 13 years, mean follow-up amongst those treated conservatively was 17 years

¹² population appears to match the population of interest, although details were limited

¹³ unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided)

¹⁴ GRADE rule of thumb: <300 events

¹⁵ wide confidence intervals

¹⁶ odds ratio and 95% confidence intervals calculated by reviewer

¹⁷ antituberculosis chemotherapy plus surgery = 28.3; antituberculosis chemotherapy alone = 32.4

¹⁸ Kim et al, 1999

¹⁹ unclear if allocation to treatment groups related to potential confounding factors, although it appears not (all those that underwent surgery had more advanced disease)

²⁰ mean follow-up was longer in those that received antituberculosis chemotherapy alone

²¹ antituberculosis regimens do not use all of or just the 4 standard recommended drugs (lacked pyrazinamide and contained streptomycin)

²² criteria for healing: no pain or tenderness over the lesion site, no pain or discomfort during walking, a return to normal value of the erythrocyte sedimentation rate, disappearance of the abscess, clearance of sclerosis of the joint margin, and fusion of the sacroiliac joint

²³ mean difference and 95% confidence intervals calculated by reviewer

²⁴ outcome is a substitute for an outcome of interest

POST-OPERATIVE COMPLICATIONS

Chow & Yau, 1980

No details provided

RANDOMISED CONTROLLED TRIALS

			Quality asse	ssment			No of J	patients	E	ffect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importanc
Iortality			years; assessed	with: number of	deaths associa	ted with spinal tube	erculosis)					
1	randomised	serious ^{2,3,4}	no serious	serious⁵	very	none	4/100	0/204	OR	-	VERY	
	trials		inconsistency		serious ^{6,7}		(4%)	(0%)	19.07 (1.02 to 357.83) ⁸		LOW	
			- complete bony o experience com				months or 9 months;	antituberculosis cher	notherapy i	n surgery gro	up = 6 moi	nths)
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁶	none	64/100 (64%)	127/204 (62.3%)	OR 1.08 (0.66 to 1.77) ⁸	2 more per 100 (from 10 fewer to 12 more)	VERY LOW	
			- complete bony mplete bony fusion			therapy alone = 6 r	months; antituberculo	osis chemotherapy in	surgery gro	oup = 6 month	ns) (assess	sed with:
	randomised			serious ⁵	serious ⁶	none	64/100	61/101	OR 1.17	4 more	VERY	
	trials		inconsistency				(64%)	(60.4%)	(0.66 to 2.06) ⁸	per 100 (from 10 fewer to 15 more)	LOW	
			- partial bony fus			rapy alone = 6 mor	nths or 9 months; and	tituberculosis chemot	herapy in s	urgery group	= 6 months	s) (assesse
1	randomised			serious ⁵	serious ⁶	none	5/100	21/204	OR 0.46	5 fewer	VERY	
	trials		inconsistency				(5%)	(10.3%)	(0.17 to 1.25) ⁸	per 100 (from 8 fewer to 2 more)	LOW	
			 partial bony fus fusion within 10- 		losis chemothe	rapy alone = 6 mor	nths; antituberculosis	chemotherapy in su	rgery group	= 6 months)	(assessed	with: numbe
1 ¹	randomised trials		no serious inconsistency	serious⁵	serious ⁶	none	5/100 (5%)	11/101 (10.9%)	OR 0.43 (0.17 to 1.25) ⁸	6 fewer per 100 (from 9 fewer to 2 more)	VERY LOW	
			- no bony fusion fusion within 10-ye		s chemotherapy	alone = 6 months	or 9 months; antitub	erculosis chemothera	apy in surge	ry group = 6	months) (a	ssessed wit
lumber c	randomised		no serious	serious ⁵	serious ⁶	none	2/100	5/204	OR 0.81	0 fewer	VERY	
	trials	501005	inconsistency	00000	00000		(2%)	(2.5%)	(0.15 to 4.26) ⁸	per 100 (from 2 fewer to 7 more)	LOW	

patients to have no bony fusion within 10-year follow-up)

			Quality asse	ssment			No of p	oatients	Ef	ffect		
	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious ⁵	serious ⁶	none	2/100 (2%)	3/101 (3%)	OR 0.67 (0.11 to 4.08) ⁸	1 fewer per 100 (from 3 fewer to 8 more)	VERY LOW	
			- spontaneous bo to experience spor				= 6 months or 9 mon	ths; antituberculosis	chemothera	apy in surgery	group = 6	months)
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁶	none	1/100 (1%)	7/204 (3.4%)	OR 0.28 (0.03 to 2.34) ⁸	2 fewer per 100 (from 3 fewer to 4 more)	VERY LOW	
							onths; antituberculos dicated by lower valu	sis chemotherapy in s	surgery gro	up = 6 month	s) (measur	ed with: mean
1 ¹	randomised trials	1		serious ⁵	serious ⁹	none	28	79	-	MD 3 lower (0 to 0 higher) ¹⁰	VERY LOW	
						= 6 months; antitu s; better indicated b		rapy in surgery grou	p = 6 month	is) (measured	l with: mea	in angle of
1 ¹	randomised trials			serious ⁵	serious ⁹	none	28	41	-	MD 6 lower (0 to 0 higher) ¹⁰	VERY LOW	
								ths; antituberculosis	chemothera	U ,	group = 6	months)
(follow-up 1 ¹¹	o 5 years; asse randomised trials		umber of patients no serious inconsistency	to experience ar serious⁵	very serious ^{6,7}	of 11° or more in th none	eir angle of kyphosis 1/100 (1%)	5) 2/204 (0.98%)	OR 1.02 (0.09 to 11.39) ⁸	0 more per 100 (from 1 fewer to 9 more)	VERY LOW	
Changes	in signs and	symptoms	- improvement in	kyphosis (anti	tuberculosis che	emotherapy alone =	= 6 months; antituber	culosis chemotherap	y in surgery	,	onths) (fol	low-up 5 years;
assessed 1 ¹¹	randomised trials		no serious inconsistency	serious ⁵	very serious ^{6,7}	heir angle of kypho none	1/100 (1%)	0/101 (0%)	OR 3.06 (0.12 to 76.03) ⁸	-	VERY LOW	
								hs; antituberculosis o		py in surgery	group = 6	months)
(follow-up 1 ¹¹	o 5 years; asse randomised trials		umber of patients no serious inconsistency	to experience ar serious⁵	n deterioration of serious ⁶	of 11° or more in the none	eir angle of kyphosis 13/100 (13%)) 40/204 (19.6%)	OR 0.61 (0.31 to 1.21) ⁸	7 fewer per 100 (from 13 fewer to 3 more)	VERY LOW	
						motherapy alone = eir angle of kyphosi		culosis chemotherap	y in surgery	group = 6 m	onths) (foll	ow-up 5 years;
assessed 1 ¹¹	randomised trials			serious ⁵	serious ⁶	none	s) 13/100 (13%)	17/101 (16.8%)	OR 0.74 (0.34 to 1.61) ⁸	4 fewer per 100 (from 10 fewer to 8	VERY LOW	

			Quality asse	essment			No of	patients	Ef	ffect		
o of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importanc
_										more)		
								antituberculosis chem lesions; better indica			ip = 6 mon	ths) (measu
1	randomised trials			serious ⁵	serious ⁹	none	28	79	-	MD 0 higher (0 to 0 higher) ¹⁰	VERY LOW	
								sis chemotherapy in s		up = 6 month	s) (measur	ed with: me
crease	in angle of kyp randomised			r follow-up amor serious ⁵	ngst patients wit serious9	n thoracic or thorac none	28 columbar lesions; be	tter indicated by lowe 41	r values)	MD 2	VERY	
	trials	3611003	inconsistency	3611003	3611003	none	20			lower (0 to 0 higher) ¹⁰		
								months; antitubercul	osis chemo	therapy in su	rgery group	o = 6 month
Ollow-up	o 5 years; asse randomised		no serious	to experience a serious ⁵	n improvement verv	of 0.25 vertebrae o none	or more in their vertet 5/100	0/204	OR	_	VERY	
	trials	Senous	inconsistency	senous	serious ^{6,7}	none	(5%)	(0%)	23.56 (1.29 to 430.36) ⁸	-	LOW	
								months; antitubercule	osis chemot	herapy in sur	gery group	= 6 month
ollow-up							more in their vertebra	, ,		0.6		
	randomised trials	Serious ^{2,0,4}	no serious inconsistency	serious⁵	serious ⁶	none	24/100 (24%)	66/204 (32.4%)	OR 0.66 (0.38 to 1.14) ⁸	8 fewer per 100 (from 17 fewer to 3 more)	VERY LOW	
								tuberculosis chemoth	nerapy in su	rgery group =	6 months	(follow-up
ears; as						rae or more in their		07/10/	00.0.55	40.5		
	randomised trials	Serious ^{2,0,4}	no serious inconsistency	serious⁵	serious ⁶	none	24/100 (24%)	37/101 (36.6%)	OR 0.55 (0.3 to 1.01) ⁸	13 fewer per 100 (from 22 fewer to 0 more)	VERY LOW	
								ths; antituberculosis	chemothera	py in surgery	group = 6	months)
neasure	ed with: mean i randomised			baseline to 5 ye serious ⁵	ars; better indic serious ⁹	ated by lower value none	es) 75	157		MD 0.11	VERY	
	trials	Senous	inconsistency	senous	senous	none	75	157	-	lower (0 to 0 higher) ¹⁰		
			- increase in vert				= 6 months; antitube	rculosis chemotherap	y in surgery	group = 6 m	onths) (me	asured with
	randomised trials		,	serious ⁵	serious ⁹	none	75	75	-	MD 0.16 lower (0 to	VERY LOW	
				the house of the h		0		de de alexa de		0 higher) ¹⁰		
			- myelopathy (an sidual myelopathy			one = 6 months or 9	e months; antituberci	ulosis chemotherapy	in surgery g	roup = 6 mor	nths) (asse	ssed with:
	randomised			serious ⁵	very	none	2/100	0/204	OR	-	VERY	
	trials		inconsistency		serious ^{6,7}		(2%)	(0%)	10.38 (0.49 to		LOW	

			Quality asse	essment			No of	patients	Ef	ffect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
hando	in signs and	symptoms	now sinusos an	d/or abscesses	antituberculo	sis chemotherany a	alone = 6 months or 9	9 months; antitubercu	218.3) ⁸	otherany in si	irderv droi	n = 6 months
							luring 5-year follow-u			Suleiapy III S	ligery grou	up – o monun
13	randomised trials		no serious inconsistency	serious⁵	serious ⁶	none	21/100 (21%)	60/204 (29.4%)	OR 0.64 (0.36 to 1.13) ⁸	8 fewer per 100 (from 16 fewer to 3 more)	VERY LOW	
			 reactivation of s n whom spinal les 				ne = 6 months or 9 r	months; antituberculo	sis chemoth	nerapy in sur	gery group	= 6 months)
12 12	randomised	serious ^{2,3,4}	no serious	serious ⁵	verv	none	0/100	0/204	OR 2.03	-	VERY	
	trials	5011000	inconsistency	5611043	serious ^{6,7}	none	(0%)	(0%)	(0.04 to 103.30) ⁸		LOW	
					therapy alone =	6 months or 9 mo	nths; antituberculosis	s chemotherapy in su	rgery group	= 6 months)	(assessed	d with: numbe
			tatus during 10-ye									
1	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁶	none	70/100 (70%)	151/204 (74%)	OR 0.82 (0.48 to 1.39) ⁸	4 fewer per 100 (from 16 fewer to 6 more)	VERY LOW	
			le status (antitube 0-year follow-up ¹⁴		therapy alone =	6 months; antitube	erculosis chemothera	apy in surgery group :	= 6 months)	(assessed v	/ith: numbe	er of patients
1	randomised trials		no serious inconsistency	very serious ^{5,15}	serious ⁶	none	70/100 (70%)	73/101 (72.3%)	OR 0.90 (0.49 to 1.65) ⁸	2 fewer per 100 (from 16 fewer to 9 more)	VERY LOW	
							nonths or 9 months;	antituberculosis chen	notherapy ir	n surgery gro	up = 6 moi	nths) (assess
/ith: nun	nber of patients randomised		dditional chemoth no serious	erapy or surgery very	y during 10-yeai serious ⁶	none	5/100	6/204	OR 1.74	2 more	VERY	
	trials		inconsistency	serious ^{5,15}			(5%)	(2.9%)	(0.52 to 5.83) ⁸	per 100 (from 1 fewer to 12 more)	LOW	
			additional intervention and chemotherapy				nonths; antituberculo	osis chemotherapy in	surgery gro	up = 6 month	ns) (assess	sed with:
1	randomised trials		no serious inconsistency	very serious ^{5,15}	serious ⁶	none	5/100 (5%)	5/101 (5%)	OR 1.01 (0.28 to 3.6) ⁸	0 more per 100 (from 4 fewer to 11 more)	VERY LOW	

³ allocation concealment unclear

⁴ blinding unclear
 ⁵ antituberculosis regimens do not use all of the 4 standard recommended drugs, and the intervention and comparator differ by more than the presence of absence of surgery (some patients in the chemotherapy alone group received antituberculosis drugs for a longer period (duration of treatment = 6 or 9 months) than in the surgery group (duration of treatment = 6 months for all patients))

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	rule of thumb		S									
	nfidence interv											
			ervals calculated b	y reviewer								
⁹ insuffici	ent data to ass	sess imprecis	sion									
¹⁰ mean o	difference calc	ulated by rev	iewer									
¹¹ Darbys	shire, 1999											
¹² Reetha	a et al, 1994											
¹³ Balasu	bramanian et a	al, 1994										
	definition, see		le									
¹⁵ outcom	ne is a substitu	te for an out	come of interest									

NON-RANDOMISED CONTROLLED TRIALS

			Quality asse	essment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
•	s in signs and ng-term follow-		myelopathy (fol	low-up 27 were	followed up for	5 years. 1 for 15 m	onths and 1 for 12 m	nonths; assessed with	n: number o	f patients to	experience	myelopathy
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	very serious ^{8,9}	none	0/21 (0%)	0/8 (0%)	OR 0.40 (0.01 to 21.58) ¹⁰	-	VERY LOW	
Changes term follo	•	symptoms -	sinuses (follow-	up 27 were follo	wed up for 5 ye	ars. 1 for 15 month	is and 1 for 12 month	ns; assessed with: nu	imber of pat	ients to deve	elop a sinus	during long-
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	very serious ^{8,9}	none	0/21 (0%)	0/8 (0%)	OR 0.40 (0.01 to 21.58) ¹⁰	-	VERY LOW	
	s in signs and n follow-up)	symptoms -	abscesses (follo	ow-up 27 were fo	ollowed up for 5	years. 1 for 15 mo	nths and 1 for 12 mo	onths; assessed with	number of	patients to d	evelop an a	bscess during
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	very serious ^{8,9}	none	0/21 (0%)	0/8 (0%)	OR 0.40 (0.01 to 21.58) ¹⁰	-	VERY LOW	
			limitation of phy activity due to a				5 years. 1 for 15 mor	nths and 1 for 12 mor	nths; assess	ed with: num	ber of pation	ents to
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	very serious ^{8,9}	none	0/21 (0%)	0/8 (0%)	OR 0.40 (0.01 to 21.58) ¹⁰	-	VERY LOW	
			limitation of phy r indicated by low		surgery at any f	time) (follow-up 27	were followed up for	5 years. 1 for 15 mo	nths and 1 f	or 12 months	s; measure	d with: mean
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	serious ¹¹	none	21	8	-	MD 60 higher (0 to 0 higher) ¹²	VERY LOW	
						0 days of initiating cated by lower valu		motherapy) (follow-u	p 27 were fo	ollowed up fo	or 5 years. 7	l for 15 month
1 ¹	randomised	very	serious⁵	very	serious ¹¹	none	18	8	-	MD 44	VERY	

			Quality asse	essment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	trials	serious ^{2,3,4}		serious ^{6,7}						higher (0 to 0 higher) ¹²	LOW	
Relapse	(follow-up 27 v	were followed	l up for 5 years. 1	for 15 months a	nd 1 for 12 mor	nths; assessed with	n: number of patients	to experience relaps	se during lor	ng-term follow	w-up)	
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7}	very serious ^{8,9}	none	0/21 (0%)	0/8 (0%)	OR 0.40 (0.01 to 21.58) ¹⁰	-	VERY LOW	
Hospital values)	isation (surge	ry at any time	e) (follow-up 27 w	ere followed up f	for 5 years. 1 fo	r 15 months and 1	for 12 months; meas	sured with: mean dur	ation of hos	pital stay; be	tter indicate	ed by lower
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7,13}	serious ¹¹	none	21	8	-	MD 55 higher (0 to 0 higher) ¹²	VERY LOW	
	isation (surge al stay; better i			ntituberculosis cl	hemotherapy) (follow-up 27 were f	ollowed up for 5 yea	rs. 1 for 15 months a	ind 1 for 12	months; mea	sured with	mean duration
1 ¹	randomised trials	very serious ^{2,3,4}	serious⁵	very serious ^{6,7,13}	serious ¹¹	none	18	8	-	MD 3 higher (0 to 0 higher) ¹²	VERY LOW	
 ² only 23 ³ allocatio ⁴ blinding ⁵ unclear ⁶ 3 cases ⁷ antitube ⁸ GRADE ⁹ wide co ¹⁰ odds ra ¹¹ insuffic ¹² mean 	on concealmen i unclear if groups were cof drug resista crculosis regim E rule of thumb nfidence interv- tatio and 95% c cient data to as difference calcu	at unclear comparable ance (1 to str ens do not u: < <300 events vals onfidence int sess impreci ulate by revie	eptomycin, 1 to is se all of or just the s erval calculated b sion	ugh all 3 patient oniazid and 1 to 4 standard reco	isoniazid and n	ifampicin)	re in the surgery grou	др				

OBSERVATIONAL STUDIES

Mortality

			Quality asse	ssment			No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Mortality	(follow-up medi	an 24 mont	hs; assessed with	: number of dea	ths)							
1 ¹	observational studies ²	very serious ³	serious ⁴	serious⁵	very serious ^{6,7}	none	0/5 (0%)	0/7 (0%)	OR 1.36 (0.02 to 79.97) ⁸	-	VERY LOW	

Mortality (follow-up at least 1 year amongst those who survived; assessed with: number of deaths)

			Quality asse	essment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
1 ⁹	observational studies ²	very serious ¹⁰	very serious ¹¹	very serious ¹²	very serious ^{6,7}	none	2/11 (18.2%)	0/9 (0%)	OR 5.00 (0.21 to 118.66) ⁸	-	VERY LOW	·
Mortality	(follow-up uncle	ear; assess	ed with: number o	f deaths)								
1 ¹³	observational studies ¹⁴	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁶	none	1/22 (4.5%)	1/6 (16.7%)	OR 0.24 (0.01 to 4.5) ⁸	12 fewer per 100 (from 16 fewer to 31 more)	VERY LOW	
Mortality	- TB-related (for	ollow-up une	clear; assessed w	ith: number of T	B-related death	s)						
1 ¹³	observational studies ¹⁴	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁶	none	0/22 (0%)	1/6 (16.7%)	OR 0.08 (0 to 2.28) ⁸	15 fewer per 100 (from 17 fewer to 15 more)	VERY LOW	
Mortality	- treatment-rel	ated (follow	v-up unclear; asse	essed with: numb	per of treatment	-related deaths)						
1 ¹³	observational studies ¹⁴	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁶	none	1/22 (4.5%)	0/6 (0%)	OR 0.91 (0.03 to 25.06) ⁸	-	VERY LOW	

			Quality asse	ssment			No of p	oatients	Eff	ect		
No of studies Do	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative	Absolute	Quality	Importance

¹ Eisen et al, 2012

² retrospective

³ allocation to treatment groups was related to potential confounding factors (decision to use surgery was based on the presence of cord compression with neurological manifestations or spinal instability); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; outcome definitions were valid and precise ⁴ groups appeared to be comparable at baseline, although some baseline characteristics are not reported by group; unclear if groups received the same care apart from the intervention(s) studied; unclear if follow-up was equal between the groups; groups appear to be comparable for treatment completion and availability of outcome data

⁵ population appears to match the population of interest; antituberculosis regimens do not use all of or just the 4 standard recommended drugs; a number of patients received second-line antituberculosis drugs; some patients in the surgery group received antituberculosis chemotherapy for more than 12 months, whereas all patients in the antituberculosis chemotherapy alone group received antituberculosis chemotherapy for 12 months; outcome is not a substitute or surrogate outcome

⁶ GRADE rule of thumb: <300 events

⁷ wide confidence interval

⁸ odds ratio and 95% confidence interval calculated by reviewer

⁹ Rezai et al, 1995

¹⁰ allocation to treatment groups was related to potential confounding factors, since the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-adherence); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; study used precise definitions and reliable measures of outcom

- ¹¹ the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-adherence), whereas all patients in the 'operative' group met these criteria; the 'operative' group generally had disease of a higher grade of severity; the 'operative' group consisted of both males and females, whereas the 'non-operative' group was all-male; groups appeared to receive the same care apart from the intervention(s) studied, although bracing was undertaken for a longer period in those who did not undergo surgery; unclear if the groups were followed up for an equal time; 2 patients died in the surgery group and therefore did not complete treatment or follow-up, whereas no loss to follow-up occurred in the 'non-operative' group
- ¹² 2 patients had drug-resistant strains of tuberculosis; duration of antituberculosis chemotherapy is not reported; 2 patients in the 'non-operative' group underwent aspiration although this is an invasive technique, the authors do not consider it a surgical technique

¹³ Richardson et al, 1976

¹⁴ unclear if prospective or retrospective

¹⁵ allocation to treatment groups appears to be related to potential confounding factors, since not all patients in the antituberculosis chemotherapy alone group met the criteria for surgery; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; neurological 'improvement' was not defined

¹⁶ unclear if the groups were comparable at baseline; unclear if the groups received the same care apart from the intervention(s) studied; unclear if the groups were followed up for an equal time; groups appear to be comparable for treatment completion and availability of outcome data

¹⁷ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided)

Changes in signs and symptoms

			Quality asse	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
Changes	s in signs and s	ymptoms -	- neurological im	provement (foll	ow-up unclear;	assessed with: nur	mber of patients with	neurological improv	ement)			
1 ¹	observational studies ²	very serious ³	very serious ⁴	serious ⁵	very serious ^{6,7}	none	21/22 (95.5%)	3/6 (50%)	OR 21.00 (1.61 to 273.35) ⁸	45 more per 100 (from 12 more to 50 more)	VERY LOW	
				· · ·		mongst those who		with: number of patie		ve or remain		cally intact)
1 ⁹	observational studies ¹⁰	serious ¹¹	very serious ¹²	very serious ¹³	very serious ^{6,7}	none	10/11 (90.9%)	9/9 (100%)	OR 0.37 (0.11 to 10.18) ⁸	-	VERY LOW	
								ed neurological statu				
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁶	none	1/5 (20%)	3/4 (75%)	OR 0.08 (0 to 1.95) ⁸	56 fewer per 100 (from 75 fewer to 10 more)	VERY LOW	
Changes	in signs and s	ymptoms -	- neural recovery	(follow-up (mea	an (range). year	s) = 2.6 (2–5); ass	essed with: number	of patients to experie	nce complet	e neural reco	overy)	
1 ¹⁸	observational studies		very serious ²⁰	serious ²¹	very serious ^{6,7}	none	13/20 (65%)	2/2 (100%)	OR 0.36 (0.02 to 8.53) ⁸	-	VERY LOW	
Changes	in signs and s	ymptoms -	- residual deform	ity (follow-up m	edian 24 month	ns; assessed with: r	number of patients to	experience residual				
1 ²²	observational studies ¹⁰	very serious ²³	serious ²⁴	serious ²⁵	very serious ^{6,7}	none	0/5 (0%)	1/7 (14.3%)	OR 0.39 (0.01 to 11.76)	8 fewer per 100 (from 14 fewer to 52 more)	VERY LOW	
	s in signs and s	ymptoms -	- kyphosis (follow	-up mean 20.2	years; assesse	d with: number of p	atients to have kyph	osis)				
1 ²⁶	observational studies ¹⁰	very serious ²⁷	very serious ⁴	serious ⁵	serious ⁶	none	6/18 (33.3%)	8/8 (100%)	OR 0.03 (0 to 0.62) ⁸	-	VERY LOW	
		ymptoms -	- kyphosis (follow			d with: mean angle	of kyphosis; better	indicated by lower va	lues)			
1 ²⁶	observational studies ¹⁰	very serious ²⁷	very serious ⁴	serious⁵	serious ²⁸	none	6	8	-	MD 31.1 lower (0 to 0 higher) ²⁹	VERY LOW	
						ns; measured with:		osis at end of follow-u	up; better inc	licated by lov		
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	serious ²⁸	none	31	23	-	MD 10 lower (0 to 0 higher) ²⁹	VERY LOW	

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	U						nean angle of kyphos					
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	serious ²⁸	none	26	13	-	MD 11 lower (0 to 0 higher) ²⁹	VERY LOW	
Changes values)	in signs and s	ymptoms ·	- kyphosis (childr	en) (follow-up a	t least 24 montl	hs; measured with:	mean angle of kypho	osis amongst the chil	dren at end	of follow-up;	better indic	ated by lower
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	serious ²⁸	none	5	10	-	MD 1 higher (0 to 0 higher) ²⁹	VERY LOW	
	in signs and s		- change in kyph	osis (follow-up	at least 1 year a	amongst those who	survived; measured	with: change in mea	n angle of k	yphosis from	baseline to	o follow-up;
1 ⁹	observational studies ¹⁰		very serious ¹²	very serious ¹³	serious ²⁸	none	11	9	-	MD 11 lower (0 to 0 higher) ²⁹	VERY LOW	
Changes values)	in signs and s	ymptoms ·	- change in kyph	osis (all ages) (follow-up at lea	st 24 months; mea	sured with: change ir	n mean angle of kyph	losis at end	of follow-up;	better indic	ated by lower
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	serious ²⁸	none	31	23	-	MD 13 lower (0 to 0 higher) ²⁹	VERY LOW	
•	•		- change in kyph	osis (adults) (fo	ollow-up at least	24 months; measu	ured with: change in r	mean angle of kypho	sis amongst	U /	d of follow-i	ıp; better
1 ³⁰	by lower values observational studies ¹⁰	1	very serious ³²	very serious ³³	serious ²⁸	none	26	13	-	MD 15 lower (0 to 0 higher) ²⁹	VERY LOW	
•	in signs and s		- change in kyph	osis (children)	(follow-up at lea	ist 24 months; mea	sured with: change in	n mean angle of kypł	nosis among	st children at	end of foll	ow-up; better
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	serious ²⁸	none	5	10	-	MD 1 lower (0 to 0 higher) ²⁹	VERY LOW	
Changes kyphosis)		ymptoms ·	improvement in	kyphosis (follo	ow-up at least 7	2 months; assesse	d with: number of pa	tients to experience a	an improvem	nent (decreas	se) in their	angle of
1 ³⁴	observational studies ¹⁰	very serious ³⁵	very serious ³⁶	serious ³⁷	serious ⁶	none	4/30 (13.3%)	7/60 (11.7%)	OR 1.16 (0.31 to 4.34) ⁸	2 more per 100 (from 8 fewer to 25 more)	VERY LOW	
	in signs and s n 11°) in their an			kyphosis (follo	ow-up at least 72	2 months; assesse	d with: number of pat	ients to experience r	noderate or	severe deter	ioration (ar	increase of
1 ³⁴	observational studies ¹⁰	0 11	very serious ³⁶	serious ³⁷	serious ⁶	none	14/30 (46.7%)	34/60 (56.7%)	OR 0.67 (0.28 to	10 fewer per 100	VERY LOW	

			Quality asse	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
									1.61) ⁸	(from 30 fewer to 11 more)		
	in signs and s e) in their angle			kyphosis (<16	years) (follow-u	up at least 72 mont	hs; assessed with: n	umber of patients be	low the age	of 16 to expe	erience an	mprovement
1 ³⁴	observational studies ¹⁰	very serious ³⁵	, very serious ³⁶	serious ³⁷	very serious ^{6,7}	none	4/7 (57.1%)	6/30 (20%)	OR 5.33 (0.93 to 30.51) ⁸	37 more per 100 (from 1 fewer to 68 more)	VERY LOW	
•	•		deterioration in more than 11°) in	.	, , ,	ip at least 72 mont	ns; assessed with: ni	umber of patients bel	ow the age	of 16 to expe	rience mod	lerate or
1 ³⁴	observational studies ¹⁰	very serious ³⁵	very serious ³⁶	serious ³⁷	serious ⁶	none	3/7 (42.9%)	17/30 (56.7%)	OR 0.57 (0.11 to 3.02) ⁸	14 fewer per 100 (from 44 fewer to 23 more)	VERY LOW	
•	in signs and s in their angle			kyphosis (>16	years) (follow-i	up at least 72 mont	hs; assessed with: n	umber of patients ag	ed 16 and a	bove to expe	rience an i	mprovement
1 ³⁴	observational studies ¹⁰	very serious ³⁵	very serious ³⁶	serious ³⁷	very serious ^{6,7}	none	0/23 (0%)	1/30 (3.3%)	OR 0.42 (0.02 to 10.75) ⁸	2 fewer per 100 (from 3 fewer to 24 more)	VERY LOW	
			deterioration in more than 11°) in			ip at least 72 mont	ns; assessed with: n	umber of patients age	ed 16 and at	pove to expe	rience mod	erate or
1 ³⁴	observational studies ¹⁰	very serious ³⁵	very serious ³⁶	serious ³⁷	serious ⁶	none	11/23 (47.8%)	17/30 (56.7%)	OR 0.70 (0.24 to 2.09) ⁸	9 fewer per 100 (from 33 fewer to 17 more)	VERY LOW	
Changes	-				1		s with spinal fusion)	3/6	00.45.00	40		
	studies ²	very serious ³	very serious ⁴	serious⁵	very serious ^{6,7}	none	22/22 (100%)	(50%)	OR 45.00 (1.89 to 1071.38) ⁸	48 more per 100 (from 15 more to 50 more)	VERY LOW	
							ents to experience ra		00.040			
1 ²⁶	observational studies ¹⁰	very serious ²⁷	very serious ⁴	serious⁵	very serious ^{6,7}	none	18/18 (100%)	8/8 (100%)	OR 2.18 (0.04 to 119.22) ⁸	-	VERY LOW	
								perience intracorpor		10		
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	very serious ^{6,7}	none	26/31 (83.9%)	15/23 (65.2%)	OR 2.77 (0.77 to 10.03) ⁸	19 more per 100 (from 6 fewer to 30 more)	VERY LOW	

			Quality asse	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	in signs and s	ymptoms	- fusion (adults) (follow-up at leas	t 24 months; as	ssessed with: numb	per of adult patients t	o experience intracor	poreal fusio	n)		
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	very serious ^{6,7}	none	26/26 (100%)	13/13 (100%)	OR 1.96 (0.04 to 104.47) ⁸	-	VERY LOW	
Changes	in signs and s	symptoms	- fusion (children)	(follow-up at lea	ast 24 months;	assessed with: nur	mber of children to ex	perience intracorpor	eal fusion)			
1 ³⁰	observational studies ¹⁰	very serious ³¹	very serious ³²	very serious ³³	very serious ^{6,7}	none	0/5 (0%)	2/10 (20%)	OR 0.31 (0.01 to 7.74) ⁸	13 fewer per 100 (from 20 fewer to 46 more)	VERY LOW	
	in signs and s	ymptoms -	- pain (follow-up a	it least 1 year ar	nongst those w	ho survived; asses	sed with: number of	patients with persiste	ent pain)			
1 ⁹	observational studies ¹⁰	very serious ¹¹	very serious ¹²	very serious ¹³	serious ⁶	none	0/11 (0%)	2/9 (22.2%)	OR 0.13 (0.01 to 3.11) ⁸	19 fewer per 100 (from 22 fewer to 25 more)	VERY LOW	
	-	symptoms -				neasured with: mea	U	e of functional indepe	endence; bet		, ,	values)
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁷	none	5	4	-	MD 0.50 higher (16.06 lower to 11.66 higher) ²⁹	VERY LOW	
•	in signs and s	symptoms -	- functional inde	pendence (self-	care) (follow-u	p unclear; measure	ed with: mean change	e in self-care score; b	etter indicat	ed by higher	values)	
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁷	none	5	4	-	MD 5.5 lower (17.46 lower to 6.46 higher) ²⁹	VERY LOW	
					37 (,	5	in mobility and trans	fer score; be		, 0	r values)
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁷	none	5	4	-	MD 3.00 higher (0.64 lower to 6.64 higher) ²⁹	VERY LOW	
	in signs and s	ymptoms		pendence (loco	motion) (follow	v-up unclear; meas	ured with: mean cha	nge in locomotion sc	ore; better in		igher value	es)
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	serious ⁷	none	5	4	-	MD 0.20 lower (2.16 lower to 1.76 higher) ²⁹	VERY LOW	
		2 1					nts able to walk on d	U , U ,				
1 ¹⁴	observational studies ¹⁰	very serious ¹⁵	very serious ¹⁶	serious ¹⁷	very serious ^{6,7}	none	3/5 (60%)	3/4 (75%)	OR 0.50 (0.03 to	15 fewer per 100	VERY LOW	

			Quality asse	ssment			No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI) 8.95) ⁸	(from 67 fewer to	Quality	Importance
										21 more)		

¹ Richardson et al, 1976

² unclear if prospective or retrospective

³ allocation to treatment groups appears to be related to potential confounding factors, since not all patients in the antituberculosis chemotherapy alone group met the criteria for surgery; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; neurological 'improvement' was not defined ⁴ unclear if the groups were comparable at baseline: unclear if the groups received the same care apart from the intervention(s) studied; unclear if the groups were followed up for an equal time:

groups appear to be comparable for treatment completion and availability of outcome data

⁵ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided)

⁶ GRADE rule of thumb: <300 events

⁷ wide confidence interval

⁸ odds ratio and 95% confidence interval calculated by reviewer

⁹ Rezai et al, 1995

¹⁰ retrospective

¹¹ allocation to treatment groups was related to potential confounding factors, since the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-adherence); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; study used precise definitions and reliable measures of outcom

¹² the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-adherence), whereas all patients in the 'operative' group met these criteria; the 'operative' group generally had disease of a higher grade of severity; the 'operative' group consisted of both males and females, whereas the 'non-operative' group was all-male; groups appeared to receive the same care apart from the intervention(s) studied, although bracing was undertaken for a longer period in those who did not undergo surgery; unclear if the groups were followed up for an equal time; 2 patients died in the surgery group and therefore did not complete treatment or follow-up, whereas no loss to follow-up occurred in the 'non-operative' group

¹³ 2 patients had drug-resistant strains of tuberculosis; duration of antituberculosis chemotherapy is not reported; 2 patients in the 'non-operative' group underwent aspiration - although this is an invasive technique, the authors do not consider it a surgical technique

¹⁴ Zaoui et al, 2012

¹⁵ allocation to treatment groups related to potential confounding factors (allocation to surgery was based upon the presence of compressive abscess with neurological complications); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; outcome definitions were valid and precise

¹⁶ more patients that underwent surgery had complete neurological impairment; groups appeared to receive the same care apart from the intervention(s) studied, although details were limited; unclear of groups were followed up for an equal period; groups appear to be comparable for treatment completion and availability of outcome data

¹⁷ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided)

¹⁸ Kumar et al, 2007

¹⁹ allocation to treatment groups was related to potential confounding factors (decision to operate was based upon presence of extradural granuloma (19 patients), although 1 of the 3 patients without extradural granuloma, all of whom had intramedullary lesions, also underwent surgery - the indication for surgery in this patient is not reported); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; outcome definition unclear

²⁰ unclear if groups were comparable at baseline; groups appeared to receive the same care apart from the intervention(s) studied, although details were limited; unclear if follow-up was equal between the groups; groups appear to be comparable for treatment completion and availability of outcome data

²¹ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided); outcome not a substitute or surrogate outcome

²² Eisen et al, 2012

²³ allocation to treatment groups was related to potential confounding factors (decision to use surgery was based on the presence of cord compression with neurological manifestations or spinal instability); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; outcome definitions were valid and precise

²⁴ groups appeared to be comparable at baseline, although some baseline characteristics are not reported by group; unclear if groups received the same care apart from the intervention(s) studied; unclear if follow-up was equal between the groups; groups appear to be comparable for treatment completion and availability of outcome data

²⁵ population appears to match the population of interest; antituberculosis regimens do not use all of or just the 4 standard recommended drugs; a number of patients received second-line antituberculosis drugs; some patients in the surgery group received antituberculosis chemotherapy for more than 12 months, whereas all patients in the antituberculosis chemotherapy alone

			Quality asse	ssment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
		rculosis che	emotherapy for 12	months; outcor	ne is not a subs	stitute or surrogate	outcome					
²⁶ Pun et		rootmonta	round related to p	tantial confour	dina faatara: bli	nding uncloar that	ich unlikoly: uncloar	if attampta wara maa	la ta halana	aanfaundar	o: longth o	f follow up was
			ere valid and prec		ung raciors, bil	nuing unclear, thou	ign uninkely, unclear	if attempts were mad		ecomounder	s, ierigiri ü	i ionow-up was
	ient data to asse			30								
			nce interval, wher	e possible) calc	ulated by review	ver						
³⁰ Moon e	et al, 2007			. ,	-							
³¹ allocati	on to treatment	groups was	related to potenti	al confounding f	factors (decisio	n to operate was ba	ased upon clinical sig	gns and symptoms);	blinding unc	lear, though	unlikely; ur	nclear if
attempt	s were made to	balance co	nfounders; length	of follow-up was	s appropriate; o	utcome definitions	were valid and preci	se				
								14 vs 12)); unclear if				rt from the
								ent completion and av				rearia a wara
			an therapeutic pur		ans were infined	a, antituberculosis i	regimens do not use	all of the 4 standard	recommenta	eu urugs, an	a some su	rgenes were
	karan et al, 198		an merapeulle pui	0363								
³⁵ unclear	if allocation to t	reatment gi	roups related to po ere valid and prec		ding factors; bli	nding unclear, thou	ıgh unlikely; unclear	if attempts were mad	le to balance	e confounder	s; length o	f follow-up was
					<16 vears of a	ae than the surger	, aroun (no further de	etails are available fo	r the arouns	' characteris	tics at has	eline): unclear
if the gr		ne same ca						l period; groups appe				
³⁷ populat	tion appears to r	natch the p						use all of the 4 stand				
							e or surrogate outcor	ved antituberculosis c mes were used	irugs for a lo	nger period	auration o	t treatment = 6

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
Respons surgery)	e to treatment	- favourabl	e (follow-up range	ed from 1.5 to 3	years in the an	tituberculosis chem	otherapy alone grou	p. and from 1 month	to 3 years in	the group th	at also un	derwent
1 ¹	observational studies ²	serious ³	very serious ⁴	very serious⁵	very serious ^{6,7}	none	19/20 (95%)	5/5 (100%)	OR 1.18 (0.04 to 33.27) ⁸	-	VERY LOW	
Respons	e to treatment	- disease r	esolution (follow-	up median 24 m	nonths; assesse	ed with: number of	patients in whom the	disease fully resolve	ed)			
1 ⁹	observational studies ¹⁰	very serious ¹¹	serious ¹²	very serious ¹³	very serious ^{7,14}	none	5/5 (100%)	5/7 (71.4%)	OR 5.00 (0.19 to 130.03)	21 more per 100 (from 39 fewer to 28 more)	VERY LOW	
Respons	e to treatment	 hospitalis 	sation (follow-up ι	inclear; measur	ed with: mean o	duration of hospitali	sation; better indicat	ed by lower values)				
1 ¹⁵	observational studies ²	very serious ¹⁶	very serious ¹⁷	very serious ^{18,19}	serious ²⁰	none	22	6	-	MD 24.0 lower (0 to 0 higher) ^{21,2}	VERY LOW	

Response to treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
										2		
Response to treatment - hospitalisation (follow-up unclear; measured with: mean duration of hospitalisation; better indicated by higher values)												
1 ²³	observational studies ¹⁰	very serious ²⁴	very serious ²⁵	serious ¹⁸	serious ⁷	none	5	4	-	MD 4.00 higher (13.19 lower to 21.19 higher) ²⁶	VERY LOW	

² unclear if prospective or retrospective

³ unclear if allocation to treatment groups related to potential confounding factors; blinding unclear, though unlikely; unclear if attempts were made to balance confounders; length of follow-up was appropriate; outcome definitions were valid and precise

⁴ unclear if the groups were comparable at baseline; unclear if groups received the same care apart from the intervention(s) studied; follow-up ranged from 1.5 to 3 years in the antituberculosis chemotherapy alone group, and from 1 month to 3 years in the group that also underwent surgery; unclear if groups were comparable for treatment completion and availability of outcome data

⁵ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided); 'response to treatment' is a substitute for cure / treatment success and changes in the signs and symptoms of the disease

⁶ GRADE rule of thumb: 300 events

⁷ wide confidence interval

⁸ odds ratio and 95% confidence intervals calculated by reviewer

⁹ Eisen et al, 2012

¹⁰ retrospective

¹¹ allocation to treatment groups was related to potential confounding factors (decision to use surgery was based on the presence of cord compression with neurological manifestations or spinal instability); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; outcome definitions were valid and precise ¹² groups appeared to be comparable at baseline, although some baseline characteristics are not reported by group; unclear if groups received the same care apart from the intervention(s)

studied; unclear if follow-up was equal between the groups; groups appear to be comparable for treatment completion and availability of outcome data

¹³ population appears to match the population of interest; antituberculosis regimens do not use all of or just the 4 standard recommended drugs; a number of patients received second-line antituberculosis drugs; some patients in the surgery group received antituberculosis chemotherapy for more than 12 months, whereas all patients in the antituberculosis chemotherapy alone group received antituberculosis chemotherapy for 12 months; outcome is a substitute for an outcome of interest

¹⁴ GRADE rule of thumb: <300 events

¹⁵ Richardson et al, 1976

¹⁶ allocation to treatment groups appears to be related to potential confounding factors, since not all patients in the antituberculosis chemotherapy alone group met the criteria for surgery; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; neurological 'improvement' was not defined

¹⁷ unclear if the groups were comparable at baseline; unclear if the groups received the same care apart from the intervention(s) studied; unclear if the groups were followed up for an equal time; groups appear to be comparable for treatment completion and availability of outcome data

¹⁸ population appears to match the population of interest, although details were limited; unclear if the intervention exactly matches the intervention of interest (details of the antituberculosis regimen(s) used not provided)

¹⁹ outcome is a substitute for an outcome of interest

²⁰ insufficient data to assess imprecision

²¹ odds ratio and 95% confidence interval calculated by reviewer

²² mean difference calculated by reviewer

²³ Zaoui et al, 2012

²⁴ allocation to treatment groups related to potential confounding factors (allocation to surgery was based upon the presence of compressive abscess with neurological complications); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; outcome definitions were valid and precise

²⁵ more patients that underwent surgery had complete neurological impairment; groups appeared to receive the same care apart from the intervention(s) studied, although details were limited; unclear of groups were followed up for an equal period; groups appear to be comparable for treatment completion and availability of outcome data

²⁶ mean difference (and 95% confidence interval, where possible) calculated by reviewer

Relapse

			Quality asse	ssment		No of patients		Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
Relapse (follow-up median 24 months; assessed with: number of patients to experience relapse)												
1 ¹	observational studies ²	very serious ³	serious ⁴	serious ⁵	very serious ^{6,7}	none	1/5 (20%)	1/7 (14.3%)	OR 1.50 (0.07 to 31.58) ⁸	6 more per 100 (from 13 fewer to 70 more)	VERY LOW	

¹ Eisen et al, 2012

² retrospective

³ allocation to treatment groups was related to potential confounding factors (decision to use surgery was based on the presence of cord compression with neurological manifestations or spinal instability); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; length of follow-up was appropriate; outcome definitions were valid and precise ⁴ groups appeared to be comparable at baseline, although some baseline characteristics are not reported by group; unclear if groups received the same care apart from the intervention(s) studied;

unclear if follow-up was equal between the groups; groups appear to be comparable for treatment completion and availability of outcome data

⁵ population appears to match the population of interest; antituberculosis regimens do not use all of or just the 4 standard recommended drugs; a number of patients received second-line antituberculosis drugs; some patients in the surgery group received antituberculosis chemotherapy for more than 12 months, whereas all patients in the antituberculosis chemotherapy alone group received antituberculosis chemotherapy for 12 months; outcome is not a substitute or surrogate outcome

⁶ GRADE rule of thumb: <300 events

⁷ wide confidence interval

⁸ odds ratio and 95% confidence interval calculated by reviewer

POST-OPERATIVE COMPLICATIONS

Randomised controlled trials

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

No details provided

Non-randomised controlled trials

Rajeswari et al, 1997

No details provided

Observational studies

Arthornthurasook, 1983

No details provided

Eisen et al, 2012

None

Kumar et al, 2007

No details provided

Moon et al, 2007

No details provided

Pun et al, 1990

No significant postoperative complications

Rajasekaran et al, 1987

No details provided

Rezai et al, 1995

No details provided

Richardson et al, 1976

Blood loss:

- excessive bleeding = 1
- mean blood loss:
 - o adults = 380 ml
 - \circ children = 80 ml
- need for transfusion = 5

Operative mortality = 1

Intraoperative neurological complications = 0

Wound infection = 1

Draining sinus tracts after chest tube removal = 2

Zaoui et al, 2012

No details provided

..11.6 Adjunctive surgery in the treatment of active CENTRAL NERVOUS SYSTEM tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality assess	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Mortality	(follow-up minir	num 1 year; as	sessed with: num	ber of deaths)								
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	3/28 (10.7%)	11/28 (39.3%)	OR 0.19 (0.04 to 0.77) ¹³	28 fewer per 100 (from 6 fewer to 37 fewer)	⊙OOO VERY LOW	
	in signs and s nt2, optic atroph			elae (follow-up 1	years; assesse	ed with: number of	patients to experience	e neurological seque	elae, includi	ng neurologi	cal deficit, o	cognitive
1 ¹⁴	observational studies ¹⁵	very serious ^{16,17,18}	very serious ^{19,20}	no serious indirectness	very serious ^{12,21}	none	9/12 (75%)	17/53 (32.1%)	OR 6.35 (1.52 to 26.50) ¹³	43 more per 100 (from 10 more to 61 more)	©OOO VERY LOW	
Changes	in signs and s	ymptoms – dis	sability (follow-up	minimum 1 yea	r; assessed wit	h: number of patier	nts to experience dis	ability)				
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	16/28 (57.1%)	18/28 (64.3%)	OR 0.74 (0.25 to 2.17) ¹³	7 fewer per 100 (from 33 fewer to 15 more)	⊙OOO VERY LOW	
			ell' or minor phy nis or her lifestyle)		ity (follow-up m	inimum 1 year; ass	essed with: number	of patients to be con	sidered 'we	ll', or had a r	ninor physi	cal
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}	very serious ^{8,9,10}	serious ¹¹	very serious ^{12,21}	none	9/28 (32.1%)	2/28 (7.1%)	OR 6.16 (1.19 to 31.82) ¹³	25 more per 100 (from 1 more to 64 more)	⊙OOO VERY LOW	

			Quality assess	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Respons	se to treatment	- poor outcom	e (follow-up uncle	ar; assessed wi	th: number of p	atients (stage II or		utcome' (severe neu	rologic defic	it or death))		
1 ²²	observational studies ²	very serious ^{17,18,23} ,24,25	very serious ^{26,27,28}	very serious ^{29,30}	serious ¹²	none	85/147 (57.8%)	108/240 (45%)	OR 1.68 (1.11 to 2.54) ¹³	13 more per 100 (from 3 more to 23 more)	⊙OOO VERY LOW	
	se to treatment	 poor outcom 	e (stage II) (follow	v-up unclear; as		mber of patients w	ith stage II disease t	o have a 'poor outco	me' (severe	neurologic o		eath))
1 ²²	observational studies ²	very serious ^{17,18,23} ,24,25	very serious ^{26,27,28}	very serious ^{29,30}	serious ¹²	none	17/54 (31.5%)	23/102 (22.5%)	OR 1.58 (0.75 to 3.30) ¹³	9 more per 100 (from 5 fewer to 26 more)	⊙OOO VERY LOW	
			e (stage III) (follo	w-up unclear; as				to have a 'poor outc				leath))
1 ²²	observational studies ²	very serious ^{17,18,23} ,24,25	very serious ^{26,27,28}	very serious ^{29,30}	serious ¹²	none	68/93 (73.1%)	85/138 (61.6%)	OR 1.70 (0.97 to 3.01) ¹³	12 more per 100 (from 1 fewer to 21 more)	⊙OOO VERY LOW	
Respons	se to treatment	- poor outcom	e (follow-up 3 mo	nths; assessed	with: number of	patients to have a	â€~poor outcomeâ€	[™] , as defined by dea	ath or a Bart	hel Index sc	ore of <12)	
1 ³¹	observational studies ¹⁵	very serious ^{17,32,33} , ³⁴	very serious ^{20,35}	very serious ^{30,36}	very serious ^{12,21}	none	9/14 (64.3%)	11/35 (31.4%)	OR 3.93 (1.06 to 14.49) ¹³	33 more per 100 (from 1 more to 55 more)	⊙OOO VERY LOW	
 ² retrospo ³ study d ⁴ it is unclear ⁵ unclear ⁶ exposu ⁷ unclear ⁸ unclear ⁹ it is unclear ¹⁰ unclear ¹¹ unclear 	id not explicitly re clear if the same if measures take re status measure if the main pote for the cases and clear if the 2 grou r if follow-up was	eport the questi exclusion criter en to prevent kr red in a standar ntial confounde controls were to ps were match s equal in the 2 on exactly matc	ia was applied to nowledge of prima rd, valid and reliab rs were identified taken from compa ed in terms of the groups	cases and contr ary exposure fro- ble way and taken into a prable population participation rat	rols; cases and m influencing ca account in the d as, although the re	controls adequatel ase ascertainment esign and analysis	r age and severity of	^t disease				

² GRADE rule of thumb: <300 events ¹³ odds ratio and 95% confidence intervals calculated by reviewer

¹⁴ Kalita et al, 2007

¹⁶ Kalita et al. 2007
 ¹⁵ prospective
 ¹⁶ allocation to receive shunt was based on clinical status
 ¹⁷ blinding unclear, though unlikely
 ¹⁸ attempts do not appear to have been made to balance confounders
 ¹⁹ with the presence of hydro

¹⁹ those that received shunt were selected due to the presence of hydrocephalus and raised intracranial pressure, so groups not balanced at baseline ²⁰ unclear if groups received the same care apart from the intervention(s) studied ²¹ wide confidence intervals

²² Lee, 2000

²³ unclear if allocation to treatment groups was related to potential confounding factors

			Quality assess	sment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		Relative		Quality	Importance

²⁴ unclear if length of follow-up was appropriate

²⁵ †poor outcome' defined only as the incident of severe neurologic deficit or death (†severe neurologic deficit' not defined)

²⁶ unclear if groups were comparable at baseline

²⁷ unclear if the 2 groups received antituberculosis drugs in the same doses for the same durations

²⁸ unclear if groups were followed for an equal period

²⁹ antituberculosis regimens did not use all of or just the 4 standard recommended drugs, and the dosing and duration of the antituberculosis regimens was not reported

³⁰ outcome is a substitute for an outcome of interest

³¹ Misra et al, 1996

³² allocation to treatment groups related to potential confounding factors (allocation to receive shunt was based on presence of obstructive hydocephalus)

³³ attempts were made to balance confounders, although this only benefits the p-value and z-statistic (odds ratio was calculated by the reviewer)

³⁴ follow-up was only 3 months

³⁵ those that received shunt were selected due to the presence of obstructive hydrocephalus, and therefore the groups were not comparable at baseline

³⁶ duration of antituberculosis chemotherapy unclear, and children received streptomycin instead of ethambutol

POST-OPERATIVE COMPLICATIONS

Kalita et al, 2007

No details provided

Lee, 2000

No details provided

Misra et al, 1996

Shunt surgery complications = 6 of 14

- obstruction = 2
- infection = 2
- slit ventricles = 2
- subdural haematoma = 1
- intracerebral haematoma = 1

Peacock & Deeny, 1984

No details provided

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Respons was requ		- need for a	additional interve	ention (follow-u	p median (maxi	mum), months = 34	(62); assessed with	number of patients	in whom rec	onstructive s	urgery or I	nephrectomy
1 ¹	observational studies ²	very serious ³	serious ⁴	very serious⁵	serious ⁶	none	39/47 (83%) ⁷	30/37 (81.1%) ⁷	OR 1.14 (0.37 to 3.49) ⁸	2 more per 100 (from 20 fewer to 13 more)	VERY LOW	
Respons	se to treatment	- need for I	reconstructive su	urgery (follow-u	p median (maxi	mum), months = 34	(62); assessed with	: number of patients	in whom red	onstructive s	surgery wa	s required)
1 ¹	observational studies ²	very serious ³	serious⁴	very serious⁵	very serious ^{6,9}	none	23/47 (48.9%) ⁷	3/37 (8.1%) ⁷	OR 10.86 (2.93 to 40.32) ⁸	41 more per 100 (from 12 more to 70 more)	VERY LOW	
Respons	se to treatment	- need for I		low-up median ((maximum), mo	nths = 34 (62); asse	essed with: number of	of patients in whom n	ephrectomy	was require	d)	
1 ¹	observational studies ²	very serious ³	serious ⁴	very serious⁵	very serious ^{6,9}	none	16/47 (34%) ⁷	27/37 (73%) ⁷	OR 0.19 (0.07 to 0.49) ⁸	39 fewer per 100 (from 16 fewer to 57 fewer)	VERY LOW	
Treatme	nt failure (any s	urgery cor	npared with no s	urgery) (follow-	-up 9 to 60 mon	ths; assessed with:	number of patients t	o experience bacteri	ological failu	ire)		
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	0/74 (0%)	0/18 (0%)	OR 0.40 (0.01 to 20.42) ⁸	-	VERY LOW	
	nt failure (ablati	ive surgery		no surgery) (fo	llow-up 9 to 60	months; assessed	with: number of patie	ents to experience ba	cteriological	failure)		
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	0/45 (0%)	0/18 (0%)	OR 0.21 (0.00 to 11.19) ⁸	-	VERY LOW	
	nt failure (recor	nstructive s		d with no surg	ery) (follow-up	16 to 60 months; as	sessed with: numbe	r of patients to exper	ience bacte	iological failu	ure)	
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	0/29 (0%)	0/18 (0%)	OR 0.32 (0.01 to 17.37) ⁸	-	VERY LOW	

Adverse events - drug toxicity leading to drug withdrawal (any surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number of patients to experience drug toxicity

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
leading to	withdrawal of d	rug (withou	t change to durati	on of treatment))							
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	serious ⁶	none	9/74 (12.2%)	2/18 (11.1%)	OR 1.11 (0.22 to 5.64) ⁸	1 more per 100 (from 8 fewer to 30 more)	VERY LOW	
			ding to drug with (without change to			npared with no su	rgery) (follow-up 9 to	60 months; assesse	ed with: num	ber of patien	ts to expe	rience drug
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	5/45 (11.1%)	2/18 (11.1%)	OR 1.00 (0.10 to 9.75) ⁸	0 fewer per 100 (from 10 fewer to 44 more)	VERY LOW	
			ding to drug with drug (without cha			ery compared with	no surgery) (follow	-up 16 to 60 months;	assessed v	vith: number	of patients	to experience
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	4/29 (13.8%)	2/18 (11.1%)	OR 1.28 (0.12 to 13.17) ⁸	3 more per 100 (from 10 fewer to 51 more)	VERY LOW	
Adheren	ce (any surgery	compared		(follow-up 9 to	60 months; as	sessed with: number	er of patients to defa	ult treatment)				
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	serious ¹⁴	very serious ^{6,9}	none	1/74 (1.4%)	1/18 (5.6%)	OR 0.38 (0.02 to 6.34) ⁸	3 fewer per 100 (from 5 fewer to 22 more)	VERY LOW	

² prospective

³ allocation was based upon the time at which the patient was treated; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders

⁴ unclear if groups were comparable at baseline; groups appeared to received the same 'other' care, although details provided are limited; unclear if groups were followed for an equal period ⁵ antituberculosis regimens do not use all of or just the 4 standard recommended drugs; substitute for an outcome of interest

⁶ GRADE rule of thumbs: <300 events

⁷ unit of analysis is at the renal unit-, rather then the patient-, level

⁸ odds raio and 95% confidence interval calculated by reviewer

⁹ wide confidence interval

¹⁰ Wong et al, 1984

¹¹ unclear if prospective or retrospective

¹² unclear if method of allocation to treatment groups unrelated to potential confounding factors; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; definition for 'default' not provided, and only a loose definition provided for 'treatment failure'

¹³ groups were comparable at baseline, although only details of age and sex were provided; groups appeared to received the same 'other' care, although details provided are limited; follow-up had a wide range within each group, though the ranges appeared to be comparable

¹⁴ intervention varies by more than the presence or absence of surgery (duration of antituberculosis chemotherapy is longer amongst those patients that received surgery)

POST-OPERATIVE COMPLICATIONS

Shin et al, 2002

No details provided

Wong et al, 1984

Chest infection = 5(6.8%)

Wound infection = 2(2.7%)

Pneumothorax requiring chest drainage = 2 (2.7%)

Haemorrhage from anastomosis = 1(1.4%)

Burst abdomen = 1(1.4%)

Intestinal obstruction owing to adhesion (late complication) = 1 (1.4%)

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

Mortality

			Quality asse	essment			No of J	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
			ear; assessed wit		,							
1 ¹	observational studies	very serious ²	serious ³	very serious ⁴	very serious ^{5,6}	none	1/3 (33.3%)	1/5 (20%)	OR 22.00 (0.08 to 51.60) ⁷	65 more per 100 (from 18 fewer to 73 more)	VERY LOW	
	- all-cause (foll	ow-up uncl	ear; assessed wit	h: number of dea	aths)							
1 ⁸	observational studies ⁹	very serious ¹⁰	serious ¹¹	very serious ¹²	serious ⁶	plausible confounding would change effect ¹³	2/35 (5.7%)	12/107 (11.2%)	OR 0.48 (0.10 to 2.26) ⁷	5 fewer per 100 (from 10 fewer to 11 more)	VERY LOW	
Mortality	- all-cause (foll	ow-up uncl	ear; assessed wit	h: number of dea	aths)							
1 ¹⁴	observational studies ¹⁵	very serious ¹⁶	serious ¹⁷	very serious ¹⁸	serious ⁶	none	1/35 (2.9%)	9/120 (7.5%)	OR 0.39 (0.05 to 3.21) ⁷	4 fewer per 100 (from 7 fewer to 13 more)	VERY LOW	
Mortality			ear; assessed wit	h: number of dea	aths)							
1 ¹⁹	observational studies ¹⁵	serious ²⁰	serious ²¹	very serious ²²	very serious ^{5,6}	none	1/19 (5.3%)	13/185 (7%)	OR 0.74 (0.09 to 5.95) ⁷	2 fewer per 100 (from 6 fewer to 24 more)	VERY LOW	

			Quality asse	essment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	,		ear; assessed wit	h: number of de	aths)							
1 ²³	observational studies ¹⁵	serious ²⁴	serious ²⁵	very serious ²⁶	serious ⁶	none	5/66 (7.6%)	13/186 (7%)	OR 1.09 (0.37 to 3.19) ⁷	1 more per 100 (from 4 fewer to 12 more)	VERY LOW	
Mortality vounger)	- all-cause (pa	tients ageo	d 40 years or you	inger) (follow-up	3 to 7 years at	fter treatment initiat	ion; assessed with: n	umber of deaths of a	ny cause ar	mong patient	s aged 40	years or
1 ²⁷	observational studies ¹⁵	very serious ²⁸	serious ²⁹	very serious ³⁰	serious ⁶	none	-	-	OR 0.53 (0.17 to 1.67)	-	VERY LOW	
Mortality younger)	- TB-related (p	atients age	ed 40 years or yo	ounger) (follow-u	p 3 to 7 years	after treatment initia	ation; assessed with:	number of TB-related	d deaths am	nong patients	aged 40 y	ears or
1 ²⁷	observational studies ¹⁵	very serious ²⁸	serious ²⁹	very serious ³⁰	serious ⁶	none	-	-	OR 0.67 (0.21 to 2.14)	-	VERY LOW	
 ³ the mea baseling ⁴ 2 patien the regi ⁵ wide col ⁶ GRADE ⁷ odds rat ⁸ Karagöz 	e characteristics ts, both in the su imens of antitub nfidence interva. rule of thumb: - io and 95% con t et al, 2009	gery group s; groups ap urgery grou erculosis cl ls <300 events	ppeared to receive p, had comorbiditi nemotherapy cont	e the same 'othe ies that might af ained, on averag	r' care, although	h details provided a	re limited; unclear if the intervention of the intervent is the intervent.	ne (41 vs 27 years); (groups were followed entions used varied b <u>i</u>	l for an equa	al period		
 ³ the mea baseline ⁴ 2 patien the regine ⁵ wide con 6 GRADE ⁷ odds rat ⁸ Karagöz ⁹ prospect ¹⁰ allocati availabu unclear ¹¹ unclear 	n age in the sur e characteristics ts, both in the su mens of antitub fidence interva- rule of thumb: - io and 95% con to et al, 2009 tive cohort on to surgery wa ility of drugs with if length of follo if groups were	gery group s; groups ap urgery grou erculosis cl ls <300 events fidence inte fidence inte as based or h adequate w-up was a comparable	ppeared to receive p, had comorbidit nemotherapy cont ervals calculated b n specific criteria (efficacy to cause appropriate e at baseline; uncl	e the same 'othe ies that might af ained, on averag by reviewer 'drug resistance rapid healing of ear if groups red	r care, althoug fect the choice ge, more drugs with high proba the bronchial s reived the same	h details provided a or management of a in the surgery grou ability of failure or re tump); blinding unc e 'other' care; uncle	re limited; unclear if treatment; the interve p (3.7 vs 2) elapse, sufficiently loo lear, though unlikely; ar if follow-up was co	groups were followed entions used varied by calized disease with a attempts do not appo omparable across the	l for an equa y more than adequate ca ear to have groups	al period the presenc rdiopulmona been made t	e or abser ry reserve o balance	ace of surgery and the confounders;
 ³ the mea baseline ⁴ 2 patien the regination ⁵ wide con 6 GRADE ⁷ odds rat ⁸ Karagöz ⁹ prospec ¹⁰ allocati availabi unclear ¹¹ unclear ¹² some propose ¹³ those the lower if ¹⁴ Kwon e 	n age in the sur e characteristics ts, both in the su mens of antitub nfidence interva. rule of thumb: - io and 95% con e et al, 2009 tive cohort on to surgery wa ility of drugs with if length of follo if groups were atients had com e than the prese hat received sur this confounding t al, 2008	gery group s; groups ap urgery grou erculosis cl ls <300 events fidence inte fidence inte as based or h adequate w-up was a comparable orbidities ti nce or abso gery were s	ppeared to receive p, had comorbidit hemotherapy cont ervals calculated b of specific criteria (efficacy to cause oppropriate at baseline; uncl hat may affect the ence of surgery - i selected due to a l	e the same 'othe ies that might af ained, on averag by reviewer 'drug resistance rapid healing of cear if groups red choice or mana in particular, the	r care, althoug fect the choice ge, more drugs with high probe the bronchial s reived the same gement of treat re is insufficient	h details provided a or management of a in the surgery grou ability of failure or re tump); blinding unc e 'other' care; uncle tment (12% had dia t detail around the p	re limited; unclear if treatment; the interve p (3.7 vs 2) elapse, sufficiently loo lear, though unlikely; ar if follow-up was co betes mellitus and 2 precise regimens of a	groups were followed entions used varied by calized disease with a attempts do not appo	l for an equa y more than adequate ca ear to have groups females; it otherapy us	al period the presenc rdiopulmona been made t is unclear if t red in each g	e or abser ry reserve o balance he 2 interv roup	and the confounders; rentions varied
 ³ the mea baseline ⁴ 2 patien the regine ⁵ wide con GRADE ⁶ Karagöz ⁹ prospec ¹⁰ allocati availabu unclear ¹¹ unclear ¹² some p by more ¹³ those the lower iff ¹⁴ Kwon e ¹⁵ retrospi ¹⁶ methood lesion); 	n age in the sur e characteristics ts, both in the su mens of antitub nfidence interva- rule of thumb: - io and 95% con e et al, 2009 tive cohort on to surgery wa lity of drugs with if length of follo if groups were atients had com e than the prese hat received sur this confounding t al, 2008 ective cohort of allocation to blinding unclea	gery group s; groups ap urgery grou erculosis cl ls <300 events fidence inte as based or h adequate w-up was a comparable norbidities ti noce or absu gery were s g factor we. treatment g r, though u	ppeared to receive p, had comorbiditi nemotherapy cont ervals calculated b n specific criteria (efficacy to cause appropriate at baseline; uncl hat may affect the ence of surgery - i selected due to a l re not present groups was related nlikely; attempts d	e the same 'othe ies that might af ained, on averag by reviewer 'drug resistance rapid healing of ear if groups red choice or mana in particular, the high likelihood o d to potential co. o not appear to	r care, althoug fect the choice ge, more drugs with high proba the bronchial s eived the same gement of treat re is insufficient f treatment failu founding facto have been mac	h details provided a or management of a in the surgery grou, ability of failure or re- tump); blinding uncl a 'other' care; uncle ment (12% had dia detail around the p ure or relapse; there rs (criteria for surge le to balance confo	re limited; unclear if treatment; the interve p (3.7 vs 2) elapse, sufficiently loo lear, though unlikely; ar if follow-up was co betes mellitus and 2 precise regimens of a fore it is likely that th ery: MDR-TB refracto unders	groups were followed entions used varied by calized disease with a attempts do not appe omparable across the 1.8% had COPD); no ntituberculosis chemi e reduced incidence ry to at least 6 month	I for an equa y more than adequate ca ear to have groups females; it otherapy us of treatmen as of medica	al period the presenc ordiopulmona been made t is unclear if t red in each g t failure in thu al treatment v	e or abser ry reserve o balance he 2 interv roup is group wo	and the confounders; entions varied ould be even ary localized
 ³ the mea baseline ⁴ 2 patien the regine ⁵ wide con 6 GRADE ⁶ GRADE ⁷ odds rate ⁸ Karagöz ⁹ prospection ¹⁰ allocatina ¹¹ unclear ¹² some p ¹³ those ti ¹⁴ Kwon e ¹⁵ retrosponie ¹⁶ methodo lesion); ¹⁷ unclear ¹⁸ some p ¹⁸ some p 	n age in the sur e characteristics ts, both in the su mens of antitub fidence interva- rule of thumb: - io and 95% con e et al, 2009 tive cohort on to surgery wa ility of drugs with if length of follo if groups were atients had com this confounding this confounding this confounding this confounding this confounding to fallocation to blinding unclea- if groups were atients had a co	gery group s; groups ap urgery grou erculosis cl ls <300 events fidence inte as based or h adequate w-up was a comparable norbidities th nce or abso g factor we treatment g r, though u comparable comparable	ppeared to receive p, had comorbiditi- nemotherapy conti- ervals calculated b n specific criteria (efficacy to cause appropriate e at baseline; uncl hat may affect the ence of surgery - i selected due to a l re not present groups was related nlikely; attempts d e at baseline; group for treatment con- hat might affect th	e the same 'othe ies that might af ained, on averag by reviewer 'drug resistance rapid healing of choice or mana in particular, the high likelihood o d to potential co o not appear to ups appeared to ppletion and ava e choice or man	r' care, althoug fect the choice ge, more drugs with high proba the bronchial s eived the same gement of treat re is insufficient f treatment failu founding facto have been mac receive the sam illability of outco agement of ant	h details provided a or management of a in the surgery grou, ability of failure or re- tump); blinding unc- te 'other' care; uncle 'ment (12% had dia ' detail around the p re or relapse; there rs (criteria for surge le to balance confor ne 'other' care, altho ome data ' ituberculosis treatn	re limited; unclear if treatment; the interver p (3.7 vs 2) elapse, sufficiently loo lear, though unlikely; ar if follow-up was co betes mellitus and 2 precise regimens of a fore it is likely that th ery: MDR-TB refracto unders ough details provided ment (15% diabetes n	groups were followed entions used varied by calized disease with a attempts do not appe omparable across the 1.8% had COPD); no ntituberculosis chemo e reduced incidence	I for an equa y more than adequate ca ear to have groups females; it otherapy us of treatmen as of medica if follow-up ver disease,	al period the presenc indiopulmona been made t is unclear if t ed in each g t failure in thi al treatment v was compara , 3% maligna	e or abser ry reserve o balance he 2 interv roup is group wo vith a prima able betwe incy); it is u	and the confounders; rentions varied ould be even ary localized en the groups unclear if the 2

			Quality asse	essment		No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	chemotherapy	Antituberculosis chemotherapy alone	Relative	Absolute	Quality	Importance

²¹ unclear if groups were comparable at baseline; groups appeared to receive the same 'other' care, although details provided are limited; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

²² some patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

²³ Törün et al, 2007

²⁴ allocation to surgery was based on specific criteria (resistance to a high number of drugs and therefore a high possibility of relapse or treatment failure; continued localised cavitary disease; destroyed lung, and only if they had relatively robust cardiopulmonary functions); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders

²⁵ unclear if groups were comparable at baseline; groups appeared to receive the same 'other' care, although details provided are limited; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

²⁶ 18.7 % of patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

²⁷ Kim et al, 2008

²⁸ unclear if method of allocation to treatment groups unrelated to potential confounding factors; blinding unclear, though unlikely; attempts do not appear to have been made in the study design or analysis to balance confounders

²⁹ unclear if groups were comparable at baseline; groups appeared to receive the same 'other' care, although details provided are limited; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

³⁰ 22.6% of patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

Cure

			Quality asse	essment			No of p	oatients	Ef	fect		
No of		Risk of						Antituberculosis chemotherapy	Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	plus surgery	alone	(95% CI)	Absolute	Quality	Importance

Cure (follow-up unclear; assessed with: number of patients to be considered a cure, defined as negative smear and culture throughout treatment for at least 18 months (or 24 months, in the absence of first line drugs) and if only 1 positive culture was reported during that time and there was no concomitant evidence of deterioration, a patient may still be considered cured, provided that this positive culture was followed by a minimum of 3 consecutive negative cultures)

and pool				eneedaare nega								
1 ¹	observational studies ²	very serious ³	serious ⁴	very serious⁵	very serious ^{6,7}	plausible confounding would change effect ⁸	31/35 (88.6%)	71/107 (66.4%)	OR 3.93 (1.29 to 11.99) ⁹	22 more per 100 (from 5 more to 30 more)	VERY LOW	
Cure (fol	low-up unclear.	assessed w	ith: number of pat	tients to achieve	a cure defined	as a patient who h	as completed treatm	ent and consistently h	had negative	e culture resi	ults (with a	at least 5
			months of treatme						aa nogaan			
1 ¹⁰	observational studies ¹¹	very serious ¹²	serious ¹³	very serious ¹⁴	serious ⁶	plausible confounding would change effect ¹⁵	26/35 (74.3%)	60/120 (50%)	OR 2.89 (1.25 to 6.68) ⁹	24 more per 100 (from 6 more to 37 more)	VERY LOW	
Cure (fol treatmen	• • •	assessed w	ith: number of pat	tients to achieve	a cure, defined	as patients who co	ompleted treatment a	nd were <i>M. tuberculo</i>	sis culture r	egative for t	he last 12	months of
1 ¹⁶	observational studies ¹¹	serious ¹⁷	serious ¹³	very serious ¹⁸	serious ⁶	none	1/19 (5.3%)	113/185 (61.1%)	OR 1.78 (0.62 to 5.17) ⁹	13 more per 100 (from 12	VERY LOW	

			Quality asso	essment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
										fewer to 28 more)		
Cure (foll	ow-up unclear;	assessed w	vith: of patients to	achieve a cure,	defined as com	pletion of treatmen	t and at least 5 conse	ecutive negative cultu	ures from sa		ted at leas	t 30 days apart
in the fina 1 ¹⁹	al 12 months)	: 20					55/00	400/400	00450	7		
1.2	observational studies ¹¹	serious20	serious ¹³	very serious ²¹	serious ⁶	none	55/66 (83.3%)	138/186 (74.2%)	OR 1.50 (0.64 to 3.46) ²²	7 more per 100 (from 9 fewer to 17 more)	VERY LOW	
unclear unclear some pa by more GRADE wide co those th confour odds ra ² Kwon e ¹ retrosp ² methoo lesion); ³ unclear	if length of follo if groups were of atients had come than the prese rule of thumb: indidence interva the ceived surg nding factor were to and 95% come tot al, 2008 ective cohort of allocation to blinding unclear if groups were	w-up was a comparable orbidities th nce or abse <300 events Is gery were s e not prese fidence inte treatment comparable	appropriate at baseline; uncle lat may affect the ence of surgery - i s elected due to a h nt ervals calculated b groups was relate nlikely; attempts d e at baseline; grou	ear if groups rece choice or manag n particular, ther igh likelihood of by reviewer d to potential con o not appear to l ups appeared to	eived the same lement of treatm e is insufficient treatment failur nfounding factor nave been mad received the sa	'other' care; unclea nent (12% had dial detail around the p re or relapse; there rs (criteria for surge te to balance confo me 'other' care, alt	lear, though unlikely; ar if follow-up was cou betes mellitus and 21 precise regimens of a fore it is likely that the fore it is likely that the ery: MDR-TB refracto unders though details provide	mparable across the .8% had COPD); no ntituberculosis chem e higher incidence of ry to at least 6 month	groups females; it is otherapy use cure in this ns of medica	s unclear if th ed in each g group would I treatment v	ne 2 interve roup be even h vith a prima	entions varied igher if this ary localized
 ¹⁴ some p interver ¹⁵ those t treatme ¹⁶ Leimar ¹⁷ unclear confour 	patients had a contions varied by that received sur- ent); therefore it a the et al, 2005 r if method of all aders; unclear if	omorbidity t more than gery were s is likely that ocation to t length of fo	the presence or a selected due to a t the higher incide reatment groups u blow-up was appro	e choice or man bsence of surger high likelihood of nce of cure in th unrelated to pote opriate	agement of ant y - in particular treatment failu is group would i ntial confoundir	ituberculosis treatn ; there is insufficier re (criteria for perfo be even higher if th ng factors; blinding	nent (15% diabetes n nt detail around the p orming surgery: MDR nis confounding factor unclear, though unlik	recise regimens of ai -TB was refractory to were not present xely; attempts do not	ntituberculos chemothera appear to ha	sis chemothe apy after at l ave been ma	erapy used east 6 mor de to bala	in each group hths of nce
surgery ¹⁹ Törün e	r - in particular, t et al, 2007	here is insu	ıfficient detail aroı	ind the precise r	egimens of anti	tuberculosis chemo	nent; it is unclear if th otherapy used in eacl e a high possibility of	h group	-			
destroy analysi	ed lung, and on s	ly if they ha	d relatively robust	t cardiopulmonai	y functions); bli	inding unclear, thou	ugh unlikely; attempts	appear to have bee	n made to b	alance confo	ounders in	the multivariate
surgery							eatment; it is unclear otherapy used in eacl		varied by m	nore than the	presence	or absence of

Treatment failure

			Quality asse	essment			No of p	atients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importanc
	n t failure (follow over at least a 3-			number of patien	ts to experience	e microbiological fa	ilure, defined as patie	ents who failed to ach	nieve three	consecutive	negative s	putum
1	observational studies ²	very serious ³	serious ⁴	serious ⁵	serious ⁶	plausible confounding would change effect ⁷	9/108 (8.3%)	16/54 (29.6%)	OR 0.22 (0.09 to 0.53) ⁸	21 fewer per 100 (from 11 fewer to 26 fewer)	VERY LOW	
reatmei ionths)	nt failure (follow	-up unclea	r; assessed with: r	number of patien	ts to be conside	ered a treatment fai	lure, defined as persi	stence of positive sm	near and cu	lture despite	treatment	for 18-24
9	observational studies ¹⁰	very serious ¹¹	serious ¹²	very serious ¹³	very serious ^{6,14}	none	1/35 (2.9%)	9/107 (8.4%)	OR 0.32 (0.04 to 2.62) ⁸	6 fewer per 100 (from 8 fewer to 11 more)	VERY LOW	
	nt failure (follow any 1 of the final			number of patien	ts to experience	e treatment failure,	defined as ≥2 positiv	e culture results reco	rded during	,	months or	a positive
15	observational studies ²	very serious ¹⁶	serious ¹⁷	very serious ¹⁸	serious ⁶	none	3/35 (8.6%)	19/120 (15.8%)	OR 0.50 (0.14 to 1.79) ⁸	7 fewer per 100 (from 13 fewer to 9 more)	VERY LOW	
							defined as patients w istently <i>M. tuberculos</i>					
19	observational studies ²			very serious ²¹		none	1/19 (5.3%)	28/185 (15.1%)	OR 0.31 (0.04 to 2.43) ⁸	10 fewer per 100 (from 14 fewer to 15 more)	VERY LOW	
			r; assessed with: r final 3 cultures we		ts to experience	e treatment failure,	defined as 2 or more	positive cultures am	ongst final {		ollected in t	the final 12
22	observational studies ²	,		very serious ²⁴	serious ⁶	none	2/66 (3%)	14/186 (7.5%)	OR 0.38 (0.08 to 1.74) ⁸	5 fewer per 100 (from 7 fewer to	VERY LOW	

² retrospective cohort

³ allocation to surgery was broadly based on potential confounding factors (a high likelihood of medical failure based on extensive drug resistance, localized cavitary disease within a lobe or total destruction of one lung, and predictably adequate postoperative lung function), although the authors also state that because of the retrospective nature of the study, there were no rigid criteria for selection or exclusion for surgery; blinding unclear, though unlikely; attempts were not made within the design or analysis to balance the groups for potential confounders

⁴ unclear if groups were comparable at baseline; unclear if the groups received the same care apart from the intervention(s) studied; unclear if follow-up was balanced between the groups; unclear of groups were comparable for treatment completion and availability of outcome data

⁵ it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

⁶ GRADE rule of thumb: <300 events

⁷ those that received surgery were selected due to a high likelihood of treatment failure; therefore it is likely that the reduced incidence of treatment failure in this group would be even lower if this

			Quality asse	essment			No of p	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
	nding factor we											
		nfidence int	ervals calculated b	y reviewer								
[°] Karago.	z et al, 2009											
	ctive cohort ion to surgery y	vas hased o	n specific criteria (drug resistance	with high proba	hility of failure or re	lapse, sufficiently loca	alized disease with a	idenuate cai	rdionulmona	nı reserve	and the
							ear, though unlikely; a					
	if length of foll			apia noaning or		anip), sintanig anon	our, though unintery, t				o balanco	comoundoro,
¹² unclea	r if groups were	, comparabl	e at baseline; uncl	ear if groups rec	eived the same	'other' care; unclea	ar if follow-up was coi	mparable across the	groups			
							betes mellitus and 21					entions varied
			ence of surgery - i	n particular, ther	e is insufficient	detail around the p	recise regimens of an	tituberculosis chemo	otherapy use	ed in each g	гоир	
	onfidence interv et al. 2008	/als										
	· ·	o treatment	arouns was related	d to notential co	ofounding factor	s (criteria for surge	ry: MDR-TB refractor	v to at least 6 month	s of medica	l treatment v	vith a nrim	ary localized
					0	e to balance confou	· ·		s of mealea		nur a prim	ary localized
							ough details provide	d are limited; unclea	r if follow-up	was compa	rable betw	een the
groups	unclear if grou	ips were coi	mparable for treatr	nent completion	and availability	of outcome data	. .			·		
			•		0		ent (15% diabetes m	· ·	· · · ·			
		more than	the presence or al	bsence of surger	ry - in particular,	there is insufficien	t detail around the pro	ecise regimens of an	tituberculos	is chemothe	rapy used	in each group
	ne et al, 2005 r if mothod of o	llocation to t	traatmant around i	unrolated to note	ntial confoundin	a faatara: blinding	unclear, though unlike	alu: attamata da natu	oppoor to be	wa haan ma	da ta hala	noo
			ollow-up was appro		nilai comountain	ig laciors, billiuling i	unciear, though unlike		appear to ne		ue lo bala	lice
					agement of anti	tuberculosis treatm	ent; it is unclear if the	e 2 interventions vari	ed by more	than the pre	sence or a	bsence of
							therapy used in each					
	et al, 2007				-							
²³ allocat	ion to surgery v	vaa haaad a		waalatawaa ta a k	and number of	drugs and therefore	- high measibility of	colonno or trootmont	failura: conf	inuad laaalig	ad an ita	v diagona
			n specific criteria (
destroy		nly if they ha	ad relatively robust	cardiopulmonar	y functions); bli	nding unclear, thou	gh unlikely; attempts atment; it is unclear i	do not appear to hav	/e been mad	de to balanc	e confound	lers

Adherence

			Quality ass	essment			No of p	atients	Ef	fect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative	Absolute	Quality	Importance		
Adheren	Adherence (follow-up unclear; assessed with: number of patients to complete the intended course of therapy)													
1 ¹	observational studies	very serious ²	serious ³	very serious ⁴	very serious ^{5,6}	none	1/3 (33.3%)	2/5 (40%)	OR 0.75 (0.04 to 14.97) ⁷	7 fewer per 100 (from 37 fewer to 51 more)	VERY LOW			

¹ Cameron & Harrison, 1997

² unclear if method of allocation was related to potential confounding factors; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate

³ the mean age in the surgery group was significantly older than in the group that received antituberculosis chemotherapy alone (41 vs 27 years); unclear if groups were comparable for other

	Quality assessment							atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		chemotherapy	Relative		Quality	Importance

baseline characteristics; groups appeared to received the same 'other' care, although details provided are limited; unclear if groups were followed for an equal period

⁴ 2 patients, both in the surgery group, had comorbidities that might effect the choice or management of treatment; the interventions used varied by more than the presence or absence of surgery - the regimens of antituberculosis chemotherapy contained, on average, more drugs in the surgery group (3.7 vs 2)

⁵ wide confidence intervals

⁶ GRADE rule of thumb: <300 events

⁷ odds ratio and 95% confidence intervals calculated by reviewer

Treatment default

			Quality asse	ssment			No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
Adheren	ce - default (foll	ow-up uncle	ear; assessed with	: number of pati	ents to be cons	idered a defaulter,	defined as failure to	complete treatment f	or any reas	on)		
1 ¹	observational studies ²	very serious ³	serious ⁴	very serious⁵	serious ⁶	none	1/35 (2.9%)	15/107 (14%)	OR 0.18 (0.02 to 1.42) ⁷	11 fewer per 100 (from 14 fewer to 5 more)	VERY LOW	
Adheren	ce - default (foll	ow-up uncle	ear; assessed with	: number of pati	ents to default	on treatment, define	ed as patients who in	terrupted treatment f	or 2 or more	e consecutive	e months)	
1 ⁸	observational studies ⁹	serious ¹⁰	serious ¹¹	very serious ¹²	serious ⁶	none	1/19 (5.3%)	25/185 (13.5%)	OR 0.36 (0.05 to 2.78) ⁷	8 fewer per 100 (from 13 fewer to 17 more)	VERY LOW	
Adheren	ce - incomplete	e treatment	(follow-up unclea	r; assessed with	number of pat	ients to experience	incomplete treatmen	nt, defined as treatme	ent interrupte	ed for 2 or m	ore consec	cutive months
for any re	eason)											
1 ¹³	observational studies ⁹	serious ¹⁴	serious ¹¹	very serious ¹⁵	serious ⁶	none	4/66 (6.1%)	21/186 (11.3%)	OR 0.51 (0.17 to 1.54) ⁷	5 fewer per 100 (from 9	VERY LOW	

¹ Karagöz et al, 2009

² prospective cohort

³ allocation to surgery was based on specific criteria (drug resistance with high probability of failure or relapse, sufficiently localized disease with adequate cardiopulmonary reserve and the availability of drugs with adequate efficacy to cause rapid healing of the bronchial stump); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate

fewer to 5 more)

⁴ unclear if groups were comparable at baseline; unclear if groups received the same 'other' care; unclear if follow-up was comparable across the groups

⁵ some patients had comorbidities that may affect the choice or management of treatment (12% had diabetes mellitus and 21.8% had COPD); no females; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

⁶ GRADE rule of thumb: <300 events

⁷ odds ratio and 95% confidence intervals calculated by reviewer

⁸ Leimane et al, 2005

⁹ retrospective cohort

¹⁰ unclear if method of allocation to treatment groups unrelated to potential confounding factors; blinding unclear, though unlikely; attempts do not appear to have been made to balance

	Quality assessment							oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		Relative (95% CI)	Absolute	Quality	Importance

confounders; unclear if length of follow-up was appropriate

¹¹ unclear if groups were comparable at baseline; groups appeared to received the same 'other' care, although details provided are limited; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

¹² some patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

¹³ Törün et al, 2007

¹⁴ allocation to surgery was based on specific criteria (resistance to a high number of drugs and therefore a high possibility of relapse or treatment failure; continued localised cavitary disease; destroyed lung, and only if they had relatively robust cardiopulmonary functions); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders

¹⁵ 18.7 % of patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group

Favourable response to treatment

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importan
						ients to experience	an initial favourable	response, defined as	patients wi	th at least th	ree consec	utive
•			od of at least 3 m		,							
1 ¹	observational studies ²	serious ³	serious⁴	very serious⁵	serious ⁶	plausible confounding would change effect ⁷	99/108 (91.7%)	38/54 (70.4%)	OR 4.23 (1.28 to 13.93) ⁸	21 more per 100 (from 5 more to 27 more)	VERY LOW	
	ble response to	treatment	(follow-up unclea	r; assessed with	: number of pat	ients to experience	a favourable outcom	e, defined as treatme	ent complet	ion or cure)		
1 ⁹	observational studies ²	very serious ¹⁰	serious ¹¹	very serious ¹²	serious ⁶	none	-	-	OR 1.24 (0.69 to 2.26)	-	VERY LOW	
			egression of ches				avourable clinical res e-negative sputum sp				s and symp	otoms
1 ¹³	observational studies	very serious ¹⁴	serious ¹⁵	very serious ¹⁶	very serious ^{6,17}	none	2/3 (66.7%)	4/5 (80%)	OR 0.50 (0.02 to 12.90) ¹⁸	13 fewer per 100 (from 73 fewer to 18 more)	VERY LOW	
				ears after treatr	ment initiation; a	assessed with: num	ber of patients to exp	perience treatment su	iccess, defi	ned as the su	um of cure,	treatment
	on, and short-ter								1			
1 ²⁰	observational studies ²	very serious ²¹	serious ²²	very serious ²³	very serious ^{6,17}	none	-	-	OR 3.87 (1.69 to 8.88) ²⁴	-	VERY LOW	
	ble response to	treatment	(follow-up unclea	r; assessed with	: number of pat	ients to achieve a f	avourable outcome, o	defined as cure or tre	atment con	pletion)		
1 ²⁵	observational studies ²	very serious ²⁶	serious ²²	very serious ²⁷	serious ⁶	plausible confounding would change effect ²⁸	31/35 (88.6%)	71/120 (59.2%)	OR 11.35 (3.02 to 42.74) ²⁴	35 more per 100 (from 22 more to 39 more)	VERY LOW	

³ allocation to surgery was broadly based on potential confounding factors (a high likelihood of medical failure based on extensive drug resistance, localized cavitary disease within a lobe or total destruction of one lung, and predictably adequate postoperative lung function), although the authors also state that because of the retrospective nature of the study, there were no rigid criteria for selection or exclusion for surgery; blinding unclear, though unlikely; a stepwise selection procedure was used to create a multiple predictor model for the incidence of favourable response ⁴ unclear if groups were comparable at baseline; unclear if the groups received the same care apart from the intervention(s) studied; unclear if follow-up was balanced between the groups;

unclear of groups were comparable for treatment completion and availability of outcome data

⁵ it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group; outcome is a substitute for outcomes of interest

⁶ GRADE rule of thumb: <300 events

⁷ those that received surgery were selected due to a high likelihood of treatment failure; therefore it is likely that the increased incidence of favourable response in this group would be even higher if this confounding factor were not present

⁸ a stepwise selection procedure was used to create a multiple predictor model for the incidence of favourable response

⁹ Keshajvee et al, 2008

¹⁰ unclear if method of allocation to treatment groups unrelated to potential confounding factors; blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate; 'favourable outcome' is defined as treatment completion or cure, but the definitions for treatment completion and cure are not provided

			Quality asse	ssment			No of p	oatients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importan
unclea groups it is un used in Camer unclea length the me baselin 2 patie vide co odds ra see ev Kim et unclea the mu unclea the mu unclea 22.6% surgery multive Kwon o methoo lesion), some p interve. group; those t	r if groups were ; unclear if group clear if the 2 into each group; 'fa on & Harrison, r if method of al of follow-up was ean age in the si e characteristic nts, both in the gimens of antitu onfidence intervatio and 95% co idence table in al, 2008 r if method of al ltivariate analysis et al, 2008 d of patients had / - in particular, ariate analysis et al, 2008 d of allocation to batients had a co ntions varied by substitute for ou that received su	ps compara erventions v avourable ou 1997 llocation was s appropriate urgery group surgery group surgery group uberculosis of vals onfidence int the appendiz llocation to the s were com a comparable ps were com a comorbidit there is insu	e at baseline; grou, ble for treatment c varied by more than itcome' is a compo- s related to potenti bowas significantly opeared to receive- up, had comorbidit chemotherapy con tervals calculated to x for full definition reatment groups u e at baseline; grou, mparable for treatm ity that might affect ifficient detail arou. groups was related fikely; attempts ap hat might affect the the presence or at selected due to a fi	ps appeared to i completion and a in the presence of posite of outcomes ial confounding f older than in the d the same 'othe ties that might ef tained, on avera by reviewer inrelated to poten ps appeared to in the choice or in nd the precise re of to potential cor- ppear to have be e choice or many psence of surger high likelihood of	received the sar vailability of out or absence of su s of interest actors; blinding group that rece r' care, althoug fect the choice ge, more drugs ntial confoundin received the sar and availability hanagement of antit of ounding factor agement of anti y - in particular, treatment failur	me 'other' care, alth come data irgery - in particular unclear, though un eived antituberculos h details provided a or management of in the surgery grou g factors; blinding u me 'other' care, alth of outcome data antituberculosis treat uberculosis chemo s (criteria for surge ance confounders i tuberculosis treatm there is insufficien re (criteria for perfo	nough details provide r, there is insufficient likely; attempts do no sis chemotherapy alo are limited; unclear if treatment; the interve up (3.7 vs 2); outcom unclear, though unlik nough details provide atment; it is unclear i therapy used in each therapy used in each ry: MDR-TB refractor in the multiple logistic rent (15% diabetes m t detail around the pr rming surgery: MDR-	d are limited; unclear detail around the pre of appear to have bee ne (41 vs 27 years); groups were followed entions used varied b e is a surrogate for ou ely; attempts appear d are limited; unclear f the 2 interventions v group; outcome is a cregression ellitus, 5% chronic liv ecise regimens of an TB was refractory to nfounding factor were	if follow-up cise regime en made to unclear if g d for an equ y more tha utcomes of to have bee to have bee to have bee to follow-up raried by m substitute is s of medica rer disease, tituberculos chemother	b was compa ens of antitut balance con roups were c ial period n the presen- interest en made to b b was compa ore than the for outcomes I treatment v 3% maligna sis chemothe apy after at l	rable betw perculosis of founders; i comparable ce or abset palance con rable betw presence of s of interest with a prima incy); it is u rapy used	een the chemothera unclear if e for other nce of surg nfounders in een the or absence t ary localize unclear if th in each

Poor response to treatment

			Quality asse	ssment			No of p	patients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importan
oor res	sponse to treatn	nent (follow-	-up unclear; asses	sed with: numbe	er of patients to	experience a poor	outcome, defined as	treatment failure, de	eath during t	reatment or	default)	
1 ¹	observational studies ²	serious ³	serious ⁴	very serious⁵	serious ⁶	none	8/37 (21.6%)	171/343 (49.9%)	OR 0.28 (0.12 to 0.62) ⁷	28 fewer per 100 (from 12 fewer to 39 fewer)	VERY LOW	
					1 · · · · ·		1	treatment failure, de	-			
1 ⁸	observational studies ⁹	very serious ¹⁰	serious ¹¹	very serious ¹²	serious ⁶	plausible confounding would change effect ¹³	4/13 (30.8%)	110/129 (85.3%)	OR 0.18 (0.04 to 0.78) ¹⁴	34 fewer per 100 (from 3 fewer to 66 fewer)	VERY LOW	
the final the first t	12 months or any reatment becaus	y 1 of the fin	al 3 cultures being ergence of MDR-t	g positive), relap uberculous bacil	se (defined as a li) or death)	a cured patient or a	patient who comple	s failure (defined as a ted therapy who resu	imed treatm	ent 16 mont	ns after cor	
1 ¹⁵	observational studies ⁹	very serious ¹⁶	very serious ¹⁷	very serious ¹⁸	serious ⁶	none	17/60 (28.3%)	48/137 (35%)	OR 0.73 (0.38 to 1.42) ¹⁹	7 fewer per 100 (from 18 fewer to 8 more)	VERY LOW	
Poor res	sponse to treatn	nent (follow-	-up unclear: asses	sed with: numbe	er of patients to	experience a long-	term poor outcome.	defined as death, tre	atment failu		lete treatm	ent)
1 ²⁰	observational studies ⁹	serious ²¹		very serious ²³	serious ⁶	none	11/66 (16.7%)	48/186 (25.8%)	OR 0.58 (0.28 to 1.19) ¹⁹	9 fewer per 100 (from 17 fewer to 3 more)	VERY LOW	,
² prospendic ³ decisio tolerate indepe ⁴ unclean groups	e resection and a ndent association r if groups were c comparable for t	localised le n of potentia comparable a treatment co	sion amenable to Il risk factors with J at baseline; unclea ompletion and ava	resection were r poor outcome; u ar if groups appe ilability of outcor	equired; blindin nclear if the len ared to receive ne data	g unclear, though u gth of follow-up wa d the same 'other'	Inlikely; a binary mul s appropriate care; unclear if the le	vas dependent upon tivariable logistic reg ength of follow-up wa s unclear if the 2 inter	ression moo s comparab	e sufficient p del was used le across the	to evaluate groups; ui	e the nclear if

⁵ some patients had comorbidities that may affect the choice or management of treatment (e.g. 9% had diabetes mellitus); it is unclear if the 2 interventions varied by more than the presence or absence of surgery; in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group; 'poor outcome' is a substitute outcome ⁶ GRADE rule of thumb: <300 events</p>

⁷ a binary multivariable logistic regression model was used to evaluate the independent association of potential risk factors with poor outcome

⁸ Jeon et al, 2009

⁹ retrospective cohort

¹⁰ allocation to surgery was based on specific criteria (surgical resection was considered for patients with localised cavitary lesions and anticipated adequate postoperative lung function, and for selected patients with bilateral lesions if medical treatment had failed or was expected to fail); blinding unclear, though unlikely; binary logistic regression analysis was performed; unclear if the length of follow-up was appropriate

¹¹ unclear if groups were comparable at baseline; unclear if groups appeared to received the same 'other' care; unclear if follow-up was comparable across the groups; unclear if groups comparable for treatment completion and availability of outcome data

¹² some patients had comorbidities that may affect the choice or management of treatment (15% had diabetes mellitus); it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group; 'poor outcome' is a substitute for outcomes of

	Quality assessment							oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance

interest

¹³ those that received surgery were selected due to a high likelihood of treatment failure or because they had already failed; therefore it is likely that the reduced incidence of poor outcome in this group would be even lower if this confounding factor were not present

¹⁴ binary logistic regression analysis with the backward elimination method was performed for variables with p < 0.2 in the univariate analysis, which included the use of surgery, and the Hosmer-Lemeshow test was used for testing the goodness-of-fit of the models

¹⁵ Kim et al, 2007

¹⁶ method of allocation to treatment groups related to potential confounding factors (criteria for surgery: MDR-TB refractory to at least 6 months of medical treatment with a primary localized lesion); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders; unclear if length of follow-up was appropriate

¹⁷ surgery was performed more frequently in patients with XDR-TB (p<0.001); unclear if groups received the same 'other' care; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

¹⁸ 34.1% of patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group; outcome is a substitute for outcomes of interest

¹⁹ odds ratio and 95% confidence intervals calculated by reviewer

²⁰ Törün et al, 2007

²¹ allocation to surgery was based on specific criteria (resistance to a high number of drugs and therefore a high possibility of relapse or treatment failure; continued localised cavitary disease; destroyed lung, and only if they had relatively robust cardiopulmonary functions); blinding unclear, though unlikely; attempts do not appear to have been made to balance confounders

²² unclear if groups were comparable at baseline; groups appeared to received the same 'other' care, although details provided are limited; unclear if follow-up was comparable between the groups; unclear if groups were comparable for treatment completion and availability of outcome data

²³ 18.7 % of patients had a comorbidity that might affect the choice or management of antituberculosis treatment; it is unclear if the 2 interventions varied by more than the presence or absence of surgery - in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group; outcome is a substitute for outcomes of interest

Adjunctive surgery in the treatment of active DRUG RESISTANT tuberculosis .11.9

Mortality – all-cause

Cure

Treatment failure

Poor response to treatment

A.12 RQ S

.12.1 Any resistance

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		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
London	0-14 years	Observational with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	234	1.0 (0.3 to 3.4)	VERY LOW
Date: 2004	15-29 years	analysis				no serious imprecision		1.0 (0.8 to 1.6)	
	≥60 years					no serious imprecision		0.6 (0.4 to 1.0)	
	reference: 30-59 years					-		-	

² Multivariate analysis used, but unclear which confounders were controlled for

		Quality assessmen	t				Number of	Summary of findings	
Study	•	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
³ Analyses not re	eported for a number	of variables recorded	and reported in popula	ation characteristics					

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

Abbreviations: CI, confidence interval; OR, odds ratio

Sex

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007	Male	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	234	1.0 (0.7 to 1.4)	VERY LOW
London Date: 2004	reference: multivariate female analysis Female Observationa				indirectness	imprecision		-	
Melzer, 2010	Female Observat	Observational with	very serious ^{1,2,3}	no serious	no serious	no serious	380	0.70 (0.33 to 1.49)	LOW
East London/ Essex Date: 2003-6	reference: male	multivariate analysis		inconsistency	indirectness	imprecision		-	
² Multivariate an	alysis used, but uncl	come measurement b ear which confounders	s were controlled for	lation characteristics					

Abbreviations: CI, confidence interval; OR, odds ratio

HIV status

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Melzer, 2010	HIV-positive	Observational with	very serious ^{1,2,3}	no serious	no serious	serious ⁵	380	1.93 (0.70 to 5.23)	VERY LOW
East London/ Essex Date: 2003-6	reference: HIV- negative	multivariate analysis		inconsistency	indirectness			-	
² Multivariate and ³ Analyses not re ⁴ Unclear if loss ⁵ Wide confidence	alysis used, but uncle eported for a number to follow-up sufficien	tly unrelated to key ch	were controlled for and reported in popul	ation characteristics					

Previous history of tuberculosis

		Quality assessmen	t	Inconsistency Indirectness Imprecision Number of patients Summary of findings Quality					
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Adjusted OR (95% CI)	Quality
Story, 2007	Previous	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	234	3.0 (1.9 to 4.9)	VERY LOW

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
London Date: 2004	history of tuberculosis	multivariate analysis			indirectness	imprecision			
	reference: no history of disease							-	
Melzer, 2010 East London/ Essex	Previous treatment of tuberculosis	Observational with multivariate analysis	h very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	serious⁵	380	1.53 (0.41 to 5.62)	VERY LOW
Date: 2003-6	reference: no history of treatment							-	
² Multivariate an ³ Analyses not r	nalysis used, but unc reported for a numbe	Itcome measurement to clear which confounder or of variables recorded ntly unrelated to key cl	rs were controlled for d and reported in popu	lation characteristics					

⁵ Wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio

Exposure

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Melzer, 2010 East London/ Essex Date: 2003-6	London/ exposure to drug mu resistant an	Observational with multivariate analysis	n very serious ^{1.2,3}	no serious inconsistency	no serious indirectness	serious ⁵	380	12.84 (0.68 to 240.2)	VERY LOW
	reference: no previous exposure to drug resistant tuberculosis							-	

² Multivariate analysis used, but unclear which confounders were controlled for

³ Analyses not reported for a number of variables recorded and reported in population characteristics

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

⁵ Wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio

Place of birth

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality

		Quality assessmer	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Melzer, 2010 East London/ Essex Date: 2003-6	Country of origin with high incidence of drug resistance	Observational with multivariate analysis	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	380	0.61 (0.25 to 1.47)	LOW
	reference: country of origin without high incidence of drug resistance		vith very serious ^{1.2.3} no serious					-	
Melzer, 2010 East London/ Essex Date: 2003-6	Date of arrival in the UK ≥2000 i.e. less than 3-6 years in the UK	Observational with multivariate analysis	with very serious ^{1.2,3} no serious inconsistency		no serious indirectness	no serious imprecision	380	0.71 (0.27 to 1.87)	LOW
2000 2000 0	reference: date of arrival in the UK <2000 i.e. more than 3-6 years in the UK						-		
² Multivariate an ³ Analyses not r	nalysis used, but uncl reported for a numbe	tcome measurement b lear which confounder r of variables recorded ntly unrelated to key ch	s were controlled for I and reported in popu	lation characteristics					

Abbreviations: CI, confidence interval; OR, odds ratio

Ethnicity

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007 London	South Asian	Observational with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	234	1.0 (0.6 to 1.6)	VERY LOW
Date: 2004	analysia					no serious imprecision		1.3 (0.8 to 2.0)	
				serious ⁵		3.0 (1.2 to 7.7)			
	Other					no serious imprecision		1.9 (1.0 to 3.4)	
	reference: white					-		-	

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³ Analyses not reported for a number of variables recorded and reported in population characteristics

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

⁵ Wide confidence interval

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Abbreviations: C	I, confidence interva	al; OR, odds ratio							

Imprisonment

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007	Prison	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	234	3.0 (1.7 to 5.5)	VERY LOW
London Date: 2004	reference: not in prison	multivariate analysis			indirectness	imprecision		-	
² Multivariate an ³ Analyses not re	alysis used, but uncl eported for a numbe	come measurement b ear which confounders of variables recorded tly unrelated to key ch	s were controlled for and reported in popul	ation characteristics					

Abbreviations: CI, confidence interval; OR, odds ratio

Homelessness

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007	Homeless	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	234	1.6 (1.1 to 2.2)	VERY LOW
London Date: 2004	reference: not homeless	multivariate analysis			indirectness	imprecision		-	
² Multivariate an ³ Analyses not re ⁴ Unclear if loss	alysis used, but uncl eported for a number	come measurement b ear which confounders of variables recorded thy unrelated to key ch al: OR odds ratio	were controlled for and reported in popul	ation characteristics					

.12.2 First-line drug resistance

Adherence

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003	Poor adherence	Matched case- control ¹ with	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	104	4.8 (1.6 to 14.4)	VERY LOW
Leicestershire	reference: no	multivariate						-	

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Data: 1993-8	evidence of poor adherence	analysis							
 ² Unclear if prog ³ Authors had to ⁴ Multivariate and ⁵ Wide confidence 	nostic factor and out rely on others' notes alysis used, but uncl	on ethnic group, gend come measurement b (potential for recall bi ear which confounders I; OR, odds ratio	linded ias)						

Previous history of tuberculosis

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003 Leicestershire	Previous history of tuberculosis	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	104	3.7 (1.2 to 11.8)	VERY LOW
Data: 1993-8	reference: no history of tuberculosis	analysis						-	
² Unclear if prog ³ Authors had to	nostic factor and out rely on others' notes	on ethnic group, gend tcome measurement b s (potential for recall b	blinded ias)						
⁴ Multivariate an	alysis used, but uncl	ear which confounder	s were controlled for						
⁵ Wide confiden	ce interval								
Abbreviations: C	CI, confidence interva	al; OR, odds ratio							

Site of disease

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003 Leicestershire	Extrapulmonary	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	104	No statistic provided Authors state that the effect was not significant	VERY LOW
Data: 1993-8	reference: pulmonary	analysis						-	
² Unclear if prog	nostic factor and out	on ethnic group, gend come measurement b s (potential for recall b	linded						
⁴ Multivariate an	alysis used, but uncl	ear which confounder	s were controlled for						

⁵ Insufficient data provided to assess imprecision

Abbreviations: CI, confidence interval; OR, odds ratio

Place of birth

		Quality assessmen	nt				Number of		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003 Leicestershire	Non-UK birth	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	104	No statistic provided Authors state that the effect was not significant	VERY LOW
Data: 1993-8	reference: UK birth	analysis						-	
² Unclear if prog	nostic factor and out	on ethnic group, gend tcome measurement t s (potential for recall b	blinded						
	alysis used, but uncl a provided to assess	ear which confounder s imprecision	s were controlled for						
Abbreviations: C	I, confidence interva	al; OR, odds ratio							

Foreign travel

		Quality assessmen	it				Number of	Summary of findings	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Pritchard, 2003 Leicestershire	Travel outside the UK	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	104	No statistic provided Authors state that the effect was not significant	VERY LOW
Data: 1993-8	reference: no travel outside the UK	analysis						-	
 ² Unclear if prog ³ Authors had to ⁴ Multivariate an 	gnostic factor and out o rely on others' note:	on ethnic group, gend tcome measurement b s (potential for recall b ear which confounders s imprecision	linded ias)						

Abbreviations: CI, confidence interval; OR, odds ratio

Time in the UK

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003 Leicestershire	Recent immigration to the UK	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ⁶	104	No statistic provided Authors state that the effect was not significant	VERY LOW
Data: 1993-8	reference: no recent immigration to the UK	analysis						-	

		Quality assessme	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
¹ Cases and c	ontrols were match	ed on ethnic group, geno	der and age group						
² Unclear if pr	ognostic factor and	outcome measurement	blinded						
³ Authors had	to rely on others' no	otes (potential for recall b	pias)						
⁴ Multivariate a	analysis used, but u	inclear which confounder	rs were controlled for						
⁵ Effect estimation	ate not reported								
⁶ Insufficient c	lata provided to ass	ess imprecision							
Abbreviations	: CI, confidence inte	erval; OR, odds ratio							

.12.3 Isoniazid resistance

Age

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients living	in London								
Kruijshaar, 2008 London Data: 1998 and 2005	Age (linear)	Observational with multivariate analysis	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	11 848	0.99 (0.98 to 0.99)	LOW
Maguire, 2011 London	0-14 years	Unmatched case- control with	very serious ^{1,2,7,8}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	0.30 (0.09 to 1.01)	LOW
Data: 1995 to the third	25-34 years	multivariate analysis				no serious imprecision		0.79 (0.52 to 1.20)	
2006	arter of 35-44 years					no serious imprecision		0.64 (0.41 to 1.00)	
	45-64 years					no serious imprecision		0.45 (0.27 to 0.74)	
	≥65 years					no serious imprecision		0.23 (0.10 to 0.51)	
	reference: 15-24 years					-		-	
Neely, 2009 London	≤24 years		ol with	serious ⁴	no serious indirectness	no serious imprecision	355	1.7 (0.5 to 6.3)	VERY LOW
Data: 2004	25-44 years					serious⁵		2.1 (0.6 to 7.7)	
	reference: ≥45 years					-		-	

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007 London (non-	0-14 years	Observational with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	129	0.8 (0.2 to 4.6)	VERY LOW
outbreak) Date: 2004	15-29 years	analysis				no serious imprecision		1.1 (0.7 to 1.7)	
	≥60 years					no serious imprecision		0.5 (0.3 to 1.2)	
	reference: 30-59 years					-		-	
Patients living	outside of London								
Kruijshaar, 2008 England, Wales and Northern Ireland, excluding London Data: 1998 and 2005	Age (linear)	Observational with multivariate analysis	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	16 633	0.99 (0.98 to 0.99)	LOW
Patients with n	no previous tubercu	losis							
French, 2008 England and	45-64 years	Unmatched case- control with multivariate	very serious ^{1,2,8,9}	no serious inconsistency	no serious indirectness	no serious imprecision	18005	0.70 (0.59 to 0.83)	LOW
Wales Data: 1999- 2005	≥65 years	analysis				no serious imprecision		0.34 (0.26 to 0.44)	
2003	reference: 15-44 years					-		-	
² Multivariate an ³ Analyses not r ⁴ Unclear if loss ⁵ Wide confiden ⁶ Loss to follow- ⁷ Approach to d ⁸ Cases and cor ⁹ A number of fa	alysis used, but uncl eported for all variab to follow-up sufficier ice interval up, its reasons and t rug susceptibility test ntrols unmatched	e univariate analyses v	s were controlled for rted in population cha naracteristics nose lost not reported		selective reporting)				

Sex

		Quality assessmen	t				Number of	Summary of findings	ł
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients living	in London								
Kruijshaar, 2008 London Data: 1998	Female reference: male	Observational with multivariate analysis	serious ¹	serious ^{5,6}	no serious indirectness	no serious imprecision	11 848	0.92 (0.79 to 1.08) -	LOW
and 2005 Maguire, 2011 London Data: 1995 to the third guarter of	Male reference: female	Unmatched case- control with multivariate analysis	very serious ^{1,2,7,8}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	1.34 (0.98 to 1.83) -	LOW
2006	lemale								
Neely, 2009	Male	Unmatched case-	very serious ^{1,2,3}	serious ⁴	no serious	serious ⁹	355	2.7 (1.1 to 6.6)	VERY LOW
London Data: 2004	reference: female	control with multivariate analysis			indirectness			-	
Story, 2007	Male	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	129	1.0 (0.7 to 1.6)	VERY LOW
London (non- outbreak) Date: 2004	reference: female	multivariate analysis			indirectness	imprecision		-	
Patients living	outside of London								
Kruijshaar, 2008 England, Wales and Northern	Female	Observational with multivariate analysis	serious ¹	serious ^{5,6}	no serious indirectness	no serious imprecision	16 633	0.81 (0.69 to 0.96)	LOW
Ireland, excluding London Data: 1998 and 2005	reference: male							-	
 ² Multivariate an ³ Analyses not re ⁴ Unclear if loss ⁵ Loss to follow- ⁶ Approach to du ⁷ Cases and cor ⁸ Some data col ⁹ Wide confidence 	alysis used, but uncl eported for a number to follow-up sufficien up, its reasons and t rug susceptibility test ntrols unmatched lected by questionna	aire (i.e. may be some	s were controlled for I and reported in popu haracteristics hose lost not reported	lation characteristics					

Exposure

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Degree of exp	osure to drug resist	ant tuberculosis							
Neely, 2009 London Data: 2004	Close reference: casual	Unmatched case- control with multivariate analysis	very serious ^{1,2,3}	serious ⁴	no serious indirectness	serious ⁵	355	6.2 (1.7 to 21.8) -	VERY LOW
Neely, 2009 London Data: 2004	Cases to whom contact was exposed: ≥2 reference: 1	Unmatched case- control with multivariate analysis	very serious ^{1.2.3}	serious ⁴	no serious indirectness	serious ⁵	355	3.1 (1.1 to 8.4)	VERY LOW
Exposure to s	mear-positive drug	resistant tuberculosi	S						
Neely, 2009 London Data: 2004	Exposure to cases with smear-positive drug resistant tuberculosis	h control with sitive multivariate stant analysis	Unmatched case- control with multivariate	ry serious ^{1,2,3} serious ⁴	no serious indirectness	serious⁵	355	2.2 (0.8 to 6.2)	VERY LOW
	reference: no exposure to smear-positive drug resistant tuberculosis							-	
 ² Multivariate a ³ Analyses not ⁴ Unclear if loss ⁵ Wide confider 	nalysis used, but unc reported for number o s to follow-up sufficier	ntly unrelated to key cl	s were controlled for whom contact expose	ed, which was record	ed and reported in pop	oulation characteristic	ŝ		

Previous history of tuberculosis

		Quality assessmen	t				Number of	Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality	
Patients living	in London									
Kruijshaar, 2008 London	Previous history of tuberculosis	Observational with multivariate analysis	serious ²	serious ^{6,7}	no serious indirectness	no serious imprecision	11 848	1.35 (1.02 to 1.78)	LOW	
Data: 1998 and 2005	reference: no history of tuberculosis	anaiysis							-	
Patients living	outside of London									
Kruijshaar,	Previous	Observational with	serious ²	serious ^{6,7}	no serious	no serious	16 633	1.80 (1.40 to 2.32)	LOW	

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
2008 England,	history of tuberculosis	multivariate analysis			indirectness	imprecision			
Wales and Northern Ireland, excluding London Data: 1998 and 2005	reference: no history of tuberculosis							-	
 ² Unclear if prog ³ Authors had to ⁴ Multivariate and ⁵ Wide confidence ⁶ Loss to follow-i ⁷ Approach to dr 	nostic factor and out rely on others' notes alysis used, but uncl ce interval	ing not reported	linded ias)						

Smear status

		Quality assessmer	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Smear-positive reference: smear-negative	Unmatched case- control with multivariate analysis	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	1.37 (0.98 to 1.93) -	LOW
Patients with p	revious tuberculos	is							
Conaty, 2004	Smear-positive	Unmatched case- control with multivariate analysis	very serious ^{1,6,7}	no serious	no serious	serious⁵	639	3.2 (1.1 to 9.2)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: smear-negative			inconsistency	indirectness			-	
Patients with n	o previous tubercu	losis							
Conaty, 2004	Smear-positive	Unmatched case-	very serious ^{1,6,7}	no serious	no serious	no serious	8762	1.1 (0.8 to 1.4)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: smear-negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
¹ Unclear if prog	gnostic factor and out	come measurement b	linded						
² Cases and co	ntrols unmatched								
³ Some data co	llected by questionna	ire (i.e. may be some	reliance on recall)						
⁴ Multivariate a	nalysis used, but unc	lear which confounder	s were controlled for						
⁵ Wide confider	nce interval								
⁶ Not all factors	that underwent univa	ariate analysis were er	tered into the multiva	iate analyses; unclear	how factors were sele	ected for the multivaria	te analyses		
7 Multivariate a	nalysis used, althoug	h effect estimates only	adjusted for age and	two periods of analysi	s (1993–1994 and 199	98–2000)			

Abbreviations: CI, confidence interval; OR, odds ratio

Site of disease

		Quality assessmen	nt				Number of	Summary of findings	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Patients living	in London								
Maguire, 2011 London	Extrapulmonary tuberculosis	Unmatched case- control with	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	1.52 (0.98 to 2.36)	LOW
Data: 1995 to the third quarter of 2006	reference: pulmonary tuberculosis	multivariate analysis						-	
Kruijshaar, 2008	Pulmonary tuberculosis	Observational with multivariate analysis	serious ¹	serious ^{5,6}	no serious indirectness	no serious imprecision	11 848	1.06 (0.89 to 1.25)	LOW
London Data: 1998 and 2005	reference: extrapulmonary tuberculosis	analysis						-	
Patients living	outside of London								
Kruijshaar, 2008	Pulmonary tuberculosis	Observational with multivariate	with serious ¹	serious ^{5,6}	no serious indirectness	no serious imprecision	16 633	0.82 (0.69 to 0.98)	LOW
England, Wales and Northern Ireland, excluding London Data: 1998 and 2005	reference: extrapulmonary tuberculosis	analysis						-	

⁴ Multivariate analysis used, but unclear which confounders were controlled for

⁵ Loss to follow-up, its reasons and the characteristics of those lost not reported

⁶ Approach to drug susceptibility testing not reported

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Abbreviations: C	I, confidence interva	l; OR, odds ratio							

HIV status

Patients with no pr Conaty, 2004 HI	Factor previous tubercu HIV-positive		Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Adjusted OR (95% CI)	Quality
Conaty, 2004 HI								Adjusted OR (95% CI)	Quality
	HV-positive								
	ni poolaro	Unmatched case-	very serious ^{1,2,3}	no serious	no serious	no serious	8762	1.3 (0.8 to 1.9)	LOW
Malaa	eference: HIV- negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
French, 2008 HI	HIV-positive	Unmatched case-	very serious ^{1,4,5,6}	no serious	no serious	no serious	18005	1.02 (0.80 to 1.30)	LOW
Walaa	eference: HIV- negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
Patients with previo	/ious tuberculos	is							
Conaty, 2004 HI	HIV-positive	Unmatched case-	very serious ^{1,2,3}	no serious	no serious	no serious	639	0.6 (0.1 to 4.6)	LOW
Walaa	eference: HIV- negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	

Abbreviations: CI, confidence interval; OR, odds ratio

Place of residence

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients with n	o previous tubercu	losis							
Conaty, 2004 England and	London residence	Unmatched case- control with	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	8762	1.4 (1.1 to 1.7)	LOW
Wales	reference: non-	multivariate						-	

		Quality assessment	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Data: 1993-4 and 1998- 2000	London residence	analysis							
French, 2008 England and	London residence	Unmatched case- control with	very serious ^{1,4,5,6}	no serious inconsistency	no serious indirectness	no serious imprecision	18005	1.52 (1.34 to 1.72)	LOW
Wales Data: 1999- 2005	reference: non- London residence	multivariate analysis						-	
Patients with p	revious tuberculos	sis							
Conaty, 2004 England and	London residence	Unmatched case- control with	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	639	1.8 (0.9 to 3.7)	LOW
Wales Data: 1993-4 and 1998- 2000	reference: non- London residence	multivariate analysis						-	
² Not all factors ³ Multivariate an	that underwent univ	tcome measurement t ariate analysis were e h effect estimates only	ntered into the multiva				ariate analyses		

⁵ Multivariate analysis used, although it was unclear which confounders were accounted for

⁶ A number of factors reported in the univariate analyses were not reported as multivariate analyses

Abbreviations: CI, confidence interval; OR, odds ratio

Place of birth

		Quality assessmen	nt				Number of	Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality	
Time in the UK	in patients with pr	evious tuberculosis								
Conaty, 2004 England and	In the UK <5 years	Unmatched case- control with	very serious ^{1,3,6}	no serious inconsistency	no serious indirectness	serious⁵	639	2.8 (0.8 to 9.7)	VERY LOW	
Wales Data: 1993-4	In the UK 5-9 years	multivariate analysis			serious⁵		5.3 (1.2 to 23.5)	VERY LOW		
and 1998- 2000	In the UK ≥10 years						no serious imprecision		0.9 (0.3 to 3.8)	LOW
	reference: born in the UK					-		-	-	
Time in the UK	in patients with no	previous tuberculos	sis							
Conaty, 2004 England and	In the UK <5 years	Unmatched case- control with	Unmatched case- very serious ^{1,3,6} control with multivariate	bus ^{1,3,6} no serious no serious inconsistency indirectness		no serious imprecision	8762	1.1 (0.8 to 1.5)	LOW	
Wales Data: 1993-4	In the UK 5-9 years	multivariate analysis			no serious imprecision		1.2 (0.8 to 1.7)	LOW		

and 1998- 2000 yea refe	the UK ≥10	Design	Risk of bias						
2000 yea			Trisk Of Dias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings Adjusted OR (95% CI)	Quality
	ears					no serious imprecision		0.9 (0.7 to 1.3)	LOW
in t	ference: born the UK					-		-	-
Time in the UK in pa	patients who have	e residence in Lond	on						
, ,	inear)	Observational with multivariate analysis	serious ¹	serious ^{7,8}	no serious indirectness	no serious imprecision	11 848	1.04 (1.00 to 1.07)	LOW
Time in the UK in pa	patients who have	e residence outside	of London						
	near)	Observational with multivariate analysis	serious ¹	serious ^{7,8}	no serious indirectness	no serious imprecision	16 633	1.01 (0.98 to 1.05)	LOW
Place of birth in pati	atients who have	residence in Londo	n						
2008 the	ne UK	Observational with multivariate	serious ¹	serious ^{7,8}	no serious indirectness	no serious imprecision	11 848	0.76 (0.60 to 0.95)	LOW
	eference: born the UK	analysis						-	
0 /		Unmatched case-	very serious ^{1,2,9,10}	no serious	no serious	no serious	18040	2.40 (1.68 to 3.43)	LOW
	terence: born	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
		Observational with	very serious ^{1,2,3}	serious ⁴	no serious	serious⁵	38	2.8 (1.1 to 7.0)	VERY LOW
	eterence: born utside of the	multivariate analysis			indirectness			-	
Place of birth in pati	atients who have	residence outside o	of London						
Kruijshaar, Bo	orn outside of	Observational with	serious ¹	serious ^{7,8}	no serious	no serious	16 633	1.49 (1.16 to 1.92)	LOW

		Quality assessment	nt			Number of	Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
2008	the UK	multivariate			indirectness	imprecision			
England, Wales and Northern Ireland, excluding London Data: 1998 and 2005	reference: born in the UK	analysis						-	
² Multivariate ana ³ Analyses not re ⁴ Unclear if loss t ⁵ Wide confidence ⁶ Multivariate ana ⁷ Loss to follow-u ⁸ Approach to dru ⁹ Cases and con	alysis used, but uncl ported for a number to follow-up sufficien ce interval alysis used, althoug up, its reasons and t ug susceptibility test trols unmatched	ntly unrelated to key ch h effect estimates only he characteristics of t	s were controlled for and reported in popul naracteristics adjusted for age and hose lost not reported		is (1993–1994 and 19	98–2000)			

Ethnicity

		Quality assessmen	it				Number of	Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality	
Kruijshaar, 2008	Black Caribbean	Observational with multivariate	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	11 848	2.93 (2.11 to 4.09)	LOW	
₋ondon Data: 1998	Black African	analysis				no serious imprecision		1.08 (0.80 to 1.45)	LOW	
and 2005	Black other					no serious imprecision		1.38 (0.75 to 2.55)	LOW	
	Indian, Pakistani, Bangladeshi						no serious imprecision		0.89 (0.66 to 1.19)	LOW
	Chinese					no serious imprecision		1.41 (0.75 to 2.64)	LOW	
	Other					no serious imprecision		1.04 (0.74 to 1.46)	LOW	
	reference: white					-		-	-	
Kruijshaar, 2008	Black Caribbean	Observational with multivariate	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	16 633	1.35 (0.77 to 2.36)	LOW	

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
England, Wales and Northern	Black African	analysis				no serious imprecision		0.99 (0.68 to 1.43)	LOW
Ireland, excluding	Black other					no serious imprecision		0.99 (0.30 to 3.28)	LOW
London Data: 1998 and 2005	Indian, Pakistani, Bangladeshi					no serious imprecision		1.26 (0.94 to 1.69)	LOW
	Chinese					no serious imprecision		1.71 (0.99 to 2.95)	LOW
	Other					no serious imprecision		1.65 (1.11 to 2.44)	LOW
	reference: white					-		-	-
Maguire, 2011 London	Black Caribbean	Unmatched case- control with	very serious ^{1,2,8,9}	no serious inconsistency	no serious indirectness	serious ⁵	18040	12.52 (7.69 to 20.37)	VERY LOW
Data: 1995 to	Black (other)	multivariate analysis				serious ⁵		3.29 (1.35 to 8.02)	VERY LOW
the third quarter of 2006	White	analysis				no serious imprecision		2.94 (1.79 to 4.83)	LOW
	Indian subcontinent					no serious imprecision		0.57 (0.30 to 1.10)	LOW
	Chinese						serious ⁵		0.68 (0.09 to 5.05)
	Other					no serious imprecision		1.210 (0.67 to 2.19)	LOW
	reference: Black African					-		-	-
Patients with p	revious tuberculos	sis							
Conaty, 2004 England and	Indian subcontinent	Unmatched case- control with	very serious ^{1,2,10}	no serious inconsistency	no serious indirectness	no serious imprecision	639	1.2 (0.4 to 3.7)	LOW
Wales Data: 1993-4	Black African	multivariate analysis				no serious imprecision		0.9 (0.2 to 3.8)	LOW
and 1998- 2000	Other					no serious imprecision		0.5 (0.1 to 2.6)	LOW
	reference: white					-		-	-
Story, 2007	South Asian	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	serious ⁵	38	1.1 (0.2 to 6.7)	VERY LOW
ondon	Black African	multivariate			indirectness			0.8 (0.1 to 7.2)	VERY LOV
outbreak) Date: 2004	() Black African analysis					9.7 (2.6 to (35.4)	VERY LOV		
	Other							6.1 (1.6 to 23.3)	VERY LOW
	reference: White						-	-	

		Quality assessmer	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007	South Asian	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	serious ⁵	129	1.0 (0.5 to 2.1)	VERY LOW
London (non- outbreak)	Black African	multivariate analysis			indirectness			1.4 (0.7 to 2.6)	VERY LOW
Date: 2004	Black Caribbean	analyere						1.6 (0.3 to 10.2)	VERY LOW
	Other							2.5 (0.9 to 7.1)	VERY LOW
	reference: White							-	-
Patients with r	no previous tubercu	llosis							
Conaty, 2004 England and	Indian subcontinent	Unmatched case- control with	very serious ^{1,2,10}	no serious inconsistency	no serious indirectness	no serious imprecision	8762	1.6 (1.2 to 2.1)	LOW
Wales Data: 1993-4	Black African	multivariate analysis				no serious imprecision		1.7 (1.2 to 2.4)	LOW
and 1998- 2000	Other					no serious imprecision		Adjusted OR (95% Cl) 1.0 (0.5 to 2.1) 1.4 (0.7 to 2.6) 1.6 (0.3 to 10.2) 2.5 (0.9 to 7.1) - 1.6 (1.2 to 2.1)	LOW
	reference: white					-			-
French, 2008 England and	Black Caribbean	Unmatched case- control with	very serious ^{1,2,8,11}	ery serious ^{1,2,8,11} no serious inconsistency		no serious imprecision	18005	Adjusted OR (95% Cl) 1.0 (0.5 to 2.1) 1.4 (0.7 to 2.6) 1.6 (0.3 to 10.2) 2.5 (0.9 to 7.1) - 1.6 (1.2 to 2.1) 1.7 (1.2 to 2.4) 1.9 (1.3 to 2.8) - 3.11 (2.36 to 4.08) 1.22 (1.00 to 1.50) 1.18 (0.99 to 1.42)	LOW
Wales Data: 1999-	Black African	multivariate analysis				no serious imprecision			LOW
2005	Indian/ Pakistani/ Bangladeshi					no serious imprecision		1.18 (0.99 to 1.42)	LOW
	Other					no serious imprecision		1.40 (1.12 to 1.76)	LOW
	reference: white					-		-	-
² Multivariate an ³ Analyses not r	nalysis used, but uncl reported for a numbe s to follow-up sufficier	tcome measurement b lear which confounders r of variables recorded ntly unrelated to key ch	s were controlled for I and reported in popu	lation characteristics					

⁶ Loss to follow-up, its reasons and the characteristics of those lost not reported

⁷ Approach to drug susceptibility testing not reported

⁸ Cases and controls unmatched

⁹ Some data collected by questionnaire (i.e. may be some reliance on recall)

¹⁰ Multivariate analysis used, although effect estimates only adjusted for age and two periods of analysis (1993–1994 and 1998–2000)

¹¹ A number of factors reported in the univariate analyses were not reported as multivariate analyses

Abbreviations: CI, confidence interval; OR, odds ratio

Employment

Study Factor Quality assessment Quality assessment Quality
--

		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Healthcare									
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Healthcare profession reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	Unmatched case- control with multivariate analysis	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	1.53 (0.67 to 3.51) -	LOW
Education									
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Educational profession reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	Unmatched case- control with multivariate analysis	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	1.22 (0.67 to 2.23) -	LOW
Drug dealer/ se	ex worker								
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Drug dealer/ sex worker reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	Unmatched case- control with multivariate analysis	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	serious⁵	18040	187.07 (28.40 to 1232.35) -	VERY LOW
Unemployed									
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Unemployed reference: other (not: prisoner, healthcare, unemployed, asylum seeker/	Unmatched case- control with multivariate analysis	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	18040	4.09 (2.97 to 5.63) -	LOW

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
	refugee, drug dealer/sex worker, educational, retired)								
Retired									
Maguire, 2011	Retired	Unmatched case-	very serious ^{1,2,3,4}	no serious	no serious	no serious	18040	1.69 (0.71 to 4.06)	LOW
London Data: 1995 to the third quarter of 2006	reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
 ² Cases and cor ³ Some data col ⁴ Multivariate an ⁵ Wide confiden 	ntrols unmatched lected by questionna nalysis used, but unc	toome measurement b lire (i.e. may be some lear which confounder	reliance on recall)						

Drug use

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007 London	Problem drug use	multivariate	multivariate indirectness		serious⁵	38	38 3.5 (1.6 to 7.7)	VERY LOW	
(outbreak) Date: 2004	reference: no problem drug use	analysis						-	
• •	•	tcome measurement b ear which confounders							

³Analyses not reported for a number of variables recorded and reported in population characteristics

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

⁵ Wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio

Asylum seekers/refugee

_		V				
	Study	Factor	Quality assessment	Number of	Summary of findings	Quality

		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Maguire, 2011 London	Asylum seeker/ refugee	Unmatched case- control with	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	serious ⁵	18040	8.09 (1.02 to 64.41)	VERY LOW
Data: 1995 to the third quarter of 2006	reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	multivariate analysis						-	
		come measurement b	linded						
	ntrols unmatched								
³ Some data col	lected by questionna	ire (i.e. may be some	reliance on recall)						
⁴ Multivariate an	alysis used, but unc	lear which confounder	s were controlled for						
⁵ Wide confiden	ce interval								
Abbreviations: C	CI, confidence interva	al; OR, odds ratio							

Imprisonment

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Maguire, 2011 London Data: 1995 to the third quarter of 2006	Imprisonment reference: other (not: prisoner, healthcare, unemployed, asylum seeker/ refugee, drug dealer/sex worker, educational, retired)	Unmatched case- control with multivariate analysis	very serious ^{1,2,6,7}	no serious inconsistency	no serious indirectness	serious⁵	18040	20.21 (6.75 to 60.56) -	VERY LOW
Story, 2007	Imprisonment	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	serious⁵	38	10.3 (4.0 to 26.5)	VERY LOW
London (outbreak) Date: 2004	reference: not being imprisoned	multivariate analysis			indirectness			-	

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³ Analyses not reported for a number of variables recorded and reported in population characteristics

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

⁵ Wide confidence interval

⁶ Cases and controls unmatched

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
⁷ Some data	collected by questionna	aire (i.e. may be some	reliance on recall)						
Abbreviation	ns: CL confidence interv	al [.] OR odds ratio							

Homelessness

	Quality assessmen	t				Number of		
Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Hostel/street homeless	Observational with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	129	2.0 (0.9 to 4.5)	VERY LOW
reference: not homeless	analysis						-	
alysis used, but uncl	ear which confounders	s were controlled for						
	Hostel/street homeless reference: not homeless nostic factor and out alysis used, but uncl	Factor Design Hostel/street homeless Observational with multivariate analysis reference: not homeless on thomeless nostic factor and outcome measurement b alysis used, but unclear which confounders	Hostel/street homeless Observational with multivariate analysis very serious ^{1,2,3} reference: not homeless Observational with multivariate analysis very serious ^{1,2,3} nostic factor and outcome measurement blinded alysis used, but unclear which confounders were controlled for	FactorDesignRisk of biasInconsistencyHostel/street homelessObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ reference: not homelessoutcome measurement blindedserious ⁴	FactorDesignRisk of biasInconsistencyIndirectnessHostel/street homelessObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessreference: not homelesson outcome measurement blinded alysis used, but unclear which confounders were controlled forserious ⁴ no serious indirectness	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionHostel/street homelessObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessno serious imprecisionreference: not homelessObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessnostic factor and outcome measurement blinded alysis used, but unclear which confounders were controlled for	Factor Design Risk of bias Inconsistency Indirectness Imprecision patients Hostel/street homeless Observational with multivariate analysis very serious ^{1,2,3} serious ⁴ no serious indirectness no serious imprecision 129 nostic factor and outcome measurement blinded alysis used, but unclear which confounders were controlled for serious ⁴	Factor Design Risk of bias Inconsistency Indirectness Imprecision Patients Adjusted OR (95% CI) Hostel/street homeless Observational with multivariate analysis very serious ^{1,2,3} serious ⁴ no serious indirectness no serious imprecision 129 2.0 (0.9 to 4.5) nostic factor and outcome measurement blinded alysis used, but unclear which confounders were controlled for - -

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

Abbreviations: CI, confidence interval; OR, odds ratio

.12.4 Rifampicin resistance

Age

		Quality assessmen	t				Number of	,	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008 England, Wales and Northern Ireland Data: 1998 and 2005	Age (linear)	Observational with multivariate analysis	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	28481	0.98 (0.97 to 0.99)	LOW
² Loss to follow ³ Approach to d	5	• •							

Sex

		Quality assessmen	t				Number of	Summary of findings	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Kruijshaar,	Female	Observational with	serious ¹	serious ^{2,3}	no serious	no serious	28447	0.83 (0.64 to 1.08)	LOW
2008 England, Wales and Northern Ireland Data: 1998 and 2005	reference: male	multivariate analysis				imprecision		-	
² Loss to follow ³ Approach to d	•	• •							

Previous history of tuberculosis

		Quality assessmen	nt				Number of	Summary of findings	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Kruijshaar, 2008 England,	Previous history of tuberculosis	Observational with multivariate analysis	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	22671	4.72 (3.50 to 6.35)	LOW
Wales and Northern Ireland Data: 1998 and 2005	reference: no history of tuberculosis							-	
² Loss to follow ³ Approach to c	•	• ·							

Site of disease

		Quality assessmen	ıt			Number of	Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008	Pulmonary	Observational with multivariate	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	28341	1.48 (1.10 to 1.98)	LOW
England, Wales and Northern Ireland Data: 1998	reference: extrapulmonary	analysis						-	

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
and 2005									
¹ Unclear if pro	gnostic factor and ou	utcome measurement b	blinded						
² Loss to follow	v-up, its reasons and	the characteristics of t	hose lost not reported						
³ Approach to	drug susceptibility tes	sting not reported							
Abbroviationa	CL confidence inter	al: OB adda ratio							

Abbreviations: CI, confidence interval; OR, odds ratio

Place of residence

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar,	London	Observational with	serious ¹	serious ^{2,3}	no serious	no serious	28485	0.81 (0.62 to 1.05)	LOW
2008 England, Wales and Northern Ireland Data: 1998 and 2005	reference: Outside London	multivariate analysis			indirectness	imprecision		-	
² Loss to follow- ³ Approach to d	•	•							

Place of birth

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Place of birth									
Kruijshaar, 2008	Not born in the UK	Observational with multivariate	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	25557	1.88 (1.24 to 2.86)	LOW
England, Wales and Northern Ireland Data: 1998 and 2005	reference: born in the UK	analysis						-	
Time in the UK	Σ.								
Kruijshaar, 2008 England, Wales and Northern	Years in the UK (linear)	Observational with multivariate analysis	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	28485	1.03 (0.98 to 1.09)	LOW

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Ireland									
Data: 1998 and 2005									
		come measurement b he characteristics of th							
³ Approach to di	rug susceptibility test	ing not reported							
Abbreviations: C	CI, confidence interva	al; OR, odds ratio							

Ethnicity

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008	Black Caribbean	Observational with multivariate	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	27257	1.28 (0.59 to 2.79)	LOW
England, Wales and Northern	Black African	analysis				no serious imprecision		0.98 (0.59 to 1.64)	LOW
Ireland	Black other					serious ⁴		1.87 (0.69 to 5.06)	VERY LOW
Data: 1998 and 2005	Indian, Pakistani, Bangladeshi					no serious imprecision		0.94 (0.59 to 1.50)	LOW
	Chinese					no serious imprecision		0.83 (0.28 to 2.45)	LOW
	Other					no serious imprecision		0.97 (0.54 to 1.75)	LOW
	reference: white					-		-	-

¹ Unclear if prognostic factor and outcome measurement blinded

² Loss to follow-up, its reasons and the characteristics of those lost not reported

³ Approach to drug susceptibility testing not reported

⁴ Wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio

.12.5 Multidrug resistance

Age

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008 England, Wales and Northern Ireland Data: 1998 and 2005	Age (linear)	Observational with multivariate analysis	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	28481	0.98 (0.59 to 1.08)	LOW
Patients with r	no previous tubercu	llosis							
French, 2008 England and	45-64 years	Unmatched case- control with	very serious ^{1,2,3,4}	no serious inconsistency	no serious indirectness	no serious imprecision	16935	0.52 (0.27 to 0.99)	LOW
Wales	≥65 years	multivariate analysis				serious ⁵		0.35 (0.14 to 0.90)	VERY LOW
Data: 1999- 2005	reference: 15-44 years					-		-	-
¹ Unclear if prog	gnostic factor and ou	tcome measurement b	blinded						
		lear which confounder	s were controlled for						
	ntrols unmatched								
	•	e univariate analyses v	vere not reported as n	nultivariate analyses					
⁵ Wide confiden									
		he characteristics of the	nose lost not reported						
••	Irug susceptibility tes	• •							
Abbreviations: (CI, confidence interva	al; OR, odds ratio							

Sex

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar,	Female	Observational with	serious ¹	serious ^{2,3}	no serious	no serious	28447	0.80 (0.59 to 1.08)	LOW
2008 England, Wales and Northern Ireland Data: 1998 and 2005	reference: male	multivariate analysis			indirectness	imprecision		-	

¹ Unclear if prognostic factor and outcome measurement blinded

² Loss to follow-up, its reasons and the characteristics of those lost not reported

³ Approach to drug susceptibility testing not reported

Abbreviations: CI, confidence interval; OR, odds ratio

Previous history of tuberculosis

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008	Previous history of tuberculosis	Observational with multivariate	serious ²	serious ^{6,7}	no serious indirectness	no serious imprecision	28485	1.04 (0.76 to 1.42)	LOW
England, Wales and Northern Ireland Data: 1998 and 2005	reference: no history of tuberculosis	analysis						-	
 ² Unclear if prog ³ Authors had to ⁴ Multivariate an ⁵ Wide confident ⁶ Loss to follow- ⁷ Approach to data 	nostic factor and out rely on others' notes alysis used, but uncl ce interval	ing not reported	linded ias)						

Smear status

		Quality assessmen	nt				Number of	F Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients with p	revious tuberculos	is							
Conaty, 2004	Smear-positive	Unmatched case-	very serious ^{1,3,4}	no serious	no serious	serious ²	630	5.9 (1.8 to 19.0)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: smear-negative	control with multivariate analysis		inconsistency	indirectness			-	
Patients with n	o previous tubercu	losis							
Conaty, 2004	Smear-positive	Unmatched case-	very serious ^{1,6,7}	no serious	no serious	no serious	8210	1.4 (0.7 to 2.5)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: smear-negative	Unmatched case- control with multivariate analysis	with inconsistency indirectness riate	imprecision		-			

¹ Unclear if prognostic factor and outcome measurement blinded

² Wide confidence interval

³ Not all factors that underwent univariate analysis were entered into the multivariate analyses; unclear how factors were selected for the multivariate analyses

⁴ Multivariate analysis used, although effect estimates only adjusted for age and two periods of analysis (1993–1994 and 1998–2000)

Abbreviations: CI, confidence interval; OR, odds ratio

Site of disease

		Quality assessmen	t		Number of	Summary of findings			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008	Pulmonary tuberculosis	Observational with multivariate	serious ¹	serious ^{2,3}	no serious indirectness	no serious imprecision	28341	1.40 (1.00 to 1.96)	LOW
England, Wales and Northern Ireland	reference: extrapulmonary tuberculosis	analysis						-	
Data: 1998 and 2005									
		come measurement b							
	• •	he characteristics of th	lose lost not reported						
••	rug susceptibility test	• •							

HIV status

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients with n	o previous tubercu	losis							
Conaty, 2004	HIV-positive	Unmatched case-	very serious ^{1,2,3}	no serious	no serious	serious ⁷	662	2.5 (1.2 to 5.2)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: HIV- negative	control with multivariate analysis		inconsistency	indirectness			-	
French, 2008	HIV-positive	Unmatched case-	very serious ^{1,4,5,6}	no serious	no serious	no serious	16935	0.91 (0.47 to 1.76)	LOW
England and Wales Data: 1999- 2005	reference: HIV- negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
Patients with p	revious tuberculos	is							
Conaty, 2004	HIV-positive	Unmatched case-	very serious ^{1,2,3}	no serious	no serious	serious ⁷	8210	2.8 (0.6 to 11.9)	LOW
England and Wales Data: 1993-4 and 1998- 2000	reference: HIV- negative	eference: HIV- control with	multivariate				-		

¹ Unclear if prognostic factor and outcome measurement blinded

² Not all factors that underwent univariate analysis were entered into the multivariate analyses; unclear how factors were selected for the multivariate analyses

³ Multivariate analysis used, although effect estimates only adjusted for age and two periods of analysis (1993-4 and 1998-2000)

⁴ Cases and controls unmatched

		Quality assessme	nt			Number of	Summary of findings			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality	
⁵ Multivariate	e analysis used, althoug	gh it was unclear which	confounders were ac	counted for						
⁶ A number	⁶ A number of factors reported in the univariate analyses were not reported as multivariate analyses									

Abbreviations: CI, confidence interval; OR, odds ratio

Place of residence

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients with n	o previous tubercu	losis							
Conaty, 2004 England and	London residence	Unmatched case- control with	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	662	2.0 (1.2 to 3.3)	LOW
Wales Data: 1993-4 and 1998- 2000	reference: non- London residence	multivariate analysis						-	
Patients with p	revious tuberculos	is							
Conaty, 2004 England and	London residence	Unmatched case- control with	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	8210	1.2 (0.6 to 2.4)	LOW
Wales Data: 1993-4 and 1998- 2000	residence control with reference: non- London residence						-		
² Not all factors	that underwent univa	•	linded ntered into the multival adjusted for age and	•			ate analyses		

Abbreviations: CI, confidence interval; OR, odds ratio

Place of birth

		Quality assessmen	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Time in the UK									
Kruijshaar, 2008 England, Wales and Northern Ireland Data: 1998 and 2005	Years in the UK (linear)	Observational with multivariate analysis	serious ¹	serious ^{4,5}	no serious indirectness	no serious imprecision	25557	1.62 (0.99 to 2.66)	LOW
Time in the UK	in patients with pro	evious tuberculosis							

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Conaty, 2004 England and	In the UK <5 years	Unmatched case- control with	very serious ^{1,2,6}	no serious inconsistency	no serious indirectness	serious ³	8210	5.8 (1.8 to 18.5)	VERY LOW
Wales Data: 1993-4	In the UK 5-9 years	multivariate analysis				serious ³		2.2 (0.4 to 11.6)	VERY LOW
and 1998- 2000	In the UK ≥10 years					serious ³		1.7 (0.4 to 6.9)	LOW
	reference: born in the UK					-		-	-
Time in the UK	in patients with no	previous tuberculos	sis						
Conaty, 2004 England and	In the UK <5 years	Unmatched case- control with	very serious ^{1,2,6}	no serious inconsistency	no serious indirectness	serious ³	630	3.2 (1.4 to 7.4)	LOW
Wales Data: 1993-4	In the UK 5-9 : 1993-4 years 1998- In the UK >10	multivariate analysis				serious ³		3.0 (1.1 to 8.5)	LOW
and 1998-	In the UK ≥10 years					no serious imprecision		1.2 (0.4 to 3.7)	LOW
	reference: born in the UK					-		-	-
Place of birth									
Kruijshaar, 2008	Born outside of the UK	Observational with multivariate	serious ¹	serious ^{4,5}	no serious indirectness	no serious imprecision	25557	1.01 (0.95 to 1.08)	LOW
England, Wales and Northern Ireland Data: 1998 and 2005	reference: born in the UK	analysis						-	
 ² Analyses not re ³ Wide confiden ⁴ Loss to follow- ⁵ Approach to de 	eported for a numbe ce interval up, its reasons and rug susceptibility tes	tcome measurement to r of variables recorded the characteristics of to ting not reported h effect estimates only	l and reported in popu hose lost not reported	I		1998–2000)			

Abbreviations: CI, confidence interval; OR, odds ratio

Ethnicity

		Quality assessmen	t		Number of	Summary of findings			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Kruijshaar, 2008	Black Caribbean	Observational with multivariate	serious ¹	serious ^{6,7}	no serious indirectness	no serious imprecision	27257	1.01 (0.30 to 3.43)	LOW

		Quality assessme	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
England, Wales and	Black African	analysis				no serious imprecision		1.77 (0.92 to 3.41)	LOW
Northern Ireland Data:	Black other					serious⁵		2.44 (0.68 to 8.81)	VERY LOW
1998 and 2005	Indian, Pakistani, Bangladeshi					no serious imprecision		1.63 (0.91 to 2.95)	LOW
	Chinese					no serious imprecision		1.77 (0.56 to 5.54)	LOW
	Other					no serious imprecision		1.32 (0.62 to 2.84)	LOW
	reference: white					-		-	-
Patients with p	previous tuberculos	sis							
Conaty, 2004 England and	Indian subcontinent	Unmatched case- control with	very serious ^{1,2,10}	no serious inconsistency	no serious indirectness	serious⁵	8210	5.8 (1.8 to 18.5)	VERY LOW
Wales	Black African	multivariate analysis				serious⁵		2.2 (0.4 to 11.6)	VERY LOW
Data: 1993-4 and 1998-	1993-4 Other	analysis				serious⁵		1.7 (0.4 to 6.9)	VERY LOW
2000	reference: white					-		-	-
Story, 2007 London	South Asian	Observational with multivariate analysis	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	1540	1.6 (0.8 to 3.0)	LOW
Date: 2004	Black African					no serious imprecision		2.5 (1.2 to 5.7)	LOW
	Black Caribbean					serious⁵		1.6 (0.3 to 10.2)	VERY LOW
	Other					serious⁵		2.5 (0.9 to 7.1)	VERY LOW
	reference: White					-		-	-
Patients with n	no previous tubercu	Ilosis							
Conaty, 2004 England and	Indian subcontinent	Unmatched case- control with	very serious ^{1,2,10}	no serious inconsistency	no serious indirectness	no serious imprecision	630	0.8 (0.4 to 1.5)	LOW
Wales Data: 1993-4	Black African	multivariate analysis				no serious imprecision		0.6 (0.3 to 1.2)	LOW
and 1998- 2000	Other					serious ⁵		0.3 (0.1 to 0.9)	VERY LOW
	reference: white					-		-	-
French, 2008 England and	Black Caribbean	Unmatched case- control with	very serious ^{1,2,8,11}	no serious inconsistency	no serious indirectness	no serious imprecision	16935	1.40 (0.39 to 5.01)	LOW
Wales Data: 1999-	Black African	multivariate analysis				no serious imprecision		2.02 (0.88 to 4.64)	LOW
2005	Indian/ Pakistani/ Bangladeshi					no serious imprecision		1.33 (0.61 to 2.90)	LOW

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
	Other					no serious imprecision		1.39 (0.56 to 3.45)	LOW
	reference: white					-		-	-
³ Analyses not r ⁴ Unclear if loss ⁵ Wide confiden ⁶ Loss to follow- ⁷ Approach to d ⁸ Cases and con ⁹ Some data co ¹⁰ Multivariate a ¹¹ A number of t	eported for a number to follow-up sufficient ce interval -up, its reasons and t lrug susceptibility test ntrols unmatched llected by questionna unalysis used, althoug	nire (i.e. may be some gh effect estimates onl e univariate analyses	and reported in popu- naracteristics hose lost not reported reliance on recall) ly adjusted for age an	d two periods of analy	sis (1993–1994 and	1998–2000)			

Homelessness

		Quality assessmen	t				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Story, 2007	Ever homeless	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	1540	2.1 (1.1 to 4.1)	VERY LOW
London Date: 2004	reference: not homeless	multivariate analysis			indirectness	imprecision		-	
¹ Unclear if prognostic factor and outcome measurement blinded									

²Multivariate analysis used, but unclear which confounders were controlled for

³Analyses not reported for a number of variables recorded and reported in population characteristics

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

Abbreviations: CI, confidence interval; OR, odds ratio

A.12.6 International surveillance data

Countries with a high burden of multidrug resistant tuberculosis, according to the World Health Organisation¹:

A.13 RQ U, V & W

Quality	assessment	:					No of patie		Effect		
No of studie s	Design	Risk of bias	Inconsistency	Indirectness	Impreci sion	Other consideratio ns	7RE	4 RE	Relative (95% Cl)	Absolute	Quali ty
Respons	se										
1	randomis ed trials	very seriou s1	no serious inconsistency2	no serious indirectness3	serious 4	none	110/ 113 (97. 3%)	105/ 113 (92. 9%)	RR 1.05 (0.99 to 1.11)	46 more per 1000 (from 9 more to 102 more)	VERY LOW
Relapse											
1	randomis ed trials	very seriou s1	no serious inconsistency2	no serious indirectness3	serious 4	none	2/92 (2.2 %)	6/86 (7%)	RR 0.31 (0.06 to 1.5)	48 fewer per 1000 (from 66 fewer to 35 more)	VERY LOW
Adverse	effects										
1	randomis ed trials	very seriou s1	no serious inconsistency2	no serious indirectness3	serious 4	none	1/11 3 (0.8 8%)	1/11 3 (0.8 8%)	RR 1 (0.06 to 15.79)	0 fewer per 1000 (from 8 fewer to 131 more)	VERY LOW

¹ Serious risk of bias due to concerns over trail methodology re blinding, allocation concealment, method of allocation
 ² Single study analysis
 ³ Population and intervention as specified in the review protocol
 ⁴ Confidence intervals around point estimate cross line of no effect

3RSZH or 3RSHZ + 2SHZ

Quality assessment No of patients								
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response								
1	randomis	very	serious2	serious3	serious4	RCT but data not	32/35 (91%)	VERY

Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
(Balasubramanian , 1990)	ed trials	serious1				stratified by Resistance status		LOW
Relapse at 5 years								
1 (Balasubramanian , 1990)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	6/32 (19%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

6RSH

Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 6RSH	l							
1 (East African/ British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	19/20 (95%)	VERY LOW
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	34/40 (85%)	VERY LOW
Relapse at 24 – 30	months							
1 (East African/ British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	3/13 (23%)	VERY LOW

Quality assessm	ent	No of patients						
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	4/29 (14%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

SHRZ/S₂H₂Z₂

Quality assessm	ent						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to SHR	Z/S2H2Z2							
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	16/20 (80%)	VERY LOW
Relapse at 24 mo	nths							
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	3/14 (21%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

SHRE/S₂H₂Z₂SHR

Quality assessme	ent						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to SHRE	E/S2H2Z2SHI	२						
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	22/22 (100%)	VERY LOW
Relapse at 24 mon	iths							
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	9/21 (43%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used
 SHRE/S₂H₂Z₂SHR

Quality assessme	ent						No of patients		
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality	
Response to SHRE/S2H2Z2SHR									
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	22/22 (100%)	VERY LOW	
Relapse at 24 mor	nths								
1 (Hong Kong Chest	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	9/21 (43%)	VERY LOW	

Quality assessme	nt	No of patients						
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Service/British MRC, 1977)			-					

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

$S_{3}H_{3}Z_{3}R_{3}/S_{2}H_{2}Z_{2}$

Quality assessme	ent						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to S3H	3Z3R3/ S2H22	Z2						
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	20/21 (95%)	VERY LOW
Relapse at 24 mor	nths							
1 (Hong Kong Chest Service/British MRC, 1977)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	20/15 (13%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

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BRSZH							1	
Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 3RSZ	Н							
1 (Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore, 1986)	randomis ed trials	very serious1	serious2	serious3	serious4	none	32/34 (94%)	VERY LOW
Relapse at 24 mont	ths							
1 (Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore, 1986)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	7/33 (21%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

6SRZH

Quality assessment	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 6SRZI	4							
1 (Tanzania/British MRC Collaborative Investigation,	randomis ed trials	very serious1	serious2	serious3	serious4	none	12/18 (67%)	VERY LOW

Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
1997)								
Relapse								
1 (Tanzania/British MRC Collaborative Investigation, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	2/10 (20%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

2EHRZ2/4EHR ₂ -	
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Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 2EHR	Z2/4EHR2-							
1 (Tuberculosis Research Centre/Indian Council of Medical Research, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	none	47/59 (80%)	VERY LOW
Relapse (timepoint	not stated)							
1 (Tuberculosis Research Centre/Indian Council of Medical	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	11/21 (54%)	VERY LOW

Quality assessme	nt	No of patients						
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Research, 1997)								

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

2EHRZ7/6EH7

Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 2EHR	Z7/6EH7							
1 (Tuberculosis Research Centre/Indian Council of Medical Research, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	none	16/94 (83%)	VERY LOW
Relapse (timepoint	not stated)							
1 (Tuberculosis Research Centre/Indian Council of Medical Research, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	6/21 (29%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

2HRZ2/4HR2-

Quality assessme	nt						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 2HRZ	2/4HR2-							
1 (Tuberculosis Research Centre/Indian Council of Medical Research, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	none	28/74 (38%)	VERY LOW
Relapse (timepoint	not stated)							
1 (Tuberculosis Research Centre/Indian Council of Medical Research, 1997)	randomis ed trials	very serious1	serious2	serious3	serious4	RCT but data not stratified by Resistance status	4/21 (19%)	VERY LOW

¹ Very serious risk of bias due to concerns over randomisation, allocation concealment, blinding
 ² Single study analysis
 ³ Intervention not as specified in review protocol
 ⁴ Descriptive only results used

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A.14 RQ Z

A.14.1 Management of treatment interruptions

Sequential reintroduction without pyrazinamide SE \rightarrow H \rightarrow R compared to simultaneous reintroduction HRZE in patients receiving treatment for pulmonary or pleural tuberculosis who have experienced drug-induced hepatotoxicity¹

	Quality ass	sessment				Number of pat	ients			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n without pyrazinamide $SE \rightarrow H \rightarrow R$	Simultaneous reintroduction HRZE	Summary of findings	Qualit y	
Adverse event	Adverse events – recurrence of drug-induced hepatitis ¹ (number of patients in whom drug-induced hepatitis ¹ recurred following treatment reintroduction)									
1 ²	RCT	serious ⁴	serious ⁵	no serious indirectness	serious ⁶	0/20	6/25	OR 0.07 (95% CI 0.00 to 1.39)	VERY LOW	
Cure ³ (number	of patients to	achieve a cure ³)								
1 ²	RCT	serious ⁴	serious ⁵	no serious indirectness	very serious ^{6,7}	20/20	20/25	OR 1.24 (95% CI 0.02 to 65.4)	VERY LOW	
¹ Drug-induced	hepatitis was	defined as normalis	ation of liver function	ns after withdrawal o	of all antitubercu	losis drugs, and a	at least one of the f	ollowing criteria:		

• a rise to five times the normal levels (40 U/L) of serum AST and/or ALT

• a rise in the level of serum total bilirubin over 1.5 mg/dl

• any increase in AST and/or ALT above pretreatment levels, together with anorexia, nausea, vomiting and jaundice

² Tahaoglu, 2001

³ Cure was defined as a sputum smear-positive patient who is smear-negative at completion of treatment

⁴ Unclear method of randomisation; unclear if allocation concealment used; unclear blinding

⁵ Risk factors for hepatotoxicity (age, sex, alcohol consumption, hepatitis markers, radiological extension of the disease in the lungs, pretreatment serum albumin level, diabetes mellitus, additional hepatotoxic drug use, body weight and body mass index) were compared statistically to ensure that there was no increased susceptibility to hepatotoxicity in either group; however, reintroduction without pyrazinamide group had more individuals with extensive disease (P = 0.001) and more individuals with hypoalbuminemia (P = 0.053)

⁶ GRADE rule of thumb: <300 events

⁷ Wide confidence interval

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; S, streptomycin; Z, pyrazinamide

Sequential reintroduction $R \rightarrow H \rightarrow Z$ compared to simultaneous reintroduction HRZ in patients receiving treatment for tuberculosis who have experienced drug-induced hepatotoxicity¹

	Quality asso	essment				Number of pat	ients	findings y				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n R→H→Z	Simultaneous reintroduction HRZ	· · · · · · · · · · · · · · · · · · ·	Qualit y			
Adverse events	s – recurrence	e of drug-induced	hepatitis ¹ (number	of patients in whom	drug-induced he	epatitis ¹ recurred	following treatmen	t reintroduction)				
1 ²	RCT	serious ³	serious ⁴	no serious indirectness	serious⁵	6/59	4/29	OR 0.71 (95% CI 0.18 to 2.73)	VERY LOW			

¹ Drug-induced hepatotoxicity was diagnosed if criteria 1, 2, or 3 were present in combination with criteria 4 and 5:

1) an increase ≥5 times the upper limit of the normal levels (50 IU/I) of serum AST and/or ALT on 1 occasion, or >3 times the upper limit of normal (>150 IU/I) on 3 consecutive occasions;

2) an increase in serum total bilirubin >1.5 mg/dl;

3) any increase in serum AST and or ALT level above pretreatment values together with anorexia, nausea, vomiting, and jaundice;

4) absence of serological evidence of infection with hepatitis A, B, C, or E virus; and

5) improvement in liver function test results (serum bilirubin level <1 mg/dl; AST and ALT level <100 IU/I) after withdrawal of antituberculosis drugs

² Sharma, 2010

³ Unclear blinding; unclear length of follow-up

⁴ Unclear if length of follow-up equal in each group

⁵ GRADE rule of thumb: <300 events

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide

Sequential reintroduction $H \rightarrow R \rightarrow Z$ compared to simultaneous reintroduction HRZ in patients receiving treatment for tuberculosis who have experienced drug-induced hepatotoxicity¹

	Quality ass	essment				Number of pati	ents		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n H→R→Z	Simultaneous reintroduction HRZ	Summary of findings	Qualit y
Adverse event	s – recurrenc	e of drug-induced	hepatitis ¹ (number	of patients in whom	drug-induced h	epatitis ¹ recurred	following treatment	reintroduction)	
1 ²	RCT	serious ³	serious ⁴	no serious	serious ⁵	5/58	4/29	OR 0.59 (95%	VERY

	Quality as	sessment				Number of pat	ients		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n H→R→Z	Simultaneous reintroduction HRZ	Summary of findings	Qualit y
				indirectness				CI 0.15 to 2.39)	LOW
3) any increase4) absence of s	e in serum AS serological evi	dence of infection w	above pretreatment vith hepatitis A, B, C	, or E virus; and					
5) improvemen ² Sharma, 2010		ion test results (ser	um bilirubin level <1	mg/dl; AST and AL	T level <100 IU/l)) after withdrawal	of antituberculosis	drugs	
	•	ngth of follow-up							
	•	p equal in each gro	ир						
⁵ GRADE rule	of thumb: <30	0 events							

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; H, isoniazid; OR, odds ratio; R, rifampicin; Z, pyrazinamide

Sequential reintroduction compared to simultaneous reintroduction in patients receiving treatment for tuberculosis who have experienced drug-induced hepatotoxicity^{1,2}

	Quality asso	essment				Number of pati	Number of patients Sequential				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n	Simultaneous reintroduction	Summary of findings	Qualit y		
Adverse events	Adverse events – recurrence of drug-induced hepatitis ^{1,2} (number of patients in whom drug-induced hepatitis ^{1,2} recurred following treatment reintroduction)										
2 ^{3,4}	RCT	serious ^{5,6}	serious ^{7,8}	no serious indirectness	serious ⁹	11/137	14/83	OR 0.44 (95% CI 0.18 to 1.03)	VERY LOW		

¹ Drug-induced hepatitis in Tahaoglu (2001) was defined as normalisation of liver functions after withdrawal of all antituberculosis drugs, and at least one of the following criteria:

• a rise to five times the normal levels (40 U/L) of serum AST and/or ALT

• a rise in the level of serum total bilirubin over 1.5 mg/dl

	Quality asso	essment				Number of pati	ients		
Number of						Sequential reintroductio	Simultaneous	Summary of	Qualit
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		reintroduction		y

• any increase in AST and/or ALT above pretreatment levels, together with anorexia, nausea, vomiting and jaundice

² Drug-induced hepatotoxicity in Sharma (2010) was diagnosed if criteria 1, 2, or 3 were present in combination with criteria 4 and 5:

1) an increase ≥5 times the upper limit of the normal levels (50 IU/I) of serum AST and/or ALT on 1 occasion, or >3 times the upper limit of normal (>150 IU/I) on 3 consecutive occasions;

2) an increase in serum total bilirubin >1.5 mg/dl;

3) any increase in serum AST and or ALT level above pretreatment values together with anorexia, nausea, vomiting, and jaundice;

4) absence of serological evidence of infection with hepatitis A, B, C, or E virus; and

5) improvement in liver function test results (serum bilirubin level <1 mg/dl; AST and ALT level <100 IU/l) after withdrawal of antituberculosis drugs

³ Tahaoglu, 2001

⁴ Sharma, 2010

⁵ Tahaoglu, 2001: unclear method of randomisation; unclear if allocation concealment used; unclear blinding

⁶ Sharma, 2010: unclear blinding; unclear length of follow-up

⁷ Tahaoglu, 2001: risk factors for hepatotoxicity (age, sex, alcohol consumption, hepatitis markers, radiological extension of the disease in the lungs, pretreatment serum albumin level, diabetes mellitus, additional hepatotoxic drug use, body weight and body mass index) were compared statistically to ensure that there was no increased susceptibility to hepatotoxicity in either group; however, reintroduction without pyrazinamide group had more individuals with extensive disease (P = 0.001) and more individuals with hypoalbuminemia (P = 0.053)

⁸ Sharma, 2010: unclear if length of follow-up equal in each group

⁹ GRADE rule of thumb: <300 events

¹⁰ Forest plot:

Abbreviations: CI, confidence interval; OR, odds ratio

A.15 RQs AA and BB

A.15.1 Behrman 1998. Tuberculosis control in an urban emergency department

Number of	Quality asses	sment				Number of				
evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patien		Summary	of findings	Quality
Phase I	Prospective cohort	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	ED ² 6/50	OHEs ³ 51/2514	RR ⁴ 5.9 (95% CI 2.7- 13.1) ⁵	Absolute difference 10% (1- 19%)	VERY LOW
Phase II	Prospective cohort	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	ED ² 0/64	OHEs ³ 36/3000	NC	1.2% (1- 2%)	VERY LOW

¹ Unclear blinding participants, personnel and investigators, and how authors addressed potential confounders

² ED emergency department employees except physicians

³ OHEs Other hospital employees

⁴ RR risk ratio

⁵ Wide confidence interval

Abbreviations: ED: emergency department; OHEs other health employees; CI, confidence interval; NC, not calculable, RR, risk ratio;

A.15.2 Blumerg et al. 1995. Preventing the nosocomial transmission of tuberculosis

•	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of individuals	Summary of Findings	Quality	
escriptive	Variante 1				mannauais	ourninary of Finanigs	Quality	
se series' servational	Very Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision ^{2,}	35/103 18/358	OR 95% CI 9.72 (4.99 to 19.25) ²	VERY LOW	
escriptive se series' oservational	Very Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision		Jan 1992 3.3% to June 1994 0.04%	VERY LOW	
escriptive se series' oservational	Very Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision		35.4/month at 8 month 3.3/month at 28 month (p < 0.001)	VERY LOW	
es es es	e series' ervational scriptive e series' ervational	e series' ervational scriptive e series' ervational	e series' ervational scriptive e series' ervational	e series' ervationalinconsistency indirectnessscriptive e series' ervationalVery Serious1 inconsistencyNo serious inconsistencyVery Serious1 inconsistencyNo serious indirectness	e series' ervational Very Serious ¹ No serious ervational Very Serious ¹ No serious inconsistency No serious indirectness No serious indirectness imprecision	e series' ervational inconsistency indirectness imprecision scriptive e series' Very Serious ¹ No serious e series' No serious inconsistency No serious imprecision	e series' ervationalinconsistencyindirectnessimprecisionJune 1994 0.04%scriptive e series' ervationalVery Serious1No serious inconsistencyNo serious indirectnessNo serious imprecision35.4/month at 8 month 3.3/month at 28 month (p < 0.001)	

A.15.3 Chamie et al 2013. Household ventilation and tuberculosis transmission in Kampala, Uganda

	Quality asses	sment			Summary of findings Co-prevalent (n) vs no-co-			
Outcome of Interest	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Homes (household s)	prevalent (n) households median ACH [IQR] p = 0.05	Quality
Index case sleeping room ventilation rates	Nested case control	Very Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	61 (208)	12 [8-15] (12) vs 15 [11-18] (49) <i>P</i> = 0.12 (12)	VERY LOW
AFB smear- positive index cases	Nested case control	Very Serious ¹	No serious inconsistency	No serious inconsistency	Serious imprecision ²	61 (208)	11 [8-14] (11) vs 15 [11-19] (48) <i>P</i> = 0.06	VERY LOW
AFB smear positive index case, non-HIV infected	Nested case control	Very Serious ¹	No serious inconsistency	No serious inconsistency	Serious imprecision ²	61 (208)	11 [8-14] (11) vs 17 [10-20] (12) <i>p</i> = 0.1	VERY LOW

¹ Limitations in study design, unclear/lack of blinding, potential recruitment bias

² Uncertainty about the results due to low number of households participating

Abbreviations: ACH: air changes per hour; AFB: acid fast bacilli; Co-prevalent: IQR: interquartile range; TB: presence of TB in household acquired from or not from index case;

A.15.4 Da Costa 2009

Outcome and evaluations	Quality asses	ssment			Number of conversions observed	Summary of Findings			
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of particip ants	/months Conversions/10 00 person- month; 95% Cl	Adjusted ^a HR (95% Cl)	Quality
TST conversion	on								
Period I (1999- 2001)	Prospective Cohort	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	406	25/4307 5.8; 4.9-6.7		VERY LOW
Period II (2002- 2003)	Prospective Cohort	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	193	15/3858 3.7;2.8-4.6 <i>P</i> = 0.006	0.24 (0.10-0.54)	VERY LOW
Exposure to p	ulmonary TB	case in hospita	l (ves)						
Period I (1999- 2001)	Prospective Cohort	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	406	11/1661 6.6;5.1-8.1		VERY LOW
Period II (2002- 2003)	Prospective Cohort	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	193	8/1997 4;2.7-5.3	0.31 (0.13-0.73)	VERY LOW

^a Adjusted for exposure to pulmonary TB case and professional category (i.e., admin clerk, physician, nurse, social worker, lab & technician, housekeeper)

¹ Unclear inclusion and exclusion of participants; unclear/lack blinding; unclear reasons and characteristics of individuals lost at follow up.

²GRADE rule of thumb <300 events

Abbreviations: CI, confidence interval; HR: hazard ratios, TST: Tuberculin skin test

A.15.5 Gonzalez-Angulo et al 2013. Knowledge and acceptability of patient specific infection control measures for TB

Outcome of Interest	Quality assess	ment				Acceptability of IC measure (TB treatment		
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Infection Control Measure	only). % of Absolute difference (CI) <i>p</i> value	Quality
Acceptability of nfection control neasures	Prospective (questionnaire) cohort	Very Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ² [100 participants (50 diagnosed, 50 suspects)]	Hospital Use of face mask Cough hygiene Complete a course of TB treatment Isolation from other patients Home Cough hygiene Use of mask Cosleeping Ventilation (natural) Ventilation (mechanical) Isolation Workplace Stop working-2 wks Cough hygiene Use of mask	5 (-3.34-4.88) p 0 .5 - - 5 (-15.71-23.61) p 0.804 2 (32-2.44) p 1 22 (2.89-30.49) p 0.23 12 (-4339-20.72) p 0.18 24 (2.07-38.27) p 0.31 22 (4.68-26.71) p 0.12 5 (-5.97-9.63) p 0.625 (-4.39-20.72) p 0.18 - 15 (-1.03-19.39) p 0.70 Spearman correlation coefficient 0.5288 p = .0033	VERY LOW

² GRADE rule of thumb <300 events

Abbreviations: CI: confidence interval TB: tuberculosis; '-' no difference between baseline and end of treatment: wks: weeks

A.15.6 Hubad et al 2012. Inadequate hospital ventilation system increases the risk of nosocomial TB

Outcome of Interest / Location	Quality asses	sment		Area (IS6110 copy per m ³ of air/ calculated TB				
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	cell equivalent per m ³ of air)	Calculated time (hrs) ³	Quality
Risk of exposure / TB Ward	Prospective interventional study	Very Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	Patient room (<10) /- Corridor 177 ±32 / 19±3 Collection room (<10) /-	- 1 -	VERY LOW
Risk of exposure – Diagnostic Laboratory		Very Serious ¹	No serious inconsistency	No serious inconsistency	Serious imprecision ²	Incubation room 187±49 / 20±5 Corridor 55±22 / 6±2 Lab room (culture) (<10) /-	1 3 -	VERY LOW
Risk of exposure –non TB areas		Very Serious ¹	No serious inconsistency	No serious inconsistency	Serious imprecision ²	Corridor 98±30 / 10±3 Bioch Lab (<10) /-	2	VERY LOW

² Uncertainty about the results due to low number of measurements and locations observed

³ Time after which it is believed that a person would have been exposed to an *M tuberculosis* infectious dose

Abbreviations: hrs: hours, m³: cubic meter, TB: tuberculosis

A.15.7 Lygizos et al 2013. Natural ventilation reduces high TB transmission risk in traditional homes in rural KwaZulu-natal, SA

Outcome	Quality assess	sment				Summary of Findings					
of Interest	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	% Risk of TB, SD % (p value)	Quality				
TB risk estimation after 10	Prospective Interventional Cohort	Very Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	a) windows and door closed was 55.4%, 27.8,	VERY LOW				
hours of exposure						b) upon opening windows 21.5%, SD 14.1 (p <0.001)					
						c) upon opening windows and door together was 9.6%, SD 4.7 (p <0.001)					
						Estimated risk of TB infection increased in parallel to exposure time (p <0.001)					
² Uncertainty	¹ Limitations in study design, unclear/lack of blinding, potential recruitment bias ² Uncertainty about the results due to low number of households participating (n=24) Abbreviations: SD: standard deviation, TB: tuberculosis										

A.15.8 Nardell et al 2008. Safety of upper-room ultraviolet germicidal air disinfection for room occupants: results from the TB UV shelter study

	Quality assessme	nt						
Outcome of Interest	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Summary	of Findings	Quality
TST conversion	Double blind placebo/control field trial	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	33611 staff and homeless residents	"inconclusive results"	VERY LOW
Adverse Effects	Double blind placebo/control field trial	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	223/3,611 interviews (6%) included a report of a <i>skin or eye symptom</i>		VERY LOW
						Skin or eye symptom		
						95/223 (43%) occur UV periods	95/223 (43%) occurred entirely in active UV periods	
							92/223 (42%) occurred entirely in placebo UV periods	
						36/223 (16%) uncer occurred	tain when symptoms	
						Pearson Chi-square statistically significa	e value of 0.066 (not nt)	
						One instance of UV keratoconjunctivitis human error	-related occurred, caused by	

¹ Limitations in study design, unclear how participant and shelter staff blinding was achieved, potential bias due to loss to follow up, unclear how confounding factors were addressed

² Uncertainty about the results due to low number of shelters participating (n=14), <300 events as per GRADE rule of thumb Abbreviations: SD: standard deviation, TB: tuberculosis; UV: ultraviolet

A.15.9 Richardson 2014. Shared air: a renewed focus on ventilation for the prevention of tuberculosis transmission

Outcome	Quality assess	sment				Summary of Findings			
of Interest	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rudnick and Milton TB transmission risk	Quality		
TB risk or transmission	Prospective Interventional Cohort	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²	Classrooms had 5 to 6 air changes per hour (average sizes of 31 students and class volume of 180,000 litters or 180 m ³)	VERY LOW		
						Ventilation rate: 60.2% of students time was spent above the recommended threshold			
¹ Limitations in study design, unclear/lack of blinding, lack on information on confounders and how they were addressed, loss to follow up ² Uncertainty about the results due to low number of students participating (n=64) Abbreviations: TB: tuberculosis									

A.16 RQ CC and DD

A.16.1 Duration of isolation to minimise risk of infection to others

Length of isolation

		Quality assessment	t							
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings	Quality	
Ritchie 2007 NZ	Length of isolation	observational	serious ^{1,}	Serious ²	No serious indirectness ³	serious imprecision ⁴	143	1516 days saved	VERY LOW	
Kalamuddi n 2014 Singapore	Time spent in isolation	observational	serious ^{1,}	Serious ²	No serious indirectness ³	serious imprecision ⁴	121	3 days vs 5 days <i>p</i> , 0.01	VERY LOW	
 ¹ Unclear if outcome measurement blinded ² Heterogeneity in populations, ³ Does not directly asses infectivity, and does not directly measures the outcome of interest ⁴ Small sample size according to GRADE rule of thumb >300 events Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio 										

Number of sputum samples

		Quality assessment	t						
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings	Quality
Lippincott 2014 US	Xpert MTB/RIF strategy	observational	serious ^{1,}	Serious ²	serious indirectness ³	serious imprecision ⁴	207	68hrs(IQR 47.1-97.5) smear 3-samples vs	VERY LOW
							180	2-samples 41.2 (IQR 26.6-54.8) and	
							148	3-samples 54.0 (IQR 43.3-80)	
Wilmer 2011 Canada	Third AFB smear	observational	serious ^{1,}	Serious ²	serious indirectness ³	serious imprecision ⁴	116	Average delay for third specimen 0.95 days/patient	VERY LOW

¹ Unclear if outcome measurement blinded

² Heterogeneity in populations,

³ Does not directly asses infectivity, and does not directly measures the outcome of interest

⁴ Small sample size according to GRADE rule of thumb >300 events

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio

Appendix E: GRADE profiles

A.16.2 Determining level of infectiousness – time to sputum smear conversion

Age		Quality assessmen	t						
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% Cl)	Quality
Rekha 2007 India	Age >45 yr	observational with multivariate analysis	very serious ^{1,2}	No serious	no serious indirectness	serious imprecision ³	86	OR 1.8 (1.02 – 3.16)	VERY LOW
		l outcome measurement bli unclear which confounders		d for					

³ Small sample size and wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio

Sputum smear grade

		Quality assessmen	t						
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% Cl)	Quality
Bouti 2013 Morocco	Grade 3+	observational with multivariate analysis	very serious ^{1,2}	serious ³	no serious indirectness	serious imprecision ⁴	37	OR: 7.1 (2.5-11.2) ⁴	VERY LOW
Horne 2010 USA	Grades 1+ to 4+	observational with multivariate analysis	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision ⁴	98	HR: 0.45 (0.35-0.57)	VERY LOW
Rekha 2007 India	Higher pre-treatment grade (grades 2+ to 3+)	observational with multivariate analysis	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision ⁴	157	OR 2.64 (1.76-3.96)	VERY LOW
Wang 2009	Grade 2+	observational with	very	serious ³	no serious	no serious	75	HR: 0.6 (0.43-0.84)	VERY
Taiwan	Grade 3+	multivariate	serious ^{1,2}		indirectness	imprecision ⁴	72	HR: 0.47 (0.33-0.66)	LOW
F	Grade 4+ Reference: Grade 1+	analysis				82	HR: 0.5 (0.35-0.71)		

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³Heterogeneity in populations,

⁴Wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio

Miliary

		Quality assessment					Number of	Summary of findings		
Study		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	(95% CI)	Quality	
Bouti 2013 Morocco	Miliary	Observational with multivariate analysis	very serious ^{1,2}	No serious inconsistency	no serious indirectness	no serious imprecision ³	ns	Adjusted OR: 8.8 (2.3-19.4) ³	VERY LOW	
¹ Unclear if prognostic factor and outcome measurement blinded ² Multivariate analysis used, but unclear which confounders were controlled for										

³ Wide confidence interval

Abbreviations: CI, confidence interval; ns, no statistically significant (value no reported) ; OR, odds ratio

Two zones involved in X-ray

		Quality assessment							
Study		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	Quality
Rekha 2007 India	>2 zones involved	observational with multivariate analysis	very serious ^{1,2}	No serious	no serious indirectness	serious imprecision ³	179	1.31 (1.09 - 1.57)	VERY LOW
	prognostic factor and out te analysis used, but uncle			l for					

³ Small sample size and wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio

Bilateral radiological lesions

		Quality assessment				Number of	Summary of findings (95%		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	CI)	Quality
Morocco	Bilateral radiological lesions	Observational with multivariate analysis	very serious ^{1,2,}	no serious inconsistency	no serious indirectness	Serious ³	68	OR (95% CI) 13.4 (1.8-55.6) 3	VERY LOW
USA	Bilateral radiological lesions	Observational with multivariate analysis	very serious ^{1,2,}	no serious inconsistency	no serious indirectness	Serious ³	43	Ns (values not reported)	VERY LOW

² Multivariate analysis used, but unclear which confounders were controlled for

³ Sample size, and wide confidence interval

Abbreviations: CI, confidence interval; ns, no statistically significant; OR, odds ratio

Cavitation

		Quality assessment					Number of	Summary of findings (95%	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	CI)	Quality
Bouti 2013 Morocco	Cavitation	Observational with multivariate analysis	very serious ^{1,2,}	serious inconsistency	no serious indirectness	Serious ³	42	ns	VERY LOW
Horne 2010 USA	Cavitation	Observational with multivariate analysis	very serious ^{1,2,}	serious inconsistency	no serious indirectness	Serious ³	44	ns	VERY LOW
Wang 2009 Taiwan	Cavitation	Observational with multivariate analysis	very serious ^{1,2,}	serious inconsistency	no serious indirectness	Serious ³	85	HR 95% CI 0.26 (0.18-0.38)	VERY LOW

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³ Sample size and wide confidence interval

Abbreviations: CI, confidence interval; ns, no statistically significant (values not reported); HR, hazard ratio

First two month regimen

		Quality assessment			Number of	Summary of findings (95%			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	CI)	Quality
Wang 2009 Taiwan	Treatment interruption	Observational with multivariate analysis	5		no serious indirectness	Serious ³	15	HR: 0.46 (0.27-0.79)	VERY LOW
	Other than HERZ				99	HR: 0.63 (0.53-0.87)			
	Reference: HERZ								
¹ Unclear if pro	anostic factor a	ind outcome measureme	ent blinded						

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

⁵ Small sample size and wide confidence interval

Abbreviations: CI, confidence interval; HR, hazard ratio; HERZ, isoniazid, rifampicin, ethambutol and pyrazinamide

Drug Resistance

		Quality assessmen	t					Summary of findings (95%	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	CI)	Quality
Horne 2010 USA	Drug resistance	Observational with multivariate analysis	very serious ^{1,2,}	no serious inconsistency	no serious indirectness	serious ³	22	HR: 2.30 (1.08-4.89)	VERY LOW
Wang 2009 Taiwan	Drug resistance	Observational with multivariate analysis	very serious ^{1,2,}	no serious inconsistency	no serious indirectness	serious ³	48	ns	VERY LOW

A.16.3 Risk factors for continued risk of infection – time to culture conversion

Age

		Quality assessment	t							
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% Cl)	Quality	
Rekha 2007 India	Age >45 yr	observational with multivariate analysis	very serious ^{1,2}	No serious	no serious indirectness	serious imprecision ³	67	OR 3.5 (1.56 – 7.84)	VERY LOW	

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³ Small sample size and wide confidence interval

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio

2 zones involved in X-ray

		Quality assessment							
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	Quality
Rekha 2007	>2 zones involved	observational with multivariate	very serious ^{1,2}	No serious	no serious indirectness	serious imprecision ³	152	OR 1.41 (1.04-1.90)	VERY LOW

Appendix E: GRADE profiles

		Quality assessmen	t						
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	Quality
India		analysis							
² Multivariat	prognostic factor and out te analysis used, but uncle nple size and wide confide	ear which confounders		l for					
Abbreviatio	ns: CI, confidence interva	l; OR, odds ratio; HR, l	hazard ratio						

Culture grade

		Quality assessmen	t					Summary of findings (95%			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	CI)	Quality		
Horne 2010 USA	Grades 1+ to 4+ scale	Observational with multivariate analysis	very serious ^{1,2,}	serious inconsistency ³	no serious indirectness	serious imprecision ⁴	98	HR: 0.52 (0.40-0.67)	VERY LOW		
Rekha 2007 India	Higher pre- treatment grade (grades 2+ to 3+)	observational with multivariate analysis	very serious ^{1,2}	serious ³	no serious indirectness	serious imprecision ⁴	205	OR 3.5 (1.35-9.26)	VERY LOW		
² Multivariate ³ measureme	1 Unclear if prognostic factor and outcome measurement blinded 2 Multivariate analysis used, but unclear which confounders were controlled for 3 measurement and sample heterogeneity 4 Small sample size and wide confidence interval										

Drug resistance

		Quality assessment						Summary of findings (95%	
Q. La la	Frater	Protect			In all an effect of		Number of	CI)	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients		
Horne 2010 USA	Drug resistance	Observational with multivariate analysis	very serious ^{1,2,}	No serious inconsistency	no serious indirectness	serious imprecision ³	22	HR: 2.30 (1.02-5.21)	VERY LOW

¹ Unclear if prognostic factor and outcome measurement blinded

² Multivariate analysis used, but unclear which confounders were controlled for

³ Small sample size and wide confidence interval

Abbreviations: CI, confidence interval; HR, hazard ratio

Appendix E: GRADE profiles

A.17 RQ HH

GRADE tables for outcome of risk of developing active tuberculosis in those diagnosed with latent tuberculosis

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of tuberculosis (Hazard ratio)	Relative (95% CI)	Quality	Importance
Radhakr	ishnan et al (as	sessed wit	h: clinical and bi	ochemical diag	nosis) follow u	p adjusted for pe	rson years (follow up period 15 y	vears)		
1	observational studies		no serious inconsistency	no serious indirectness	no serious imprecision	none	 253,186 participant Infected= 3118 Hazard ratios Not infected female child- 1.0 Infected female child- 8.3 Infected male child- 12.2 Infected female adult- 15.8 Infected male adult- 50.6 No TB case at home- 1.0 INH susceptible contact- 1.8 INH resistant contact- 2.2 	 Not infected female child: Infected female child: (5.6-12.3) Infected male child: (8.4-17.6) Infected female adult: (11.0-22.7) Infected male adult: (34.2-74.8) No TB case at home: INH susceptible contact: (1.4-2.2) INH resistant contact: (1.5-3.3) 	⊙OOO VERY LOW	CRITICAL
Casado	(follow-up medi	ian 43 mon	ths)							
1	observational studies		no serious inconsistency	no serious indirectness	serious ³	none	 131 participants Hazard ratios CD4 cell count (per each unit of increase)- 0.995 (P=0.06) Persistence of predisposing factors for TB- 3.17 (P=0.0002) 	 CD4 cell count (per each unit of increase)- (0.992-1.003) Persistence of predisposing factors for TB- (1.56-17) 	⊙OOO VERY LOW	CRITICAL
Mori et a	I (case control)	1								
1	observational studies	very serious ⁴	no serious inconsistency	serious⁵	Serious ⁶	none ⁷	 Case n= 46, Control n=46 Adjusted odds ratio 6 or more months of isoniazid therapy- 0.02 Alcohol abuse- 3.8 Diabetes- 5.2 	 Adjusted odds ratio 6 or more months of isoniazid therapy- (0.002-0.16) Alcohol abuse- (1.15-12.3) Diabetes- (1.22-22.1) 	⊙OOO VERY LOW	CRITICAL
Leung et	t al (cohort)									
1	observational studies	serious ⁸	no serious inconsistency	serious indirectness ⁹	no serious imprecision	none	 N=435 Adjusted odds ratio Number currently smoked per day <10- 1.00 10-<20- 1.89 ≥ 20- 2.54 Non-significant findings included age, past/current regular alcohol use, body mass 	 Adjusted odds ratio Number currently smoked per day <10- reference 10-<20- (1.19-5.05) ≥ 20- (1.63-8.16) 	⊙OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of tuberculosis (Hazard ratio)	Relative (95% Cl)	Quality	Importance
							index, presence of other co- morbidities, BCG scar, tuberculin status/treatment of latent tuberculosis infection, principle job type, duration of silica dust exposure, profusion, size and shape of lung nodules and progressive massive fibrosis			
	-Pino et al (coh				no oprious	2020	N=7002 428 perticipants with		0000	CRITICAL
1	observational studies	very serious ¹⁰	no serious inconsistency	no serious indirectness	no serious imprecision	none	N=7902, 428 participants with latent TB • Adjusted odds ratio • Age • <35- reference • ≥35 years- 6.1 • Nadir CD4 • ≥200 cells/µl- reference • <200 cells/µl- 5.6 Non-significant variables included, gender, known date of HIV diagnosis, known start date of HAART ² , HAART ² at TST ¹ , HAART ² at TB diagnosis, ethnicity, education, socio- economic strata, previous incarceration, anti-HCV antibodies, HbsAg, CD4 cell count at enrolment, CD4 <200 cells/µl at enrolment, HIV viral load at enrolment. massive fibrosis.	 Adjusted odds ratio Age <35- reference ≥35 years- (1.1-33.7) Nadir CD4 ≥200 cells/µl- reference <200 cells/µl- (1.3-23.7) 	VERY	CRITICAL
Di Perri	et al (cohort)									
1	observational studies	serious ¹¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	 N=44 Adjusted odds ratio After multivariate analysis only CD4 cell count and β-2 microglobulin serum levels retained statistical significance in the prognosis of developing active tuberculosis. Non-significant variables included, total lymphocytes 	-	⊙OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of tuberculosis (Hazard ratio)	Relative (95% CI)	Quality	Importance
Antonuc	ci et al (cohort)				, 					
1	observational studies	no Serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	N=197 • Hazard ratio • CD4 >0.35 x 109/L- 5.49 • CD4 0.20–0.35 x 109/L- 14.78 • CD4 <0.20 x 109/L- 31.18	 Hazard ratio CD4 >0.35 x 109/L-(1.32-27.09) CD4 0.20-0.35 x 109/L- (3.49-62.63) CD4 <0.20 x 109/L- (7.62-127.50) 	⊙⊙OO LOW	CRITICAL
Gessner	· et al (cohort)							·		
1	observational studies	very serious risk of bias ¹²	no serious inconsistency	no serious indirectness	no serious imprecision	none	 N=282 Odds ratio Left upper lobe lesion in adult- 12 Alaska native child- 8.9 Adult is parent of child- 8.3 Age of child- 1.5 Non-significant variables included, 3 or 4+ culture positive adults, 3 or 4+ smear positive adults, gender 	 Odds ratio Left upper lobe lesion in adult- (2.2–65) Alaska native child- (1.1–73) Adult is parent of child- (1.6–44) Age of child- (1.1–2.0) 	0000 VERY LOW	CRITICAL

Unclear it cohorts were matched for the amount that recieved BCG vaccination or placebo in the initial randomised clinical trial. Cohort was significantly older in persons in households without a TB case. Isoniazid susceptible cohort had the lowest proportion of males. Isoniazid resistant cohort had the highest proportion infected. Therefore variance was not spread evenly between groups.

² Unclear if all patients recieved the same standard of care. Definition of outcome was unclear: persistence of predisposing conditions for TB infection was highlighted as the main risk factor with no attempt to break down the data any further. Unclear if valid and reliable method used to determine outcome.

³ Low number of participants (n=131)

⁴The study does not ask a clearly focused question: It attempts to illicit the benefit of isoniazid preventive therapy in those that are tuberculin reactors however some non-reactors were also included in the analysis thereby confounding the study data. Also since documented TST¹ reactors are more likely to be offered chemoprophylaxis, the control group is likely to overestimate the proportion of latently infected people in the population who receive preventive therapy. The data on risk factors for developing tuberculosis is more useful but still confounded by the presence of non-TST¹ reactors in the case group. The cases and controls are taken from comparable populations, however, control patients were found to be more compliant to treatment when compared to tuberculosis cases. No measures appear to have been taken to prevent knowledge of primary exposure(s) from influencing case ascertainment. Exposure to diabetes may have not been measured in a standard and reliable fashion since patients with high random or fasting blood glucose recordings were listed as being diabetic, however British guidelines require more than just one isolated raised blood glucose level. Chart documentation supplied many of the other diagnosis such as notation of alcohol abuse or admissions related to alcoholism which may not have been accurate. Unclear how long participant's histories were tracked for.

⁵ Population does not exactly match population of interest: Native American people were enrolled; these people have an incidence of TB two to three times that of the surrounding populations. Not all patients in the active tuberculosis group had a documented positive TST¹ test prior to TB diagnosis. 1 had a negative TST¹ and 8 had an unknown infection status.

⁶ Number of participants was small (n=92)

⁷ funding was unclear

⁸ The sample included those who had an induration less than 10 mm however tuberculin status was later adjusted for in multivariate analysis. Patients did not receive the same standard of care for latent TB as some were treated and others were not. Information on the number treated and on which treatment regimen is provided. Patients were also seen in differing clinics with potential for variance in standard of care. Adjustments for treatment of latent tuberculosis were attempted in multivariate analysis. Data was recorded by questionnaire which is vulnerable to recall bias.

⁹ The population was amongst male high risk silicotic patients in Hong Kong, there may be some generalizability issues here

¹⁰ The patients may not have received same standard of care since participants spread over 20 different hospitals. Comparisons in baseline characteristics were not made between those that accepted treatment and those who refused to initiate therapy. Unclear why CD4 count at registration<200 vs. ≥200 cells/µl was not included in final multivariate analysis when it was significant at the univariate level. There were clear differences in populations at baseline between those who had no TB, prevalent TB and incident TB. Information on TST¹ was not available for 4848 patients. Compared with patients with available TST¹ results, these patients were more likely to have had no education or only primary education (61.8% vs 49.1%), to be of lower socio-economic status (50.5% vs 40.2%) and to have a CD4 cell count of <200 cells/µl at enrolment (18.4% vs 14.3%, P=<0.001). No information on treatment adherence was provided either for those who received isoniazid or those who received</p>

			Quality asse	ssment			No of patients	Effect		
No of		Risk of				Other	Risk of tuberculosis	Relative		
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	(Hazard ratio)	(95% CI)	Quality	Importance

HAART² therapy.

¹¹ Participants received the same standard of care in regard to monitoring however immunological evaluation was performed at baseline and subsequently at 3-6 month intervals, leaving some uncertainty about consistency of monitoring tests. Multivariate analysis was performed using the Cox model. However the study has failed to adjust for external risk factors that may be relevant such as malnutrition, alcoholism, homelessness and drug dependence.

¹² It was stated that once diagnosed infected children were treated however it is unclear under what regimen they were treated for latent tuberculosis and whether all received the same standard of care. Unclear if the 30 villages in the area performed the same level of monitoring or care for the children and the infected adults. Few baseline characteristics are reported. The methods used to observe risk factors are unlikely to be reliable as data was recorded retrospectively. Definition of diagnosis of active and latent tuberculosis was not stated in full and the methods used to observe risk factors are unlikely to be reliable as data was recorded retrospectively. Observation period was for 7 years between 1987 and 1994. Unclear if length of observation was the same for all children (or if adjustments were made).

Risk of developing hepatotoxicity for those receiving treatment for latent tuberculosis

			Quality asse	ssment	_		No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of Hepatotoxicity	Relative (95% Cl)	Quality	Importance
Tedla et	al (n=1,995)									
1 Fountair	observational studies	no serious risk of bias d with: AST	no serious inconsistency	no serious risk of indirectness1	no serious imprecision	none nal) (n=3.377)	Relative risk • CD4 lymphocyte count • CD4 <200 cells/mm ³ - 2.80 • CD4 ≥200 cells/mm ³ - 1.00 Non-significant variables Age, sex, BMI, antiretroviral therapy, efavirenz, nevirapine, NNRTI, co-trimoxazole, alcohol, alcohol-dependence, Hepatitis B viral serological testing	 Relative risk CD4 lymphocyte count CD4 <200 cells/mm³- 2.80 (1.14- 6.84) CD4 ≥200 cells/mm³- 1.00 	0000 LOW	CRITICAL
1	observational studies	Serious ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none ⁷	 Adjusted odds ratio Baseline AST > upper limit of normal- 5.398 Age ≥ 50 years- 3.699 	 Adjusted odds ratio Baseline AST > upper limit of normal- (2.081-13.999) Age ≥ 50 years- (1.428-9.584) 	⊙OOO VERY LOW	CRITICAL
Fernand	ez-Villar (n=415)								
1	observational studies	serious ⁸	no serious inconsistency	no serious indirectness	no serious imprecision	none	 Adjusted odds ratios Excessive alcohol consumption- 4.2 Baseline abnormal ALT- 4.3 (odds ratios calculated by comparing to those who did not have any of the above) 	 Adjusted odds ratios Excessive alcohol consumption- (1.6-10.8) Baseline abnormal ALT- (1.6- 11.4) 	©OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of Hepatotoxicity	Relative (95% Cl)	Quality	Importance
Nolan et	al (n=11,141)									
1	observational studies	serious ⁹	no serious inconsistency	no serious indirectness	no serious imprecision	none ¹⁰	 Adjusted odds ratios Non-significant variables were: Sex, Age and Race 	-	⊙OOO VERY LOW	CRITICAL
Dickinso	on et al, 1981									
1	observational studies	serious ¹¹	no serious inconsistency	no serious indirectness	serious ¹²	none	 Only age was found to be significantly correlated with liver dysfunction after adjustment for all other factors- (P= 0.034) Non-significant variables were: Rapid/slow acetylation phenotype, sex and race 	-	⊙OOO VERY LOW	CRITICAL
Lee et al	(n=3788)									
1	observational studies	serious ¹³	no serious inconsistency	no serious indirectness	serious ¹²	none ⁷	Odds ratio • Gender • Female- 4.1 • Male- reference Non-significant variables were: Race, age, alcohol use, illicit drug use, pyrazinamide dose, presumed recent infection	GenderFemale- (1.2-14.3)Male- reference	⊙OOO VERY LOW	CRITICAL
Lobato e	et al (N= 1,246)									
1	observational studies	no serious	no serious inconsistency	no serious indirectness	no serious risk	none ⁷	 Adjusted odds ratio Age- 0.97 Unemployed within past 24 months- 0.51 Elevated AST before therapy- 0.72 Non-significant findings included: Sex, US birth, race, homelessness, prior positive tuberculin skin test, previous incarceration, injection drug use, non-injection drug use, excess alcohol 	 Age- (0.95-0.99) Unemployed- (0.27-0.97) Elevated AST- (0.54-0.95) 	©©OO LOW	CRITICAL
	et al (N= 219)					7				
1	observational studies	very serious ¹⁴	no serious inconsistency	no serious indirectness	no serious risk	none ⁷	Hazard ratio • Hepatitis C- 3.03 Age was not associated with treatment discontinuation due to suspected toxicity.	Hazard ratio Hepatitis C- 1.08-8.52 	⊙OOO VERY LOW	CRITICAL

¹ Participants w ² The study doo analysis ther infected peo, group. The c appear to ha since patient documentatii were trackec ³ Population do patients in th	sign tree from Booses not ask a	serious ¹⁵ tswana, ho	no serious inconsistency	Indirectness	Imprecision no serious	Other considerations	 Risk of Hepatotoxicity Independent variables associated with subsequent hepatic events following treatment for latent tuberculosis infection include: Hospital admission Any physician visits for liver disease High Charlson comorbidity score during the 6 months before treatment initiation Age stratified adjusted odds ratio ≤ 35- 1.00 (reference) 36-50- 2.7 	Relative (95% Cl) • Age stratified adjusted odds ratio • ≤ 35- (reference) • 36-50- (0.5-16.0) • 54 - 55 - (4.0 - 2.7)	Quality OOOO VERY LOW	Importance
 Participants w Participants w The study doc analysis ther infected peo, group. The c appear to ha since patient documentatii were trackec Population do patients in the 	servational s idies were from Bo oes not ask a	serious ¹⁵ tswana, ho	no serious inconsistency	indirectness	no serious	none	 associated with subsequent hepatic events following treatment for latent tuberculosis infection include: Hospital admission Any physician visits for liver disease High Charlson comorbidity score during the 6 months before treatment initiation Age stratified adjusted odds ratio ≤ 35- 1.00 (reference) 36-50- 2.7 	 ≤ 35- (reference) 36-50- (0.5-16.0) 	VERY	CRITICAL
¹ Participants w ² The study doo analysis ther infected peo, group. The c appear to ha since patient documentatii were trackec ³ Population do patients in th	were from Bo oes not ask a	tswana, ho	inconsistency wever immigratio	indirectness	no serious	none	 associated with subsequent hepatic events following treatment for latent tuberculosis infection include: Hospital admission Any physician visits for liver disease High Charlson comorbidity score during the 6 months before treatment initiation Age stratified adjusted odds ratio ≤ 35- 1.00 (reference) 36-50- 2.7 	 ≤ 35- (reference) 36-50- (0.5-16.0) 	VERY	CRITICAL
² The study doo analysis ther infected peop group. The c appear to ha since patient documentatii were trackec ³ Population do patients in th	oes not ask a						ratio • ≤ 35- 1.00 (reference) • 36-50- 2.7	 ≤ 35- (reference) 36-50- (0.5-16.0) 		
² The study doo analysis ther infected peop group. The c appear to ha since patient documentatii were trackec Population do patients in th	oes not ask a						 51-65- 5.7 >65- 34.2 	 51-65- (1.0-33.7) >65- (7.6-153.8) 		
Number of pa	cases and con nave been take nts with high ra tion supplied r ed for. does not exact	ntrols are to en to preve andom or fo many of the tly match po erculosis gr	aken from compa nt knowledge of p asting blood glucc other diagnosis opulation of intere oup had a docum	rable population primary exposure ose recordings w such as notation est: Native Ameri	is, however, con e(s) from influer vere listed as bo n of alcohol abu ican people we	ntrol patients were ncing case ascertai eing diabetic, howe se or admissions re re enrolled; these p	Found to be more compliant to treat nment. Exposure to diabetes may h ver British guidelines require more elated to alcoholism which may not	tment when compared to tuberculosis c nave not been measured in a standard than just one isolated raised blood glud have been accurate. Unclear how long to three times that of the surrounding p	ases. No m and reliable cose level. participant	neasures e fashion Chart t's histories
້ funding was ເ ື Patients did n	unclear not receive th Treatment con	ne same lev mpletion wa	vel of care as parti as poor across the				re given 9 months of isoniazid inste months of therapy.	ead of 6 months. Follow up did not inclu	de the last	3 months of
⁸ Patients did i administered completion w ⁹ Treatment co made. 84% d	not receive the ed alongside. (was fairly low completion was of patients or ould be sympto	te same lev Others had with 76.9% s fairly low n the multic omatic, sub	vel of care as rules their adherence r 6 of patients comp with 64% of patien	monitored by me pleting. nts completing 6 completed thera	eans of pill cour 6 months of the py. Dose and le	nt, urine samples ar rapy. Attempts to fii	nd family supervision. Follow up did nd the systematic differences betwe	done maintenance therapy programme I not appear to continue beyond treatme een those who did or did not complete t of diagnosis was based on the assump	ent period. Treatment w	Treatment vere not
¹¹ Population d treatment. Fe ¹² low population	does not ever	tly match p	beyond treatment	t period. Treatm	ent completion	was low.		tently infected. These patients recieved or non-nucleoside reverse transcriptas		

			Quality asse	ssment			No of patients	Effect		
No of		Risk of				Other		Relative		
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	Risk of Hepatotoxicity	(95% CI)	Quality	Importance

rifampicin and pyrazinamide initially followed guidelines established for HIV infected patients and those with active tuberculosis but dose of pyrazinamide was subsequently limited based on an expert opinion published in the American Thoracic Society guidelines. Follow up did not appear to continue beyond treatment period. Treatment completion was low

¹⁴ Patients appear to have received a great variety of different standards of care. Variability included testing for comorbidities, number of isoniazid tablets provided per prescription and frequency of follow up visits. The proportion of patients in the cohort without testing for important comorbidities was not determined. Women were under-represented in this study. Treatment completion was low: 46% of veterans who initiated latent tuberculosis therapy completed treatment satisfactorily. Comparisons were not made between those that accepted treatment and those who refused to initiate therapy. Data was not available for why 46% of patients discontinued treatment. Uncertain how many variables were included in multivariate analysis. data was gathered by retrospectively examining clinical charts which is unlikely to be reliable. Definition of treatment completion outcome was unclear. Also ALT¹ levels were available for only 84% of the participants at baseline and 71% of the participants during therapy which meant diagnosis of hepatotoxicity was reliant upon the clinician reporting this is both unclear and unreliable. Baseline characteristics were not provided for all patients

¹⁵ They took patients receiving the treatment for latent for tuberculosis as having had latent tuberculosis when this may not have been the case. This is an indirect definition of latent tuberculosis. Definition of risk factors was clear but unlikely to be reliable since this was a retrospective study and data was retrieved from administrative health data.

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of adverse events	Relative (95% CI) Absolute	Quality	Importance
Lobue ef	t al (n=3,788)									
1	observational studies	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	Odds ratio • Gender • M- reference • F- 1.6 Age • 0-14- reference • 15-34- 1.3 • 35-49- 1.8 • 50-64- 2.2 • 65+- 1.5 Homeless • N- reference • Y- 2.2 Correctional facility • N- reference • Y- 2.6 The occurrence of hepatotoxicity was also associated with self-reported intravenous drug use	Odds ratio • Gender • M- • F- (1.4-2.0) Age • 0-14- reference • 15-34- (1.0-1.6) • 35-49- (1.3-2.5) • 50-64- (1.3-3.8) • 65+- (0.6-3.2) Homeless • N- reference • Y- (1.2-4.2) Correctional facility • N- reference • Y- (1.5-4.5)	0000 VERY LOW	CRITICAL

GRADE summary for those at risk of developing adverse events as a result of treatment for latent tuberculosis

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk of adverse events	Relative (95% CI) Absolute	Quality	Importance
Pettit et a	al (cohort) (n=1	323)								
1	observational studies	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	None	Isoniazid discontinuation due to adverse events Adjusted relative risk		⊙OOO VERY LOW	CRITICAL
							Female sex- 1.67Current alcohol use- 1.14	Female sex- (1.32-2.10)Current alcohol use- (1.13-1.77)		

¹ Patients did not receive the same level of care as rules regarding monitoring were altered during the study due to changes in American Thoracic Society Guidelines. Initially all patients over 35 were monitored with monthly transaminase levels as well as those at higher risk of hepatotoxicity; later this was changed to only those at higher risk. Follow up did not exceed treatment period. Treatment completion was poor with only 64% of patients completing 6 months of therapy. The paper does not provide the exact doses and lengths of regimens used.

² Adjusted relative risk was adjusted for study site, sex and current alcohol use. No other significant factors appear to have been adjusted for. Methods used to record the risk were generally reliable and valid although taken from in-person interviews which may have been subject to recall bias especially the factors of alcohol and substance use. Reasons for treatment default were taken second hand from medical charts which may not have been reliable. 15% of participants were lost to follow up.

GRADE summary for those at risk of non-completion of treatment for latent tuberculosis

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Completion of treatment	Relative (95% CI) Absolute	Quality	Importance
Gilroy (a			of 6 months ison							
1	observational studies	serious ¹	no serious inconsistency	no serious indirectness	serious ²	None ³	Only ALT level at baseline was statistically significant for non- completion after adjustment for other variables Non-significant variables recorded included: Gender, ethnicity, alcohol use and number of medications regularly taken.	-	0000 VERY LOW	CRITICAL
Lobue et	al (at risk for lo	ower comp	letion rates of an	ti-tuberculosis	regimen) (378	3)				
1	observational	serious4	no serious	no serious	no serious	none	Odds ratio	Odds ratio	0000	CRITICAL
	studies		inconsistency	indirectness	imprecision		Risk of lower completion rates Self-reported excess alcohol use • N- reference • Y- 0.1 Homelessness • N- reference • Y- 0.2	Risk of lower completion rates Self-reported excess alcohol use • N- reference • Y- (0.0-0.6) Homelessness • N- reference	VERY LOW	

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Completion of treatment	Relative (95% Cl) Absolute	Quality	Importance
							 Any other adverse event (not hep tox) N- reference Y- 0.8 Higher completion rates were associated with female sex, younger age groups, white/Hispanic race and non-USA country of birth. 	 Y- (0.1-0.5) Any other adverse event N- reference Y- (0.7-0.9) 		
			pletion rates of a		- / /	1 1				
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted odds ratio • Female sex- 0.35 • Hispanic ethnicity- 0.59 • Unemployed- 1.43 • Injection drug use within past 12 months- 0.54 • Excess alcohol- 1.35	Adjusted odds ratio • Female sex- (0.23-0.54) • Hispanic ethnicity- (0.46-0.75) • Unemployed- (1.07-1.90) • Injection drug use- (0.31-0.95) • Excess alcohol- (1.04-1.76)	©⊙OO LOW	CRITICAL
Oni et al	(cohort) (n=164	4)								
1	observational studies	serious risk of bias⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	 Adjusted odds ratio Time since HIV diagnosis: 0.81; 0.68-0.98 Alcohol drinkers: OR 4.05; 1.89-9.06 	 Time since HIV diagnosis: (0.68-0.98) Alcohol drinkers: (1.89-9.06) 	⊙OOO VERY LOW	CRITICAL
Goswam	ni et al (cohort)	(n=496)								
1	observational studies	serious risk of bias ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none	 Relative risk Risk for initiating therapy: Close contact to a TB case- 2.5 Non-employment reason for screening- 1.6 Lower educational level- 1.3 Having a regular physician- 1.4 Fear of getting sick with TB without medicine- 1.7 Prior incarceration- 1.7 Risk for treatment completion: Plan to tell friends or family about latent tuberculosis diagnosis 2.0 	 Relative risk Risk for initiating therapy: Close contact to a TB case- 1.8-3.6 Non-employment reason for screening- 1.0-2.5 Lower educational level- 1.1-1.6 Having a regular physician- 1.0-2.0 Fear of getting sick with TB without medicine- 1.2-2.6 Prior incarceration- 1.1-2.8 Risk for treatment completion: Plan to tell friends or family about latent tuberculosis diagnosis1.0-3.9 	0000 VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Completion of treatment	Relative (95% CI) Absolute	Quality	Importance
Anibarro	et al (retrospe	ctive cohoi	t) (n=599)							
1	observational studies	risk of bias ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted odds ratios Risk for treatment completion: • <36- 0.33 • ≥36-1 Sex • M-0.58 • F- 1 Immigrant (<5 years residence) • Y- 0.21 • N- 1 Social risk factors (unemployment, alcohol abuse, illegal drug abuse or residence in a correctional facility) • Y- 0.21 • N- 1	Adjusted odds ratios Risk for treatment completion: • $<36-(0.30-0.76)$ • $\geq 36-1$ Sex • M- 0.37-0.92) • F Immigrant (<5 years residence) • Y- (0.12-0.37) • N-1 Social risk factors • Y- (0.11-0.39) • N -1	0000 VERY LOW	CRITICAL
	retrospective co		5,035)							
1	observational studies	serious risk of bias ⁸	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted odds ratios Risk for treatment completion: Age, years • <18- NS • 18-24- NS • 25-35- reference • ≥35- 1.16 Race/ethnicity • Asian- 1.20 • Non-Hispanic black- 1.11 • Non-Hispanic white- reference • Hispanic- 1.10 • Other/unknown- NS Country of birth • Non-US-born- 1.08 • US-born- reference	Adjusted odds ratios Risk for treatment completion: Age, years • <18- NS • 18-24- NS • 25-35- reference • ≥35- (1.11-1.22) Race/ethnicity • Asian- (1.10-1.30) • Non-Hispanic black- (1.02-1.19) • Non-Hispanic vhite- reference • Hispanic- (1.02-1.19) • Other/unknown- (0.92-1.11) Country of birth • Non-US-born (1.03-1.13) • US-born- reference	©OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Completion of treatment	Relative (95% CI) Absolute	Quality	Importance
					•		Risk group Contact- 1.51 Medical risk- 1.45 Population risk- 1.16 Low risk- reference Ever on directly observed preventive therapy Yes- 1.26 No- reference Treatment regimen Isoniazid alone- reference Rifamycin alone- 1.20	Risk group • Contact- (1.38-1.66) • Medical risk- (1.32-1.60) • Population risk- (1.07-1.27) • Low risk- reference Ever on directly observed preventive therapy • Yes- (1.18-1.34) • No- reference Treatment regimen Isoniazid alone- reference • Rifamycin alone- 1.20 (1.14-1.26)		•
Machado	o et al (cohort) ((n=101)								
1	observational studies	serious risk of bias ⁹	no serious inconsistency	no serious indirectness	no serious imprecision	none	Relative risk Report of adverse effect- 2.69 Distance to health centre • 0-5- reference • 5.1-10- NS • >10- 0.39 Number of buses required to commute • 1- reference • 2- 1.84	Adjusted odds ratios Report of adverse effect- (1.3-5.8) Distance to health centre • 0-5- • 5.1- • >10- (0.2-0.8) Number of buses required to commute • 1- reference • 2- (1.0-3.3)	0000 VERY LOW	CRITICAL
Kwara e	t al (retrospecti	ve cohort)	(n=672)							
1	observational studies	serious risk of bias ¹⁰	no serious inconsistency	no serious indirectness	no serious imprecision	none	Odds ratio Report of adverse effect • N- reference • Y- 3.6 Medical insurance • Y-reference • N- 1.7 Non-significant variables included age, and being postpartum.	Odds ratios Report of adverse effect • N- reference • Y- (2.2-6.2) Medical insurance • Y-reference • N- (1.1-2.7)	⊙OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of patients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Completion of treatment	Relative (95% Cl) Absolute	Quality	Importance
Haley et	al (retrospectiv	e cohort) (n=749)							
1	observational studies	serious risk of bias ¹¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	 Adjusted odds ratio Hispanic subjects (n=534) Contact with an infectious TB case- 3.7 Alcohol use reported at baseline- 1.7 Other medications reported at baseline- 2.2 Non-Hispanic subjects (n=215) Black race- 2.6 Age- 0.97 Foreign birth- 0.5 Non-significant findings included 	 Adjusted odds ratio Hispanic subjects (n=534) Contact with an infectious TB case- (1.8-7.4) Alcohol use reported at baseline- (1.1-2.8) Other medications reported at baseline- (1.3-3.8) Non-Hispanic subjects (n=215) Black race- (1.5-4.7) Age- 0.94-0.99) Foreign birth- (0.2-0.9) 	oooo Very Low	CRITICAL
⁴ Patient: monito comple Multiva why al valid a valid valid a valid valid vali	red with monthly etion was poor w riate analysis wa I significant facto nd reliable methor r if the type of pro- cid participants w out unlikely to be on of risk factors out also reliant up pants did not rec al site also receive	the same le transamina ith only 64% s used how rs could noi od of measu eventive the ras 52%, co valid or relia was clear b oon retrospe eive the sai red urine tes	ase levels as well a 6 of patients comp. ever the significan t have been includ urement was not u- rrapy used was inc mpletion rate in the able since all risk f out unlikely to be re- cetive data. Due to me level of care ap sts at every visit w	as those at highe leting 6 months t factor of smoki ed. Definition of sed as patients v cluded in multiva. ose treated with actors were self- eliable since this differences in th part from interver hich may have ir	er risk of hepato of therapy. The ng was not inclu- risk factors was were assumed t riate analysis. S rifampicin was -reported at bas was a retrospe twas a retrospe e methods of e ntion studied as nproved adhere	toxicity; later this v paper does not pro uded in the multiva s unlikely to be vali o be compliant if th come patients were 61% (p=0.3). At lea eline. ctive study and dat valuating adherent different participal ence as patients kr	vas changed to only those at higher ovide the exact doses and lengths o riate analysis model as the alcohol d or reliable since alcohol use and s ney kept monthly appointments at the taking 4 months of rifampicin, som ast six months of isoniazid was com a was retrieved from administrative se on the different hospital sites trea nts were taking different drugs in van we they would be tested	variable provided a better fit of the mod moking was self-reported, as were oth e clinic and self-reported adherence. e were taking 9 months of isoniazid. C pleted by 63% of participants. Definition health data. Definition of treatment co tment completion was chosen as an e- rious combinations with different duration	nt period. T lel instead. er importar ompletion r n of risk fac mpletion ou ndpoint inst ons. Patien	reatment It is unclear It factors.A ate of ctors was tcome was ead. ts on one
outcon consid	ne was clear but ered to have con	also reliant npleted trea	upon retrospective tment if they took	e data. Different 6-9 months of is	methods of eva oniazid daily or	luating adherence twice weekly within	was used depending on the age an n a 9-12 month period; or > 4 month	icin in the rifamycin group. Definition of d regimen of the participant: patients a s of daily rifamycin doses within 6 mor within a 12 month period, or 6 or more	ged >18 ye hths. Patien	ars were ts younger

Appendix E: GRADE profiles

			Quality asse	ssment			No of patients	Effect		
No of		Risk of				Other		Relative		
studies	Design	bias	Inconsistency	Indirectness	Imprecision	consideration	Completion of treatment	(95% CI) Absolute	Quality	Importance

¹⁰ Definition of risk factors was mostly clear however the definition of "medical risk factor," wasn't. Data is unlikely to be reliable since it was obtained by looking retrospectively at medical records. Definition of treatment completion outcome was clear but may be unreliable since the patient was judged to be adherent on the basis of attending monthly appointments and picking up pills; it is uncertain if patients were actually taking the pills. Patients did not necessarily receive the same standard of care due to increased clinical monitoring and blood tests in certain age groups of patients in accordance to guidelines.

¹¹ Definition of risk factors was clear however data is unlikely to be reliable since it was obtained by looking retrospectively at medical records. Definition of treatment completion outcome was clear but may be unreliable since the patient was judged to be adherent on the basis of attending monthly appointments and picking up pills; it is uncertain if patients were actually taking the pills. Data was also retrospective.

A.18 RQ II

Author(s):

Date: 2014-03-03

Question: Should 3 months isoniazid vs 3 months placebo be used for latent tuberculosis? **Settings:** Czechoslovakia, Finland, Germany, Hungary, Poland, Romania, Yugoslavia **Bibliography:**

			Quality asse	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months isoniazid	3 months placebo	Relative (95% CI)	Absolute	Quality	Importance
Incident	ce of active tube	erculosis (fo	ollow-up median	5 years¹; asses	sed with: Clini	cal diagnosis and	biomedical testing	1)				
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	75/6956 (1.1%)	97/6990 (1.4%) 0%	-	14 fewer per 1000 (from 14 fewer to 14 fewer)	©©OO LOW	CRITICAL

¹ No average provided, however five year follow up was complete for 97.2% of the population.

² Unclear for how many participants in each group were no outcome data available or whether groups were comparable with respect to systematic differences between groups in terms of those for whom no outcome data was available. Also more patients were lost in the longer duration treatment regimens.

³ Number of events less than 300

Author(s):

Date: 2014-03-03

Question: Should 6 months isoniazid vs 6 months placebo be used for latent TB?

Settings:

			Quality asse	ssment			No of j	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months isoniazid	6 months placebo	Relative (95% CI)	Absolute	Quality	Importance
Incidend	e of active tube	erculosis (fo	llow-up median	5 years¹; asses	sed with: clini	cal and biomedica	al diagnosis)		,			
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	34/6965 (0.49%)	97/6990 (1.4%) 0%	-	14 fewer per 1000 (from 14 fewer to 14 fewer)	0000 LOW	CRITICAL
² unclear		omparable f	v up was complete for availability of o		participants							

Date: 2014-03-04

Question: Should 12 months Isoniazid vs 12 months placebo be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asse	ssment			No of p	oatients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months Isoniazid	12 months placebo	Relative (95% CI)	Absolute	Quality	Importance
Incidend	ce of active TB (follow-up m	nedian 5 years ¹ ; a	assessed with:	Clinical and bi	omedical diagnos	is)					
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	None	24/6919 (0.35%)	97/6990 (1.4%) 0%	-	14 fewer per 1000 (from 14 fewer to 14 fewer)	©©OO LOW	CRITICAL
			v up was complete for availability of c		participants.							

³ Event number below 300

Author(s):

Date: 2014-03-04

Question: Should 3 months isoniazid vs no treatment be used for latent TB?

Settings:

Bibliography:

			Quality asses	ssment			No of p	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	3 months isoniazid	No treatment	Relative (95% CI)	Absolute	Quality	Importance
Incidend	e of active TB (follow-up 8	years; assessed	with: Clinical a	and biochemic	al diagnosis)						
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none ³	10/82 (12.2%)	17/85 (20%) 0%	-	200 fewer per 1000 (from 200 fewer to 200 fewer)	⊙OOO VERY LOW	CRITICAL

¹ Unclear if an appropriate method of randomisation or allocation concealment was used. No blinding was employed. Unclear how groups were comparable for length of follow up or availability of outcome data. No precise definition of outcome. Unclear if a valid and reliable method was used to determine outcome.

² events less than 300

³ However no information given on funding

Date: 2014-03-04 Question: Should 1 month isoniazid and rifampicin vs no treatment be used for latent TB? Settings: Bibliography:

			Quality asses	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month isoniazid and rifampicin	No treatment	Relative (95% Cl)	Absolute	Quality	Importance
Incidend	ce of active tube	rculosis (fo	ollow-up 8 years;	assessed with	clinical and b	iochemical diagno	osis)					
1	randomised trials	very serious	no serious inconsistency	no serious indirectness	serious ¹	none ²	9/83 (10.8%)	17/85 (20%) 0%	-	200 fewer per 1000 (from 200 fewer to 200 fewer)	⊙OOO VERY LOW	CRITICAL
	number less than rmation on fundin											

Author(s):

Date: 2014-03-04

Question: Should 3 months isoniazid and rifampicin vs no treatment be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asses	ssment			No of J	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months isoniazid and rifampicin	No treatment	Relative (95% CI)	Absolute	Quality	Importance
Incidence	e of Active Tub	erculosis (f	follow-up 8 years	; assessed with	n: clinical and	biochemical diagr	nosis)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none ³	4/85 (4.7%)	17/85 (20%) 0%	-	200 fewer per 1000 (from 200 fewer to 200 fewer)	0000 VERY LOW	CRITICAL

outcome data. No precise definition of outcome. Unclear if a valid and reliable method was used to determine outcome.

² Event number less than 300

³ no information on funding provided

Date: 2014-03-04

Question: Should 1 month isoniazid, pyrazinamide and rifampicin vs no treatment be used for latent TB? Settings:

Bibliography:

			Quality asse	ssment			No of	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month isoniazid, pyrazinamide and rifampicin	No treatment	Relative (95% Cl)	Absolute	Quality	Importance
Inciden	ce of active tube	erculosis (fo	ollow-up 8 years;	assessed with	: clinical and b	iochemical diagn	osis)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none ³	0/80 (0%)	17/85 (20%) 0%	-	200 fewer per 1000 (from 200 fewer to 200 fewer)	⊙OOO VERY LOW	CRITICAL

outcome data. No precise definition of outcome. Unclear if a valid and reliable method was used to determine outcome. ² event rate less than 300

³ no information provided on funding

Author(s):

Date: 2014-03-04

Question: Should 36 months isoniazid vs 6 months isoniazid be used for latent tuberculosis?

Settings:

			Quality asse	ssment			No of	f patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	36 months isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incidenc	e of active tube	rculosis (fo	ollow-up 3 years ¹	; assessed with	n: clinical and	biochemical diagr	iosis)					-
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	4/252 (1.6%)	12/216 (5.6%) 0%	-	56 fewer per 1000 (from 56 fewer to 56 fewer)	⊙⊙⊙O MODE RATE	CRITICAL
Mortality	/ (follow-up 3 ye	ears ¹ ; asses	sed with: numbe	er of deaths)								
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	5/252 (2%)	13/216 (6%) 0%	-	60 fewer per 1000 (from 60 fewer to 60 fewer)	⊙⊙⊙O MODE RATE	CRITICAL

Date: 2014-03-04

Question: Should 4 months rifampicin vs 6 months isoniazid be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asses	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4 months rifampicin	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incidenc	e of adverse ev	ents leadin	g to discontinuat	tion (follow-up	1 months; ass	essed with: Any a	dverse event leadir	ng to permanent dis	continuatio	on of treatm	ent.)	
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	4/190 (2.1%)	22/183 (12%) 0%	-	120 fewer per 1000 (from 120 fewer to 120 fewer)	©⊙OO LOW	CRITICAL
Treatme	nt completion (follow-up 1	months; assesse	ed with: Numbe	r of patients w	ho completed tre	atment)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	163/190 (85.8%)	142/183 (77.6%) 0%	-	776 fewer per 1000 (from 776 fewer to 776 fewer)	©⊙OO LOW	CRITICAL

² event numbers less than 300

Author(s):

Date: 2014-03-04

Question: Should 3 months rifapentine and isoniazid vs 6 months isoniazid be used for latent tuberculosis?

Settings:

			Quality asses	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifapentine and isoniazid	6 months isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
Incidend	ce of active tube	erculosis (fo	ollow-up 3-6 year	s; assessed wit	th: clinical and	biochemical pres	sentation)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	24/328 (7.3%)	22/327 (6.7%) 0%	-	67 fewer per 1000 (from 67 fewer to 67 fewer)	⊙OOO VERY LOW	CRITICAL

			Quality asse	ssment			No of	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifapentine and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Mortality	y (follow-up 3-6	years; asse	essed with: numb	per of deaths)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	17/328 (5.2%)	25/327 (7.6%) 0%	-	76 fewer per 1000 (from 76 fewer to 76 fewer)	⊙OOO VERY LOW	CRITICAL
Hepatot	oxicity (follow-u	ip 3-6 years	; assessed with:	a grade 3 or 4	elevation in the	e aminotransferas	e levels)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	5/328 (1.5%) ³	18/327 (5.5%) ³ 0%	-	55 fewer per 1000 (from 55 fewer to 55 fewer)	⊙OOO VERY LOW	CRITICAL

¹ Neither participants nor clinicians were kept blinded to treatment regimen. Isoniazid alone treatment was self administered while other treatments were directly observed therapy. ² event number less than 300 ³ calculated from percentages

Author(s):

Date: 2014-03-04

Question: Should 3 months rifampicin and isoniazid vs 6 months isoniazid be used for latent tuberculosis?

Settings:

			Quality asse	ssment			No of J	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifampicin and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incident	ce of active tube	erculosis (fo	ollow-up 3-6 year	s; assessed wit	h: clinical and	biochemical diag	nosis)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	24/329 (7.3%)	22/327 (6.7%) 0%	-	67 fewer per 1000 (from 67 fewer to 67 fewer)	⊙OOO VERY LOW	CRITICAL
Mortalit	y (follow-up 3-6	years; asse	essed with: numb	per of deaths)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	16/329 (4.9%)	25/327 (7.6%) 0%	-	76 fewer per 1000 (from 76 fewer to 76 fewer)	⊙OOO VERY LOW	CRITICAL

			Quality asses	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifampicin and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Hepatot	oxicity (follow-u	p 3-6 years	; assessed with:	Grade 3 or 4 ra	ised aminotra	nsferases)						
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	8/329 (2.4%) ³	18/327 (5.5%) ³ 0%	-	55 fewer per 1000 (from 55 fewer to 55 fewer)	⊙OOO VERY LOW	CRITICAL
	r participants nor ate less than 300		ere kept blinded to	o treatment regin	nen. Isoniazid a	lone treatment was	self administered w	hile other treatments	were direct	,	therapy.	

³ calculated from percentages provided

Author(s):

Date: 2014-03-04

Question: Should continous isoniazid vs 6 months isoniazid be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asse	ssment			No o	f patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continous isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incidenc	e of active tube	rculosis (fo	ollow-up 3-6 year	s; assessed wit	th: clinical and	biochemical diag	nosis)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	8/164 (4.9%)	22/327 (6.7%) 0%	-	67 fewer per 1000 (from 67 fewer to 67 fewer)	⊙OOO VERY LOW	CRITICAL
Mortality	(follow-up 3-6	years; asse	essed with: numb	per of deaths)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	8/164 (4.9%)	25/327 (7.6%) 0%	-	76 fewer per 1000 (from 76 fewer to 76 fewer)	⊙OOO VERY LOW	CRITICAL
Hepatote	oxicity (follow-u	p 3-6 years	; assessed with:	grade 3 or 4 ra	ised aminotra	nsferases)						
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	46/164 (28%) ³	18/327 (5.5%) ³ 0%	-	55 fewer per 1000 (from 55 fewer to 55 fewer)	⊙OOO VERY LOW	CRITICAL

² event number less than 300

³ calculated from percentages provided

Date: 2014-03-04

Question: Should 3 months rifabutin dose 300 mg and isoniazid vs 6 months isoniazid be used for latent tuberculosis? **Settings:**

Bibliography:

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifabutin dose 300 mg and isoniazid	6 months isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
Treatme	ent completion (follow-up n	nean 18 months;	assessed with:	number achie	ving 80% adheren	ce to drugs taken)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	13/16 (81.3%)	10/14 (71.4%) 0%	-	714 fewer per 1000 (from 714 fewer to 714 fewer)	⊙OOO VERY LOW	CRITICAL

¹ Unclear if an appropriate method of randomisation was used. Unclear if adequate concealment of allocation. Unclear if groups were comparable at baseline. Neither participants nor clinicians were blinded to treatment group. Unclear if groups were comparable for treatment completion. No precise definition of outcome.
² event rate less than 300

³ Pharmacy funded with poor information about methods and trial terminated early

Author(s):

Date: 2014-03-04

Question: Should 3 months rifabutin 600 mg and isoniazid vs 6 months isoniazid be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asses	ssment			No of p	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifabutin 600 mg and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Freatme	nt completion (follow-up m	ean 17-19 month	is; assessed wi	th: adherence	to drug regimen >	•80%)					
I	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	13/14 (92.9%)	10/14 (71.4%) 0%	-	714 fewer per 1000 (from 714 fewer to 714 fewer)	⊙OOO VERY LOW	CRITICAL

² event number less than 300

Date: 2014-03-04

Question: Should 3 months rifampicin and isoniazid vs 6 months isoniazid be used for latent tuberculosis? **Settings:**

Bibliography:

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifampicin and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Treatme	nt completion (follow-up 5	years; assessed	with: adhering	to >80% of pr	escribed dose)						
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious	None	213/296 (72%)	154/294 (52.4%) 0%	-	524 fewer per 1000 (from 524 fewer to 524 fewer)	0000 LOW	CRITICAL
Hepatot	oxicity (follow-u	p 5 years; a	assessed with: L	iver enzymes >	3 times the no	ormal level)						
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	4/296 (1.4%)	10/294 (3.4%) 0%	-	34 fewer per 1000 (from 34 fewer to 34 fewer)	⊙⊙OO LOW	CRITICAL
Nausea	or vomiting (fol	low-up 5 ye	ars; assessed w	ith: without hep	atotoxicity)							
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	23/296 (7.8%)	24/294 (8.2%) 0%	-	82 fewer per 1000 (from 82 fewer to 82 fewer)	©⊙OO LOW	IMPORTANT
Cutanec	ous toxicity (follo	ow-up 5 yea	ars; assessed wit	th: Rash, pruriti	s, photosensi	tivity)				,		
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	8/296 (2.7%)	5/294 (1.7%) 0%	-	17 fewer per 1000 (from 17 fewer to 17 fewer)	©⊙OO LOW	IMPORTANT
Headach	ne (follow-up 5 y	(ears)								,		
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	None	5/296 (1.7%)	8/294 (2.7%) 0%	-	27 fewer per 1000 (from 27 fewer to 27 fewer)	©©OO LOW	IMPORTANT

¹ event number less than 300

² Neither clinicians nor participants were blinded to treatment group. Groups were not comparable at baseline for sex and number of illegal immigrants. Groups were not comparable for treatment completion and there was a high loss to follow up.

Author(s): Date: 2014-03-04

Question: Should 3 months rifapentine and isoniazid vs 9 months isoniazid be used for latent tuberculosis?

Settings: Bibliography:

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifapentine and isoniazid	9 months isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
incidenc	e of active tube	erculosis (fo	llow-up 33 months	; assessed with		ochemical diagnos						
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	4/3273 (0.12%) ³	8/2585 (0.31%) ³	-	3 fewer per 1000 (from 3 fewer to 3 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
Complet		· · · · · ·	3 months; assesse	1 · · · · · · · · · · · · · · · · · · ·								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	713/3273 (21.8%)⁴	2585/3745 (69%) ⁴	-	690 fewer per 1000 (from 690 fewer to 690 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
Disconti	nuation of treat	ment due to	o adverse events (f	ollow-up 33 mor	ths; assessed	with: Number who	discontinued	treatment due	to adverse	events)		
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	196/3986 (4.9%)	139/3745 (3.7%)	-	37 fewer per 1000 (from 37 fewer to 37 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
Mortality	/ (follow-up 33 r	nonths; ass	sessed with: Numb	er of deaths)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	31/3986 (0.78%)	39/3745 (1%)	-	10 fewer per 1000 (from 10 fewer to 10 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
Hepatote	oxicity (follow-u	ip 33 month	s months; assesse	ed with: unclear	definition)							
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	18/4040 (0.45%)	103/3759 (2.7%)	-	27 fewer per 1000 (from 27 fewer to 27 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

			Quality asso	essment			No of	patients	E	ffect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifapentine and isoniazid	9 months isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
Rash (fo	llow-up 33 mon	ths; assess	sed with: Unclear)									
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	31/4040 (0.77%)	21/3759 (0.56%)	-	6 fewer per 1000 (from 6 fewer to 6 fewer)	⊙OOO VERY LOW	IMPORTANT
								0%		-		
Possible	Hypersensitivi	ty (follow-u	p 33 months)									
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	152/4040 (3.8%)	17/3759 (0.45%)	-	5 fewer per 1000 (from 5 fewer to 5 fewer)	⊙OOO VERY LOW	IMPORTANT
								0%		-		
Adverse	event (follow-u	p 33 month	s; assessed with:	grade 3 or 4)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	229/4040 (5.7%)	244/3759 (6.5%)	-	65 fewer per 1000 (from 65 fewer to 65 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

¹ Unclear if adequate concealment of allocation. Neither clinican nor participant were blinded to treatment group. Treatment group did not recieve the same care appart from intervention studied combination therapy was directly observed, isoniazid was self administered. Unclear if groups were comparable for treatment completion or availability of outcome data. ² event number less than 300

³ Data available in the evidence table for results adjusted per patient-year ⁴ Calculated from number that discontinued treatment

Date: 2014-03-04

Question: Should 9 months isoniazid vs 3 months placebo be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asse	ssment			No of p	atients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	9 months isoniazid	3 months placebo	Relative (95% CI)	Absolute	Quality	Importance
Hepatoto	xicity (assessed	d with: raise	d aminotransferase	s)	-		•					-
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious	none ²	8/60 (13.3%)	1/60 (1.7%)	-	17 fewer per 1000 (from 17 fewer to 17 fewer)	©⊙OO LOW	CRITICAL
								0%		-		
Rash												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none ²	7/60 (11.7%)	6/60 (10%)	-	100 fewer per 1000 (from 100 fewer to 100 fewer)	©⊙OO LOW	
								0%		-		
Nausea												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none ²	2/60 (3.3%)	1/60 (1.7%)	-	17 fewer per 1000 (from 17 fewer to 17 fewer)	©⊙OO LOW	
								0%		-		

² unclear source of funding ³ event number less than 300

Date: 2014-03-04 Question: Should 12 months isoniazid vs No treatment be used for latent tuberculosis? Settings:

Bibliography:

			Quality asses	ssment			No of p	atients	l	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months isoniazid	No treatment	Relative (95% CI)	Absolute	Quality	Importance
incidenc	e of active tuber	culosis (foll	ow-up mean 33-39	months; assesse	d with: clinical	and biochemical of	liagnosis)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	2/58 (3.4%) ³	6/60 (10%) ³	-	100 fewer per 1000 (from 100 fewer to 100 fewer)	©⊙OO LOW	CRITICAL
								0%		-		
² event nu	ling of participant umber less than 3 adjusted for pers	300	s. ailable in evidence ta	ble								

aujusted for person-years avai

Author(s):

Date: 2014-03-04

Question: Should 2 months rifampicin and pyrazinamide vs 12 months isoniazid be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asse	essment			No of pat	ients	E	ffect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2 months rifampicin and pyrazinamide	12 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incidenc	e of active tube	rculosis (fo	llow-up mean 36-3	7 months; asses	sed with: clinic	al and biochemica	l diagnosis)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	28/791 (3.5%)	29/792 (3.7%)	-	37 fewer per 1000 (from 37 fewer to 37 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
Mortality	(follow-up mea	in 36-37 mo	nths; assessed wi	th: Number of de	eaths)							
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	deaths) serious ²	none	139/791 (17.6%)	159/792 (20.1%)	-	201 fewer per 1000 (from 201 fewer to 201 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

participants nor clinicians were blinded to treatment group. Groups were not comparable for treatment completion.

² Number of events less than 300

Date: 2014-03-05 **Question:** Should 12 months isoniazid vs 12 months placebo be used for latent tuberculosis? Settings: Bibliography:

			Quality asse	essment			No of pa	atients	E	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months isoniazid	12 months placebo	Relative (95% Cl)	Absolute	Quality	Importance
ncidence	e of active tuber	culosis (ass	essed with: broad	review of history	and chest xray)							
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	0/6403 (0%)	7/6484 (0.11%)	-	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

high diagnostic bias. ² event number less than 300

Author(s):

Date: 2014-03-05

Question: Should 6 months of isoniazid and ethambutol vs 36 months of isoniazid be used for latent tuberculosis? Settings:

			Quality asse	essment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of isoniazid and ethambutol	36 months of isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
Incidence	e of active tube	rculosis (as	ssessed with: clir	nical and bioche	mical diagnosi	s)				,		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	6 months, isoniazid and ethambutol n=141 TB incidence/100 personyears (95% Cl ²) 3.18 (1.38-4.97)) TB incidence/100 personyears	36 months isoniazid, n=132 TB incidence/100 personyears (95% Cl ²) 1.81 (0.69-3.04) TB incidence/100 personyears (95% Cl ²) per protocol analysis	6 months, and etham n=141 Adjusted i rate ratio (1.48 (0.55 Adjusted i rate ratio (per protoc 1.57 (0.50 36 months n=132 Adjusted i	ncidence 95% Cl ²) , 3.96) ncidence 95% Cl ²), ol analysis , 4.9) s isoniazid,	©©OO LOW	CRITICAL

			Quality asse	ssment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of isoniazid and ethambutol	36 months of isoniazid	Relative (95% CI)	Absolute	Quality	Importance
							(95% Cl ²) per protocol analysis 2.80 (1.06-4.70)	1.84 (0.37-3.32)	rate ratio (Reference Adjusted i rate ratio (per protoc reference	ncidence		
Mortality												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	6 months, isoniazid and ethambutol n=141 Mortality/100 personyears (95% Cl ²) 2.91 (1.19-4.63) Mortality/100 personyears (95% Cl ²) per protocol analysis 3.08 (1.26-4.89)	36 months isoniazid, n=132 Mortality/100 personyears (95% Cl ²) 2.53 (1.21-3.85) Mortality/100 personyears (95% Cl ²) per protocol analysis 2.15 (0.56-3.74)	1.43 (0.53 36 months n=132 Adjusted i rate ratio (Reference Adjusted i rate ratio (ncidence 95% Cl ²) , 4.02) ncidence 95% Cl ²), ol analysis , 3.8) s isoniazid, ncidence 95% Cl ²) e ncidence		

Date: 2014-03-05

Question: Should 6 months of isoniazid and ethambutol vs 36 months of isoniazid be used for latent tuberculosis? **Settings:**

Bibliography:

			Quality asse	ssment			No of p	atients	E	ffect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-9 months of isoniazid therapy	No treatment	Relative (95% CI)	Absolute	Quality	Importance
ncidence	of active tuber	culosis (foll	ow-up 10 years; as	sessed with: clin	ical or bacterio	logical diagnosis)		,		,		-
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	24/1451 (1.7%) ³	10/1519 (0.66%) ³	-	7 fewer per 1000 (from 7 fewer to 7 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		
I ortality	(follow-up 10 ye	ears; assess	ed with: number of	f deaths)								
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	7/1451 (0.48%) ³	7/1519 (0.46%) ³	-	5 fewer per 1000 (from 5 fewer to 5 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

¹ randomisation by date of birth was used, unclear if adequate concealment. Patients in the treatment group were younger. Unclear if comparison groups recieved the same care apart from treatment. Neither participants nor clinicians were blinded to treatment allocation. Unclear if groups were comparable in terms of treatment completion or availability of outcome data.
² event number less than 300

³ follow up data available on a per year basis

Author(s):

Date: 2014-03-05

Question: Should 3 months of rifapentine and isoniazid vs 2 months of rifampicin and pyrazinamide be used for latent tuberculosis? **Settings:**

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months of rifapentine and isoniazid	2 months of rifampicin and pyrazinamide	Relative (95% Cl)	Quality	Importance
Incidenc	e of active tube	rculosis (fo	llow-up at least 2 y	ears; assessed v	with: clinical an	d bacteriological d	iagnosis)				
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	Rifapentine and isoniazid group: • 3 cases in 564 person years of follow up (0.5/100 person-years)	Rifampicin and pyrazinamide group: • 1 case in 522 person- years of follow up (0.2/100 person-years)	Relative risk, 2.8; 95% Cl, 0.3-26.8; p=0.66 i.e. non significant	©OOO VERY LOW	CRITICAL

Quality assessment						No of patients			Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months of rifapentine and isoniazid	2 months of rifampicin and pyrazinamide		elative /5% Cl)	Quality	Importance
Mortality	(follow-up at le	east 2 years	; assessed with: r	number of deaths)							
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	1/206 (0.49%)	3/193 (1.6%)	, (from 16	per 1000 (from 16 fewer to 16	⊙OOO VERY LOW	CRITICAL
								0%		-		
Hepaxici	ty (follow-up at	least 2 yea	rs; assessed with	: Grade 3 or 4)								
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	2/206 (0.97%)	20/193 (10.4%)	p (f fe	104 fewer per 1000 (from 104 fewer to 104 fewer)	⊙OOO VERY LOW	CRITICAL
								0%		-		

¹ Groups did not recieve the same care apart from intervention studied; one group was mostly self administered, the other entirely directly observed. Neither participants nor clinicians were blinded to treatment groups. Groups were not comparable for availability of outcome data. TB diagnoses were confirmed from medical records and health department data bases. Trial was stopped early.
² event number less than 300 Appendix E: GRADE profiles