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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	sitivity: 2 specime	ens (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	sitivity: 3 specime	ens (assessed with: r	number of participa	ints 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
umulativ	/e PCR posit	ivity: 3 specimen	s (assessed with: nu	mber of participant	s with 1 or more p	ositive PCR)					
11	cross- sectional	very serious ^{5,7,8,12}	no serious inconsistency	no serious indirectness	very serious ^{13,1}	4 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
	ositivity by s	pecimen (subgro	up: <5 years) (asses	ssed with: number	positive/total numl	per of specimens obtain	ned)				
2,4	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 partie	cipants with 1 or more	positive culture)				
1 ⁴	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	• •	ip: <5 years) (assess	sed with: number p	ositive/total numb	er of specimens obtair	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 par	ticipants with 1 or mor	e positive smear)				
1 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 o Unclear I Calculat Jiménez Inapproj GRADE Wide co	2009 ee, 2013 5 f a random or d not obtain s of individuals tions criteria for pos f there was a ted by review z, 2013 oriate exclusio rule of thuml onfidence inte	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 unclear llection techniques non-tuberculous m	(Al-Aghbari, 2009 ycobacteria (Jiméi	nez, 2013)	005); blinding of pa	rticipants not s	tated, but unl	ikely given the r	ature of t

			Quality ass	essment			No of pa	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
¹⁶ Forest p	lot (culture po	sitivity by specime	en):								
¹⁷ Forest p	lot (cumulativ	e culture positivity:	2 specimens):								
¹⁸ Forest p	lot (cumulativ	e culture positivity:	3 specimens):								
¹⁹ Forest p	lot (smear pos	sitivity by specime	n):								
²⁰ Forest p	lot (cumulativ	e smear positivity:	3 specimens):								
²¹ Forest p	lot (culture po	sitivity by specime	en; subgroup: <5 yea	rs)							

Nasogastric aspiration/lavage vs induced or spontaneously produced sputum

			Quality asse	essment			No of	patients	Ef	ifect	
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 ⁵ Compara 	if a random or linding unclea criteria for pos	itivity is not stated pontaneously proc		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	ositivity 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	ositivity by sp	ecimen (subgrou	u p: <5 years) (asses	sed with: number	positive/total numb	per 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 asse	essment			No of patie	ents	Eff	ect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasopharyngeal aspiration	Induced sputum	Relative (95% Cl)	Absolute	Quality
Smear pos	sitivity by spe	ecimen (subgrou	p: <5 years) (asses	sed with: number p	ositive/total numbe	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)	⊙OOO VERY LOW
 ⁵ Study did ⁶ Blinding of Precise c ⁷ Precise c ⁸ Unclear it ⁹ GRADE r ¹⁰ Calculate ¹¹ Populatio 	f a random or I not obtain sa of individuals a riteria for posi f there was an 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 co re, but some over 5s	estigators (Owens llection techniques	(Al-Aghbari, 2009	unclear; blinding of pa)	nticipants not stated,	but unlikely	given the natu	e of the interv	entions

¹³ Forest plot (smear positivity by specimen):

Nasopharyngeal aspiration vs nasogastric aspiration/lavage

			Quality asses	ssment			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 po	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	tive/total number o	of 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 positiv	e/total number of	specimens 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

¹ Al-Aghbari, 2009 ² Oberhelman, 2006 ³ Oberhelman, 2010 ⁴ Unclear if a random or consecutive sample was used ⁵ Study did not obtain samples from all included participants (Al-Aghbari, 2009) ⁶ Blinding of individuals administering care (all studies) and investigators (Oberhelman, 2016; Oberhelman, 2010) unclear; blinding of participants not stated, but unlikely given the nature of interventions ⁷ Precise criteria for positivity is not stated ⁸ Unclear if there was an appropriate interval between the 2 collection techniques (Al-Aghbari, 2009) ⁹ GRADE rule of thumb: <300 events				Quality asse	ssment		No of	patients	Ef	fect	
1 Al-Aghbari, 2009 2 Oberhelman, 2006 3 Oberhelman, 2010 4 Unclear if a random or consecutive sample was used 5 Study did not obtain samples from all included participants (Al-Aghbari, 2009) 6 Blinding of individuals administering care (all studies) and investigators (Oberhelman, 2006; Oberhelman, 2010) unclear; blinding of participants not stated, but unlikely given the nature of interventions 7 Precise criteria for positivity is not stated 0 Unclear if there was an appropriate interval between the 2 collection techniques (Al-Aghbari, 2009) 9 GRADE rule of thumb: <300 events		Design	Risk of bias	Inconsistency	Indirectness	Imprecision		• • • • • • • • • • • • • • • • • • •		Absolute	Quality
 ² Oberhelman, 2006 ³ Oberhelman, 2010 ⁴ Unclear if a random or consecutive sample was used ⁵ Study did not obtain samples from all included participants (AI-Aghbari, 2009) ⁶ Blinding of individuals administering care (all studies) and investigators (Oberhelman, 2006; Oberhelman, 2010) unclear; blinding of participants not stated, but unlikely given the nature of interventions ⁷ Precise criteria for positivity is not stated ⁸ Unclear if there was an appropriate interval between the 2 collection techniques (AI-Aghbari, 2009) ⁹ GRADE rule of thumb: <300 events 									1.22) ¹⁰	fewer to 3	LOW
¹⁰ Calculated by reviewer ¹¹ Forest plot (culture positivity by specimen):	 ⁴ Unclear if ⁵ Study did ⁶ Blinding contention ⁷ Precise contention ⁸ Unclear if ⁹ GRADE r ¹⁰ Calculate 	f a random or I not obtain sa of individuals ions riteria for pos f there was ar rule of thumb: ed by reviewe	amples from all in administering car itivity is not state appropriate inte <300 events er	cluded participants re (all studies) and in d rval between the 2 d	nvestigators (Ober	helman, 2006; Ol	clear; blinding of pan	iicipants not stated, bu	ıt unlikely giv	en the nature	of the

Nasogastric aspiration/lavage vs bronchoalveolar lavage

Design tivity (asses cross- sectional	Risk of bias ssed with: numbe serious ^{4,5,6,7}	Inconsistency er of participants with no serious		Imprecision e culture (cumula	Other considerations	Nasogastric aspiration/lavage	Bronchoalveolar	Relative		
cross-	ssed with: numbe serious ^{4,5,6,7}			e culture (cumula			lavage	(95% CI)	Absolute	Quality
	serious ^{4,5,6,7}	no serious			ative yield for 3 GA sp	pecimens vs 1 BAL sp	ecimen))			
		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
		r of participants with	a positive smear ((1 GA specimen v	vs 1 BAL specimen))					
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
vity (subgr	oup: <5 years) (assessed with: num	ber of participants	with a positive si	mear (cumulative yie	Id for 3 GA specimen:	s vs 1 BAL specimen))		
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
becimen (s	ubgroup: <5 yea	ars) (measured with:	mean volume of s	specimens obtain	ed; better indicated b	oy higher values)				
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
	ross- ectional rity (subgr ross- ectional ecimen (su ross- ectional	ross- serious ^{4,6,7} ectional rity (subgroup: <5 years) (ross- serious ^{4,6,7} ectional ecimen (subgroup: <5 yea ross- serious ^{4,6,7} ectional	ross- ectional serious ^{4,6,7} no serious inconsistency vity (subgroup: <5 years)	ross- ectionalserious seriousno serious inconsistencyno serious indirectnessvity (subgroup: <5 years)(assessed with: number of participants no serious inconsistencyno serious indirectnessvity (subgroup: <5 years)(assessed with: number of participants inconsistencyno serious indirectnessectionalserious seriousno serious inconsistencyno serious indirectnessectionalserious seriousno serious inconsistencyno serious indirectness	ross- ectional serious ^{4,6,7} no serious inconsistency no serious indirectness serious ⁸ vity (subgroup: <5 years) (assessed with: number of participants with a positive sinces) no serious no serious serious ⁸ vity (subgroup: <5 years) (assessed with: number of participants with a positive sinces) no serious no serious serious ⁸ ectional serious ^{4,6,7} no serious no serious serious ⁸ ectional serious ^{4,6,7} no serious no serious serious ¹¹ ross- ectional serious ^{4,6,7} no serious no serious serious ¹¹	ectional inconsistency indirectness rity (subgroup: <5 years)	ross- ectionalseriousno serious inconsistencyno serious indirectnessseriousnone6/52 (11.5%)rity (subgroup: <5 years)(assessed with: number of participants with a positive smear (cumulative yield for 3 GA specimens ross- ectionalno seriousnone0/20 (0%)recimen (subgroup: <5 years)(measured with: mean volume of specimens obtained; better indicated by higher values) no seriousno serious no seriousserious ¹¹ none20 mean (range) = 35	ross- ectionalseriousno serious inconsistencyno serious indirectnessseriousnone6/52 (11.5%)16/52 (30.8%)rity (subgroup: <5 years)(assessed with: number of participants with a positive smear (cumulative yield for 3 GA specimens vs 1 BAL specimen no serious inconsistencyno serious indirectnessserious seriousnone6/52 (11.5%)16/52 (30.8%)ross- ectionalserious inconsistencyno serious indirectnessserious seriousnone0/20 (0%)0/20 (0%)ectionalserious inconsistencyno serious indirectnessserious seriousnone20 mean (range) = 35 (20-55) ml20 mean (range) = 35 (20-55) ml	rity (assessed with: number of participants with a positive smear (1 GA specimen vs 1 BAL specimen)) $I = 10^{-10}$ $I = 10^{-1$	indicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindicationindication<

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

			Quality asse	essment			No of p	oatients	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 ⁷ Precise o ⁸ GRADE ⁹ Calculate ¹⁰ Abadco, ¹¹ Insufficie 	994 if studies mao of individuals criteria for pos rule of thumb. ed by reviewe 1992	administering ca itivity is not state <300 events r able to appraise i	nterval between spe re and investigators d	cimen collections (unclear; blinding c	Cakir, 2008; Caki f participants not	r, 2013) stated, but unlikely g	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)						
1 ¹	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 GRADE rule of thumb: <300 events
 ⁶ Calculated by reviewer

Nasogastric aspiration/lavage vs laryngeal swab

			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
Cumulative			nens (assessed with	: number of partic	ipants with 1 or r	more positive culture)					
2 ^{1,2}	cross-	serious ^{3,4,5,6}	no serious	no serious	serious'	none	20/90	42/90	OR 0.29	26 fewer	0000

			Quality asse	essment			No c	of patients	Ef	fect	
lo of						Other	Nasogastric		Relative		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	aspiration/lavag		(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
Cumulativ						more positive smear)					
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
	e culture pos		nens (subgroup: <			of participants with 1	or more positive cult				
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)	⊙OOC VERY LOW
	/e smear posi	itivity: 3 specim	nens (<5 years) (as	sessed with: num	ber of participant	s with 1 or more posi	itive 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)	⊙OOC VERY LOW
Cumulativ	e culture pos		nens (subgroup: >	5 years) (assesse	ed with: number	of participants with 1	or more positive cult	ure)			
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)	©OOC VERY LOW
	/e smear posi	itivity: 3 specim	ens (subgroup: >	5 years) (assesse	d with: number o	f participants with 1 of	or more positive sme	ar)			
l ¹ Bhandan	cross- sectional	serious ^{3,4,5,6}	no serious inconsistency	no serious indirectness	serious'	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)	⊙OOC VERY LOW

⁴ Blinding of individuals administering care and investigators unclear; blinding of participants not stated, but unlikely given the nature of the interventions
 ⁵ Precise criteria for positivity is not stated
 ⁶ Unclear if exclusions were appropriate
 ⁷ GRADE rule of thumb: <300 events
 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	ect	
No of						Other	Nasogastric		Relative		Quality
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 p	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		nens (assessed wit	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
						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	sitivity: 3 specin		5 years) (assesse		of participants with 1 o					
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	participants with 1 or	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
Cumulativ	ve culture pos		nens (subgroup: >	5 years) (assesse	ed with: number of	of participants with 1 o	r more positive culture	e)			
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
Cumulativ	ve smear pos		ens (subgroup: >5	years) (assessed	d with: number of	participants with 1 or	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 Bhandar	i, 1976										

			Quality asse	ssment			No of p	atients	Ef	fect	
No of studies	Desian	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasogastric aspiration/lavage	Lung puncture	Relative	Absolute	Quality
² Unclear it	a random or	consecutive sam	ple was used						(
		administering car itivity is not stated		unclear; blinding c	of participants no	t stated, but unlikely g	iven the nature of the	interventions			
		ere appropriate	4								

° GRADE rule of thumb: <300 events ⁷ Calculated by reviewer

Suctioned vs coughed induced sputum

			Quality asses	ssment			No of	patients	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
Culture p	ositivity by speci	i men (assesse	d with: number pos	sitive/total numbe	r of specimens o	otained)					
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)	⊙OOC VERY LOW
	events - none (as	sessed with: n	umber of procedure	es completed with	hout adverse eve	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)	⊙OOO VERY LOW
Adverse e	events – nose ble	ed (assessed	with: number of pro	ocedures in whicl	h 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)	⊙OOO VERY LOW
Adverse e	events - wheeze	(assessed with	: number of procee	dures that led to	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)	⊙OOO VERY LOW
	events – exacerb	ation of coug		number of proced	ures that led to e	xacerbation of cough)				
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)	⊙OOO 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	atients	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 ci	riteria for positivi	ty is not stated									
⁵ Unclear if	groups were col	mparable at bas	seline								
⁶ GRADE n	ule of thumb: <3	00 events									
⁷ Calculate	d by reviewer										

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

			Quality asses	ssment			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		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 (mea	sured with: mea	an volume of speci	mens obtained; b	etter indicated by	y 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

Maciel, 2010

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% CI)	Absolute	Quality
	ity of the proce ated by higher so		s – usefulness of	the sedation (as	sessed with: sco	re derived from quest	tionnaire, answered us	sing a visual analogue	e scale ('0' f	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 proce ated by higher so		s – impact on chi	ld's outlook (ass	essed with: score	e derived from question	onnaire, answered usi	ng a visual analogue	scale ('0' foi	r worst, '10' fo	or best);
1 ¹	randomised	serious ²	no serious	no serious	serious ³	none	Median (range) =	Median (range) =	-	Difference	0000

			Quality asses	ssment			No of p	oatients	Ef	fect	
No of	Destina	Risk of		1		Other	Nasogastric	In desired sounds and	Relative	Alexalate	Quality
studies	Design trial	bias	inconsistency	Indirectness indirectness	Imprecision	considerations	aspiration/lavage 8.9 (7–10)	Induced sputum 5.8 (5–7)	(95% CI)	Absolute in medians = 3.1 ⁴	Quality LOW
			nts – impact on pa	rents' outlook (a	ssessed with: sc	ore derived from que	estionnaire, answered u	sing a visual analogu	e scale ('0' f		for best)
better indi 1 ¹	cated by higher s randomised	cores) serious ²	no serious	no serious	serious ³	none	Median (range) =	Median (range) =	1.	Difference	0000
	trial	3011003	inconsistency	indirectness	301003	hone	9.1 (8–10)	4.9 (3–7)		in medians = 4.2^4	LOW
	ility of the proce er indicated by hi		nts – child's tolera	nce of procedure	es (assessed wit	h: score derived from	n questionnaire, answer	ed using a visual and	alogue scale	('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	l analogue s	cale ('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	0000 LOW
			nts – would like to); better indicated by		l atomizer devic	e used routinely (as	ssessed with: score der	ived from questionna	ire, 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		cians – usefulness	of the sedation	(assessed with: s	score derived from qu	uestionnaire, answered	using a visual analog	gue scale ('0	' 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
	ility of the proce cated by higher s		cians – impact on c	hild's outlook (a	assessed with: so	core derived from que	estionnaire, answered u	using a visual analogu	ue scale ('0'	for worst, '10	' for best)
1 ¹	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		cians – impact on c	linician's outloc	ok (assessed with	n: score derived from	questionnaire, answer	ed using a visual ana	logue 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	⊙⊙OC LOW

Risk of plas Inconsister re to clinicians – child's er scores) - child's serious ² no serious inconsistence re to clinicians – would in oy higher scores) - would in serious ² serious ² no serious inconsistence re to clinicians – would in or best); better indicate	tolerance of proced no serious indirectness recommend to other no serious indirectness	serious ³ r clinicians (asse serious ³	none essed with: score de none	Median (range) = 8.2 (7–9) rived from questionnaire Median (range) = 9.4 (9–10)	Median (range) = 8 (7–9) e, answered using a v Median (range) = 3 (1–5)	- isual analog	Difference in medians = $\frac{4}{4}$ ue scale ('0' f Difference in medians = 6.4^4	©⊙OC LOW
er scores) serious ² no serious inconsistend by higher scores) serious ² no serious inconsistend re to clinicians – would I 10' for best); better indicate	no serious indirectness recommend to other no serious indirectness	serious ³ r clinicians (asse serious ³	none essed with: score de none	Median (range) = 8.2 (7–9) rived from questionnaire Median (range) = 9.4 (9–10)	Median (range) = 8 (7–9) e, answered using a v Median (range) = 3 (1–5)	- isual analog	Difference in medians = $\frac{4}{4}$ ue scale ('0' f Difference in medians = 6.4^4	©⊙OC LOW for worst,
inconsistence re to clinicians – would in by higher scores) serious ² no serious inconsistence re to clinicians – would I 10' for best); better indicate	recommend to other no serious indirectness	r clinicians (asse serious ³	essed with: score de none	8.2 (7–9) rived from questionnaire Median (range) = 9.4 (9–10)	8 (7–9) e, answered using a v Median (range) = 3 (1–5)	-	in medians = $_{4}^{4}$ pue scale ('0' f Difference in medians = 6.4^{4}	LOW for worst,
by higher scores) serious ² no serious inconsistence re to clinicians – would l 10' for best); better indicate	no serious indirectness ike to see the muco	serious ³	none	Median (range) = 9.4 (9–10)	Median (range) = 3 (1–5)	-	Difference in medians = 6.4^4	0000
inconsistence re to clinicians – would I 10' for best); better indicate	indirectness			9.4 (9–10)	3 (1–5)		in medians = 6.4 ⁴	
10' for best); better indicate		sal atomizer de	vice used routinely	(accord with coord				
· · ·	ed by moner scores).		vice used redditiony	(assessed with, score of	derived from question	naire, answe	ered using a v	/isual
serious ² no serious inconsistenc	no serious	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 3 (1–5)	-	Difference in medians = 7 ⁴	©©OC LOW
	he procedure more	acceptable (ass	essed with: score de	rived from questionnaire	e, answered using a v	risual analog	ue scale ('0' f	for worst
serious ² no serious	no serious cy indirectness	serious ³	none	Median (range) = 10 (10–10)	Median (range) = 3 (1–5)	-	Difference in medians = 7 ⁴	©©OC LOW
	re to clinicians – made to by higher scores) erious ² no serious inconsistenc	re to clinicians – made the procedure more by higher scores) erious ² no serious no serious inconsistency indirectness ated, but unlikely given the nature of the interve	re to clinicians – made the procedure more acceptable (assorby higher scores) erious ² no serious no serious serious ³ inconsistency indirectness ated, but unlikely given the nature of the interventions	re to clinicians – made the procedure more acceptable (assessed with: score de by higher scores) erious ² no serious no serious serious ³ none inconsistency indirectness ated, but unlikely given the nature of the interventions	re to clinicians – made the procedure more acceptable (assessed with: score derived from questionnaire by higher scores) erious ² no serious inconsistency inconsistency no serious indirectness ated, but unlikely given the nature of the interventions	re to clinicians – made the procedure more acceptable (assessed with: score derived from questionnaire, answered using a very higher scores) erious ² no serious no serious serious ³ none Median (range) = Median (range) = 10 (10–10) 3 (1–5) ated, but unlikely given the nature of the interventions	re to clinicians – made the procedure more acceptable (assessed with: score derived from questionnaire, answered using a visual analog by higher scores) erious ² no serious no serious serious ³ none Median (range) = Median (range) = - ated, but unlikely given the nature of the interventions Serious Serious	re to clinicians – made the procedure more acceptable (assessed with: score derived from questionnaire, answered using a visual analogue scale ('0' for y higher scores) erious ² no serious no serious inconsistency no serious indirectness serious ³ ated, but unlikely given the nature of the interventions

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		
Test	evaluation	_		Inconsisten Indirectnes		Other	patients/	Summary of		
details	S	Design	Risk of bias	су	S	Imprecision	considerations	specimens	findings	Quality
Sensitivit	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	serious ⁵	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	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):

² Both 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
Sensitivit	у									
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

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% Cl 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

Test	Number of	Quality assessment		Number of	Summary of	Quality
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details	evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimens	findings	
Sensitivity	,									
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% Cl 39.4 to 62.0%)	VERY 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 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 as	ssessment				Number of		
Test details	Number of evaluation	Design	Risk of bias	 Indirectnes	Imprecision	Other considerations	patients/ specimen	Summary of 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	r 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%)	MODERAT E
Fluoresce nce microsco py	Chaidir, 2013 ¹	cross- sectiona I ³	serious ^{5,6}	serious⁴	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% CI 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% Cl 100 to 100%) 99.8% (95% Cl 99.3 to 100%) 90.4% (95% Cl 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			
Test details	Number of evaluation s	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
³ Both ind	ex test and refe	erence stan	dard performed	in every patient	, with an approp	priate period of ti	ime between the two			
⁴ Referen	ce standard var	ies across	studies: culture	technique not c	onsistent					
⁵ Unclear	if a consecutive	e 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	
⁸ Wide co	nfidence interva	al	Ū						·	
⁹ Significa	ant variation in th	he point est	timates, as well	as wide confide	ence intervals wi	th limited overla	р			
¹⁰ Countrie	es/territories wit	th an estimation		ate of 40 per 10	0,000 or greate		to have a high incide	ence of tubercu	ulosis, as defined b	y 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		
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
Sensitivity	/									
Microsco py, chest x-ray plus symptom s ¹	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
Specificity	/									
Microsco py, chest x-ray plus symptom s ¹	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
¹ Any 1 of the ² Swindells	•	symptoms:	cough, fever, w	eight loss and r	hight sweats					

		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	ex test and refe	rence stand	dard performed	in every patient	, with an approp	priate period of t	ime between the two	,		
⁴ Unclear i	if inappropriate	exclusions	were avoided							
⁵ Unclear i	if test interpreta	tion was bl	inded in all or m	ost of the includ	ded comparison	s				
⁶ Unclear i	if a threshold fo	r test interp	retation was pro	especified in all	or most of the i	ncluded compar	isons			
7 Unclear I	how many parti	cipants, if a	ny, are under 1	8 years old; how	vever, it is not a	nticipated that th	he results will be sig	nificantly affec	ted by this	
⁸ Countrie	s/territories with	n an estima	ted incidence ra	te of 40 per 100	0.000 or greater	are considered	to have a high incid	ence of tuberc	ulosis, as defined	by Public

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 bias⁴	serious⁵	serious⁵	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	ts 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	k test and refe	rence stand	dard performed	in every patient,	with an approp	riate period of ti	me 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	y ¹									
LAM	2 ⁶	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	y ^{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	lots:									
⁴ Unclear	if inappropriate	exclusions	n sample used ir were avoided ir linded in Mutetw	Mutetwa (2009	•					
	•		a (2009) in the n	· · ·						
			h limited overlap		ence intervals					
⁸ Countrie	s/territories with	n an estima	•	te of 40 per 100	0,000 or greater	are considered	to have a high incid	ence of tuberculo	osis, as defined by	Public
9 Meta-an	alysis of relevar	nt data not	possible in STA	TA or R						

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	serious⁵	No industry involvement Conducted in a high incidence country ⁶	52	85.3% (95% Cl 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

²Both 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
- 1	30									-	

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% Cl 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

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% Cl 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

	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			

Appendix E: GRADE profiles ¹ Forest plots for sensitivity and specificity (grouped by technique used):

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 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	ent		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: \geq 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: \geq 56 points ¹									
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: \geq 74 points ¹	1 ²	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	1 ²	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	1 ²	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	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	7% (95% Cl 4% to 12%)	MODERAT E	
Chest radiograph – clinical officer with practical experience, but not considered 'expert' Threshold for interpretation: category 3 or 4 ⁴	1 ²	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: \geq 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	Number of				
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: \geq 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 E
Chest radiograph – CAD4TB (computer- aided detection system) Threshold for interpretation: \geq 74 points ¹	1 ²	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	1 ²	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

				Quality assessm	nent		Number of			
Test details	Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality	
category 4 ⁴										
Chest radiograph – 'expert reader' Threshold for interpretation: category 3 or 4 ⁴	1 ²	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	1 ²	cross- sectional	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	861	65% (95% CI 58 to 71%)	MODERAT E	
4 ⁴ ¹ Out of 100 poin	 scores generat score for the pr 	ed by these s	ubsystems are co	ection of textural an mbined to an overa						

				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										
4. abnorm										

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	Quality 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
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	Sensitivity and specificity:									
	Study			Sensitivity (95% CI)		Specificity (95% Cl)		

		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 of findings		Quality	
	Bock, 1996	5			81% (66 to 91%) 62% (62% (56 to 68%)	62% (56 to 68%)				
	El-Solh, 19	97			100% (78 to	0 100%)		50% (44 to 57%)	o (44 to 57%)				
	El-Solh, 19	999			100% (91 to 100%)			72% (65 to 77%)					
	Lagrange->	Xelot, 2010			96% (80 to 100%)			21% (14 to 30%)					
	Moran, 200)9			96% (91 to 99%)			49% (47 to 51%)					
	Mylotte, 19	97			88% (47 to100%)			63% (56 to 70%)					
	Solari, 200	olari, 2008			93% (86 to 97%)			42% (36 to 49%)					
	Soto, 2008	2008			93%			92%					
	Soto, 2011	2011			24% (18 to 31%)			93% (91 to 95%)					
	Wisnivesky	, 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°C – scores 0; temperature 38.5-39°C – scores 3; temperature >39°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	issessment					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		scores 4	aemoptysis – scores 2; weight loss – scores 1; age >45 years – scores -1; expectoration – scores -1; apical infiltrate – scores 3; miliary infiltrate –								
Soto, 2011		Haemoptysis – scores 4 Score ≥5 = hig		oss – scores 1; ag	ge >45 years – so	cores -1; expecto	ration – scores -1; ap	pical infiltrate – s	scores 3; miliary ir	nfiltrate –	
Wisnivesky, 2		scores -3; temp scores -3; uppe		- 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 evaluation 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 an	d specificity	/:					Γ			
	Study			Sensitivity	-		Specificity (95% C	1)		
		e-Xelot, 2010		96% (80 to	100%)		21% (14 to 30%)			
	Soto, 20	08		93%			92%			
	Soto, 20	11		24% (18 to	31%)		93% (91 to 95%)			
	Wisnives	sky, 2005		95% (74 to	100%)		35% (31 to 40%)			
² Scoring syste	ems used:									
Study	L	Details of ches	t radiograph scor	ing system						
Lagrange-Xel	ot, 2010 s	cores -3; temp cores -3; uppe	perature <38.5°C	 scores 0; temper chest x-ray – sco 	ature 38.5-39°C		erculin skin test in the berature >39°C – sco			
Soto, 2008	s	Haemoptysis – scores 4 Score >4 = hig		loss – scores 1; ag	ge >45 years – s	cores -1; expecto	pration – scores -1; a	pical infiltrate –	scores 3; miliary	infiltrate –
Soto, 2011	S	laemoptysis – cores 4 Score ≥5 = hig		loss – scores 1; a	ge >45 years – s	cores -1; expecto	pration – scores -1; a	pical infiltrate –	scores 3; miliary	infiltrate –
Wisnivesky, 2	ר 005 s	uberculosis ri cores -3; temp	sk factors or chro perature <38.5°C		ature 38.5-39°C		erculin skin test in the perature >39°C – sco			

		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 abov	е						
⁴ Unclear if int always conduct ⁵ Unclear if a conduct ⁶ Unclear if ina ⁷ Index test va ⁸ Reference st ⁸ Reference st	erpretation of r cted blind to th consecutive or appropriate exc ries significant candard was per rovide no detai	reference s e reference random sa clusions we tly across s ermitted by ils of the ag	tandard was blin e standard mple of participa re avoided tudies reviewers to be ge of the study po	ints used liquid or solid culti opulation; howeve	ure; consistency	v in the exact tec	udies (2 of 4), althou chniques used acros esults will be significa	s studies is no	t clear	est was

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% Cl 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% Cl 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% Cl 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% Cl 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	1 ⁴	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% Cl 98.3 to 99.3%)	VERY LOW

Appendix E: GRADE profiles

		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
•	for sensitivity a	and specific	city (grouped by t	echnique used):						
Amplicor										
Amplified M.	Tuberculosis D	virect Test								
BDProbeTec										
BDProbeTec	ET									
Cobas Amplic	or									
Enhanced Am	nplified M. Tub	erculosis D	irect lest							
Xpert MTB/RI	Faccov									
Apert INT D/RI	г аззау									
² Both index te	est and referen	nce standar	d performed in ev	very patient, with	an appropriate p	period of time be	etween the two			
³ Scott, 2011										
⁴ Kurbatova, 2 ⁷ Many studie		consecutiv	ve or random sar	nple or did not rep	oort the samplin	a approach user	4			
	appropriate exc				Soft the Sumplin	g approach aset				
⁹ Many studie	s did not blind	test interpr	etation or did not	report the degree						
				ecified in all or m						
							sults will be significa			
	standard varied s or smear stat		m study to study,	, using different cu	ulture technique	s and in some ca	ases employing a n	umber of additi	onal reference c	riteria (e.g. clir

Number of evaluationNumber of evaluationInconsistenc yIndirectnes sOther considerationspatients/ specimen sSummary of findingsQuality			Quality a	ssessment			Number of		I
		S	Design	Risk of bias	Indirectnes s	Imprecision		Quality	l

vvide 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% Cl 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% CI 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% Cl 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% Cl 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	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
							sponsored Majority of studies were conducted in a high incidence country ¹³			
¹ Forest plots f Amplicor	for sensitivity a	and specific	city (grouped by t	echnique used):						
Amplified M. T	uberculosis D	irect Test								
BDProbeTec B	ΞT									
Cobas Amplic	or									
Enhanced Am	plified M. Tub	erculosis D	irect Test							
Xpert MTB/RI	⁻ assay									
 ⁵ Many studies ⁶ Unclear if ina ⁷ Many studies ⁸ Unclear if a t ⁹ Unclear how ¹⁰ Reference s clinical charace ¹¹ Wide confid ¹² Significant w 	est and referent a did not use a appropriate exe a did not blind hreshold for te many particip tandard varied teristics or sm ence interval variation in the	consecutive clusions we test interpre- ants, if any d widely fro ear status) point estin	ve or random san ere avoided etation 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	oort the sampline of blinding use st of the include it is not anticipa ulture technique	g approach used ed ad comparisons ated that the res s and in some c ited overlap		umber of additi	onal reference ci	

		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
			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% CI 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		
	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	2739	96.5% (95% CI 92.3 to 98.5%)	VERY LOW
							country ¹²			

		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		Cl 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% Cl 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% Cl 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% CI 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	Qualit
Cobas Amplic	cor									
Enhanced An	nplified M. Tube	erculosis D	irect Test							
Xpert MTB/RI	F assay									
 ⁵ Unclear if ina ⁶ Many studie ⁷ Unclear if a ⁸ Unclear how 	appropriate exc s did not blind threshold for te / many particip tandard varied	clusions we test interpre st interpret ants, if any	re avoided etation or did not ation was prespe , are under 18 ye		of blinding use st of the include it is not anticipa	d d comparisons ated that the res	ults will be significar uses employing a nu			teria (e.c

i nage saeet								take: eare		
		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

Test detailsevaluation sDesignRisk of biasInconsistenc yIndirectnes sImprecisionConsiderationsspecimen considerationsSummary of findingsQualityaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa <td< th=""><th></th><th></th><th>Quality a</th><th>ssessment</th><th></th><th></th><th></th><th></th><th>Number of</th><th></th><th></th></td<>			Quality a	ssessment					Number of		
Image: Specificity Image: Specificity Image: Specificity Serious ^{4,5,6,7,8} serious ⁹ serious ^{10,11} serious ¹² Industry involvement unclear 3033 See forest plot below ^{1,13} VERY LOW ¹ Forest plots: 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 inappropriate exclusions were avoided	Test details		Design	Risk of bias	Inconsistenc y		Imprecision				Quality
Phage-based tests 5 ² cross-sectiona serious ^{4,5,6,7,8} serious ⁹ serious ^{10,11} serious ¹² Industry involvement unclear 3033 See forest plot below ^{1,13} VERY 								which studies			
based tests sectiona I based tests sectiona I based tests based based tests	Specificity ¹										
 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 		5 ²		serious ^{4.5.6,7,8}	serious ⁹	serious ^{10,11}	serious ¹²	involvement unclear Unclear TB incidence in countries in which studies	3033	See forest plot below ^{1,13}	
³ 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	² Dinnes, 2007 ⁴ Both index te ⁵ Unclear if a d ⁶ Unclear if ina ⁷ Unclear if tes ⁸ Unclear if a t	7 est and referen consecutive or appropriate exc st interpretation threshold for te	random sa clusions we n was blind est interpret	mple was used re avoided ed ation was prespe				etween the two			

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

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			

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% CI 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

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

		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	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	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
							country ¹¹			
¹ Forest plots:										
² Both index te	est and referen	ce standar	d performed in ev	very patient, with	an appropriate p	period of time be	etween the two			
³ Unclear if a	consecutive or	random sa	ample was used							
⁴ Unclear if ina	appropriate exc	clusions we	ere avoided							
⁵ Unclear if te	st interpretation	n was blind	led							
⁶ Unclear if a t	threshold for te	est interpret	tation was prespe	cified in all or mo	st of the include	ed comparisons				
7 Reference st	tandard varied	widely fror	n study to study							
		•	• •	ars old: however.	it is not anticipa	ated that the res	ults will be significar	ntly affected by	/ this	
							treatment response			
			nates, as well as v							
-		•				•	ve a high incidence	of tuberculosis	s as defined by I	Public
			cidence for in the				ave a myri meidenee		s, as achined by I	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 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% Cl 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

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
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	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
antibody detection tests		I				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 tes ⁶ Unclear if a t ⁷ Reference st ⁸ Unclear how ⁹ Reference st ¹⁰ Significant v ¹¹ Countries/tes 	consecutive or appropriate exc st interpretation threshold for te tandard varied many particip tandard somet variation in the erritories with a	random sa clusions we n was blind est interpre- widely fror ants, if any imes includ point estim n estimate	ample was used are avoided ded tation was prespen n study to study r, are under 18 ye ded more than just nates, as well as d incidence rate	very patient, with a ecified in all or mo ears old; however, st culture, for exar wide confidence i of 40 per 100,000 e UK are 13.9 per	st of the include it is not anticipa nple X-ray, clini ntervals with lim or greater are o	ed comparisons ated that the res cal features and ited overlap	ults will be sign I treatment resp	onse	d by this losis, as defined by	Public

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

	Number	Quality as	ssessment							
Test details		Design	Risk of bias	Inconsistenc y	Indirectness	Imprecisio n	Other considerations	Number of patients/ specimens	Summary of findings	Quality
Sensitivity ¹										
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% Cl 83.4 to 93.3%)	VERY LOW
Specificity ¹										

	Number	Quality as	sessment							
Fest detailsevaluatio nsGRAs32.3		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 plot	ts:									
			used in Kabeer							
good clinica ⁷ Unclear if f ⁹ Reference ⁹ Unclear ho ¹⁰ Reference ¹¹ Wide cont ¹² Countries Health Engl ¹³ Meta-ana	al and radiogra test interpreta standard vari ow many partie e standard inc fidence interva s/territories wit and; current e lysis of releva	aphic respon tion was blir ed cipants, if ar cluded histol al h an estimat estimates of nt data not p	ses to anttuber nded ogy as an alterr ed incidence ra incidence for in possible in STA	culosis treatment 18 years old in Ka ative to culture in te of 40 per 100,0 the UK are 13.9 p TA or R	ng (2007); howe Kang (2007) 00 or greater ar er 100,000	ever, it is not and	od of active TB and a ticipated that the res	ults will be sign ce of tuberculo	ificantly affected b sis, as defined by I	y this
good clinica ⁷ Unclear if f ³ Reference ⁹ Unclear ho ¹⁰ Reference ¹¹ Wide cont ¹² Countries Health Engl ¹³ Meta-ana	al and radiogra test interpreta standard vari ow many partie e standard inc fidence interva s/territories wit and; current e lysis of releva	aphic respon tion was blir ed cipants, if ar cluded histolo al h an estimat stimates of nt data not p comparec	ses to anttuber nded by, were under 7 bgy as an alterr red incidence ra incidence for in bossible in STA to culture-t	culosis treatment 18 years old in Ka ative to culture in te of 40 per 100,0 the UK are 13.9 p TA or R	ng (2007); howe Kang (2007) 00 or greater ar er 100,000	ever, it is not and	ticipated that the res	ults will be sign ce of tuberculo onary tuberc	ificantly affected b sis, as defined by l c ulosis	y this
good clinica ⁷ Unclear if f ⁹ Reference ⁹ Unclear ho ¹⁰ Reference ¹¹ Wide cont ¹² Countries Health Engl ¹³ Meta-ana	al and radiogra test interpreta standard vari ow many partie e standard inc fidence interva s/territories wit and; current e lysis of releva skin tests Number of evaluatio	aphic respon tion was blir ed cipants, if ar cluded histole al h an estimate stimates of nt data not p compared Quality	ses to anttuber nded by, were under 7 ogy as an alterr red incidence ra incidence for in bossible in STA to culture-k assessment	culosis treatment 18 years old in Ka hative to culture in te of 40 per 100,0 the UK are 13.9 p TA or R based referenc Inconsisten	ng (2007); howe Kang (2007) 00 or greater ar er 100,000 e standard ir	ever, it is not and e considered to adults with	ticipated that the res	ults will be sign ce of tuberculo onary tuberc Number o patients/	ificantly affected b sis, as defined by l c ulosis	y this

Sensitivity										
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		Quality
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	
							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	s 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 histology	as an alternativ	e to culture in Kar	ng (2007)			-		
⁹ Wide confide	ence interval									
¹⁰ Significant v	ariation in the	point estim	ates, as well as	vide confidence i	ntervals with lim	ited overlap				
¹¹ Countries/te	erritories with a	n estimated	d incidence rate of		or greater are o	•	ve a high incidence	of tuberculosis	s, as defined by P	ublic

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 o			
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 of			
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 inappropi	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	nany particip	ants, if any	, were under 18 y	ears old; howeve	r, it is not antici	pated that the re	sults will be signification	antly affected b	by this	
⁸ Wide confiden	ce interval									

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

		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 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% Cl 11.9 to 21.4%)	VERY LOW
¹ Lodha, 2013 ² Both index te		ce standard	d performed in the	e everv patient. w	ith an appropria	te period of time	e 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

Number of evaluation sNumber of evaluation sInconsistenc yIndirectnes sOther indirectnes spatients/ specimen sDesignSummary of findingsQuality		Quality a	ssessment				Number of	
	Test details	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision		Quality

Sensitivity

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
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% Cl 2.3 to 8.0%)	VERY LOW

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

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% Cl 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), EI-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	serious ⁵	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	1 ¹	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

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

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	ity (grouped by t	echnique used):						
³ Random/con enrolled in Ba ⁴ Unclear if El- ⁵ Blinding of tean and Sekadde	secutive samp tes (2013) and Sayed Zaki (2 est interpretation (2013) r interpretation	ble of patier El-Sayed 2 008) avoid on employe	nts enrolled in Nic Zaki (2008) ed inappropriate	col (2011), Sekado exclusions	de (2013) and Z	ar (2012 and 20	e between the two 13); unclear if cons employed in Bates (
	•		•	o in or wide confid						
⁹ Countries/te										

		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% Cl 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

		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
³ Unclear if co	nsecutive or ra	Indom sam	ple of patients wa	as enrolled						
⁴ Unclear if tes	st interpretatior	n was blind	ed							
⁵ Threshold fo	r interpretation	unclear								
⁶ Wide confide	nce interval									
			l incidence rate of cidence for in the			onsidered to hav	ve a high incidence o	of tuberculosis	, as defined by P	ublic

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% Cl 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

⁶Wide 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 vears 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% Cl 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%)	MODE ATE

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

⁶Wide 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										1
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% Cl 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

⁶Wide 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	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	Quality
				40 per 100,000 c UK are 13.9 per		onsidered to hav	e a high incidence c	of tuberculosis,	as defined by P	ublic

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

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	of	Quality
Test details	Number of evaluation s	Design	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other considerations	patients/ specimen s	Summary of findings	
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
 ² Iriso, 2005 ³ Both index tet ⁴ Unclear if stu ⁵ Unclear if tes ⁶ Insufficient d ⁷ Countries/ter 	ness e of tuberculos in test fever and nigh ymph nodes, j est and referen idy avoided in at interpretation ata to assess i ritories with ar	it sweats oint or bond ace standard appropriate in was blind imprecision in estimated	d performed in th exclusions ed incidence rate o	e every patient, v	vith an appropria	ate period of tim	ns, or kyphosis of the between the two re a high incidence of	·	, 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

			Quality assessme	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	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% CI 41.1 to 82.7%)	VERY LOW
¹ Lai, 2011 ² Blinding of test ³ Patients receiv	interpretation uncl ed different referer	lear nce standards						

⁴ Wide confidence interval

A.4.2 Diagnosis of active central nervous system tuberculosis

			Quality assessn	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
 ² Al-Ateah, 2013 ³ Bonington, 20 ⁴ Chedore and 5 ⁵ Malbruny, 201 ⁶ Teo, 2011 ⁷ Meta-analysis 	00 Jamieson, 20 1 of relevant d	ata not possible in	STATA or R					
 ⁸ Unclear if a ra ⁹ Unclear if test ¹⁰ Interpretation ¹¹ Unclear if a th 	ndom or cons interpretation of reference nreshold for te triation in poir	secutive sample w was blinded: Bor standard not blind est interpretation v	as used: Bonington, ington, 2000; Ched led: Teo, 2011; Fen vas used and prede ttle overlap in confid	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

Wide confidence interval

¹⁴ Feng, 2014

Use of commercial nucleic acid amplification tests 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								
29 ^{1,7}	cross- sectional	serious ^{2,3,4}	serious ⁵	no serious indirectness	serious ⁶	2810	Pooled sensitivity (95% CI) = 70.6% (53.3 to 83.5%)	LOW
Specificity								
29 ^{1,7,8}	cross-	serious ^{2,3,4}	serious ⁵	no serious	serious ⁶	2810	See forest plot below ^{1,8}	LOW

Appendix E: GRADE profiles

			Quality assessm	nent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
	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: AI-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 	of relevant da ndom or cons propriate excl tion unblinded interpretation he reference	ata not possible in a ecutive sample wa usions were avoid d: Kim, 2008 was blinded: Liao, standards in Kim (s used: Liao, 2009 ed 2009 2008)) is not a valid	ated reference sta	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}	serious⁵	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}	serious⁵	no serious indirectness	serious ⁶	35	66.7% (95% CI 47.8 to 85.5%)	VERY LOW
¹ Kim, 2008 ² Unclear if inap	propriate excl	usions were avoid	ed					

³ Test interpretation unblinded

			Quality assessm	ent		Number of					
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/	Summary of findings	Quality			
			meonsistency	mun ectriess	Imprecision	specimens	Summary or munigs	Quanty			
⁴ PCR is not a v	not a validated reference standard										
⁵ Pationte did ne	at all receive t	ha sama rafaranca	standard (PCP or o	ulturo)							

^a 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	ent		Number of		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
Sensitivity								
Threshold for	positivity: 4 L	J/I						
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	J/I						
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 p	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	J/I						
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	J/I						
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	r sensitivity ar	nd specificity at a t	hreshold for positivit	y of 4 U/I:				

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

Appendix E: GRADE profiles

			Quality assessm	ent		Number of patients/ specimens		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		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	view: Tuon (20 es that used a	010) a case-control desi	gn					
⁶ Unclear if inap ⁷ 10 of the 13 st	propriate exclude	lusions were avoid d were not blinded	ed					
 ⁹ Significant vari 	ence standard ation in point	ls used in each stu estimates with littl	ıdy e overlap in confider	nce intervals				

A.4.3 Diagnosis of active genitourinary tuberculosis

			Quality assessm	ent		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
 Forest plots for Hemal, 2000 Lai, 2010 	r sensitivity ar	nd specificity:						
⁴ Meta-analysis ⁵ Unclear if a co ⁶ Unclear if inap	nsecutive or r propriate excl	ta not possible in s andom sample wa usions were avoid	is used					
⁴ Unclear if test ⁸ Unclear if a thr ⁹ Wide confident	eshold for ind	was blinded ex 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 assessment						
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
² Hemal, 2000 ³ Unclear if a con ⁴ Unclear if inapp ⁵ Unclear if test ir	secutive or ra ropriate excluter nterpretation shold for ind	andom sample was usions were avoide	s used ed	is, cavitation, uret	eral stricture, vesi	coureteral reflux	and small capacity bladder	

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

			Quality assessm	ent		Number of		Quality
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	
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 th 	(2 evaluations 5 of relevant dat iew: Dinnes (2 nsecutive or ra propriate exclu nterpretation v reshold for inc iation in point	s) a not possible in a 2007) andom sample was usions were avoide was blinded in 3 of lex test interpretati	d the 4 evaluations					

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

				Quality assessm	ent		Number of		
Νι	umber of						patients/		
ev	aluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	specimens	Summary of findings	Quality

Number of			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}	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
¹ Lai, 2010 ² Unclear if a con ³ Unclear if inapp ⁴ Unclear if test i ⁵ Wide confidence	propriate excluinterpretation v	andom sample was usions were avoide was blinded	used d					

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	¹ Forest plots for sensitivity and specificity:								

Number of		Quality assessment						
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
⁵ Unclear if a cor ⁶ Unclear if inapp ⁷ Unclear if index ⁸ Unclear if reference ⁹ U	nsecutive or r propriate excl c test interpre ence standar eshold for tes	andom sample use usions were avoide tation was blinded d interpretation was st interpretation was	ed s blinded: Saleh (201 s used	2)				

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 fo	r sensitivity an	d specificity:							
² Systematic rev	iew: Su (2013); additional studie	s: Cho (2011), Liao (2009)					
 ³ Unclear if a consecutive or random sample used: Liao (2009) ⁴ Unclear if inappropriate exclusions were avoided 									
		isions were avoide							

⁵ Unclear if test interpretation was blinded in a number of studies
 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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evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens				
Sensitivity				·						
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									
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 t	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 t	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									
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	d specificity:								
² Hillebrand, 199 ³ Kang, 2012 ⁴ Forest plots for		d specificity at a th	reshold for positivity	of >30 U/I						
⁵ Systematic rev ⁶ Additional stud ⁷ Unclear if a cor	y: Brant (1995	13)) ndom sample use	d							

⁷ Unclear if a consecutive or random sample used ⁸ Unclear if inappropriate exclusions were avoided

			Quality assessm	ient	Number of	f				
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality		
	eshold for tes	t interpretation was								
¹¹ Patients receiv ¹² Review include	atients received different reference standards, both within and between studies eview included inappropriate reference standards									
¹³ Significant vari ¹⁴ Wide confident	ation in point	estimates with little	e overlap in confidenc	ce intervals						

A.4.5 Diagnosis of active lymph node tuberculosis

Use of microscopy 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										
7 ^{1,2}	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	serious ^{8,9}	799	Pooled sensitivity (95% CI) = 36.4% (27.5 to 46.5%)	LOW		
Children										
1 ³	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	serious ⁹	129	44.3% (95% CI 33.9 to 54.7%)	LOW		
HIV-positive										
1 ⁴	cross- sectional	serious ^{6,7}	no serious inconsistency	no serious indirectness	serious ⁹	344	51.0% (95% CI 43.0 to 59.0%)	LOW		
Specificity										
7 ^{1,2}	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	serious ^{8,9}	799	Pooled specificity (95% CI) = 94.4% (78.4 to 98.8%)	LOW		
Children										
1 ³	cross- sectional	serious ^{5,6,7}	no serious inconsistency	no serious indirectness	serious ⁹	129	58.5% (95% CI 43.5 to 73.6%)	LOW		
HIV-positive	HIV-positive									
1 ⁴	cross- sectional	serious ^{6,7}	no serious inconsistency	no serious indirectness	serious ⁹	344	96.0% (95% CI 93.1 to 98.7%)	LOW		

			Quality assessm	nent		Number of		Quality				
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality				
¹ Forest plots for s	Forest plots for sensitivity and specificity:											
 ³ Fanny, 2012 ⁴ Van Rie, 2013 ⁵ Unclear if a rand ⁶ Unclear if a inap ⁷ Unclear if test in 	om or consec propriate exc terpretation w ion in point e	cutive sample used lusions were avoid vas blinded in any o	Kerleguer, 2004; M I in a number of stud ed in a number of st of the studies overlap in confidence	lies udies	nek, 2002; Van Ri	e, 2013						

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	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 assess	nent		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 assessn	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 Determined different reference standards, both within and across 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

			Quality assessm	nent		Number of	Pooled sensitivity (95% CI) = VERY LOW			
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 referer ⁷ Unclear if a three ⁸ Different referer 	f relevant data test interpreta ence standard shold for test p nce standards tion in point es	tion was blinded: was blinded positivity was pred used, both within	vailable statistical so Reuter (2006) defined: Reuter (200 and across studies overlap in confidenc	6)						

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

			Quality assessn	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	
	ropriate exclus nterpretation w test positivity n nce standards	sions were avoide as blinded ot always predefir used, both within		on velo					

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 pe	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 pe	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 pe	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 pe	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 refere									

			Quality assessm	nent	Number of patients/ Quality on specimens Summary of findings Quality			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Summary of findings	Quality
⁴ Unclear if a thres ⁵ Different referen			lefined					

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	ooled sensitivity (95% CI) = LOW 0.5% (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 inappi ¹⁰ Unclear if test i ¹¹ Unclear if the test 	3 (2 evaluation 6 relevant data dom or consect ropriate exclus nterpretation est positivity the in point estim	ns) a not possible in S cutive sample was sions were avoide was blinded in mo nreshold was pred	used d in all studies	es ntervals					

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 LOW
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 cor ¹⁷ Unclear if inapp ¹⁸ Blinding of test ¹⁹ Unclear if threst ²⁰ Different reference 	95 iews: Denking nsecutive san propriate excl interpretatior shold for test ence standard ation in point	ger (2014), Pai (200 nple not used in all s usions avoided n not performed in a positivity predefined ls used, both within estimates with little	studies Il studies I in all studies and across studies	ce intervals				

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

	Quality assessment					Number of		
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
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

¹² Different reference standards used, both within and across studies
 ¹³ Significant variation in point estimates with little overlap in confidence intervals

		(Quality assessme	ent	Number of				
Number of		D				patients/			
evaluations	•	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	oositivity: 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	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	oositivity: 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 confiden	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 assess	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/l4						
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 LO
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 LO
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/l2						
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 LO
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 LO

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

Use of adenosine deanimase assays in conjunction with the lymphocyte-neutrophil ratio 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								
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	ent	Number of			
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients/ specimens	Summary of findings	Quality
² Unclear if test in ³ Test positivity th ⁴ Different refere	hreshold was i	not predefined						

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	Effe	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (unsupervised) dosing	Intermittent (DOT) dosing	Relative (95% Cl)	Absolute (95% CI)	Quality
Relapse (n	umber to experie	nce clinical or i	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
Te Water	han et al, 2005 Naude et al, 200 han et al, 2005: i concealment un Naude et al, 200	method of rand	on not appropriate; omisation unclear	conducted by ho	usehold unit, ana	lysis is at the level of the	individual (i.e. unit-c	of-analysis error); insu	fficient data to co	rrect

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

		Quali	ty assessment			Number of	patients	Effe	ct	
Number of studies	Design	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
Mortality (r	number of tuber	culosis-related of	leaths during the s	tudy; follow-up 24	months ¹)					
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
Response			tion (% of participa	ints with a normal		at treatment completion	; follow-up 6-9 months			
1 ¹⁴	randomised trials	very serious ^{3,4,5,15}		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
			tion (% 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	ints 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
	to treatment - o	disease resolut	tion (% of participa		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
Response	to treatment - o	disease resolut		rticipants to requir	e treatment exte	nsion due to incomplete r	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
Relapse (n		ence clinical or	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	r of patients to exp		icity; follow-up 24					
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)	G

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 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	ty assessment			Number of	patients	Effec	:t	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (Monday-Friday) (unsupervised) dosing	Twice-weekly (DOT) dosing	Relative (95% CI)	Absolute (95% CI)	Quality
				(measured with: c	composite score	obtained from parent asses	ssment, clinical sympto	oms, weight gain and	chest radiograph	range of
scores: -4-8;	better indicated	d by higher valu	les)							
1 ²	randomised trial	very serious ^{3,4,5,6}	serious'	very serious ^{8,9}	no serious imprecision ¹⁰	89	70	-	median difference 0 ¹¹	VERY LOW
Response to	o treatment at	treatment com	pletion (measured	with: composite s		om parent assessment, clir	nical symptoms, weigh	t gain and chest radio	graph; range of s	cores: -4-8;
	ted by higher va					•		U U		
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	very serious ^{8,9}	no serious imprecision ¹⁰	93	70	-	median difference 0 ¹¹	VERY LOW
Response to	o treatment 6 n	nonths after tr	eatment completion	on (measured with		re obtained from parent as	sessment, clinical sym	ptoms, weight gain a	nd chest radiogra	ph; range
			alues; follow-up 12	· ·	•			1 / 0 0	Ŭ	
1 ²	randomised trial	very serious ^{3,4,5,6}		very serious ^{8,9}	no serious imprecision ¹⁰	74	65	-	median 1 higher ¹¹	VERY LOW
Response to	o treatment 12-	24 months aft	er treatment comp	oletion (measured	with: composite	score obtained from parer	nt assessment, clinical	symptoms, weight ga	ain and chest radi	ograph;
			dher values; follow-				,			0 1 /
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	very serious ^{8,9}	no serious imprecision ¹⁰	74	71	-	median difference 0 ¹¹	VERY LOW
Symptom in	nprovement - v	veight gain (we	eight gain from trea	tment initiation un		pletion; better indicated by	higher values; follow-	up 6 months ¹)		
1 ²	randomised trial	very serious ^{3,4,5,6}	serious ⁷	serious ⁸	no serious imprecision ¹⁰	<u>1</u> 2	_12	-	median 0.25 kg higher ¹¹	VERY LOW
Relapse (nu	mber to experie	nce clinical or i	adiological recurre	nce; follow-up 30	months ¹)					

		Quali	ity assessment			Number of	patients	Effe	ect	
lumber of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily (Monday-Friday) (unsupervised) dosing	Twice-weekly (DOT) dosing	Relative (95% CI)	Absolute (95% CI)	Quality
2	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	lule; 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
	e - number adhe	erent (number o	of children taking ≥	75% of the presc		v-up 6 months ^{1,17})				
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
dherence	- number parti	ially adherent	(number of childrer	n taking ≥75% of	the prescribed do	ses but <75% during any si	ngle 4-week period;	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-adhe	erers (days to defa	ult by non-adher	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
dherence	- time to defau higher values;	It by partial ac follow-up 6 more	dherers (days to denote the denoted of the denote	efault by partial a	dherers, defined t	hose taking ≥75% of the pr	escribed doses but <	75% during any single	e 4-week period; l	petter
2	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	oses taken (% of p	prescribed doses	taken; better indic	cated by higher values; follo	ow-up 6 months ^{1,17})			
2	randomised trial	very serious ^{3,4,5,6}	serious ^{7,13}	serious ⁸	no serious imprecision ¹⁰	117	89	-	median 2% lower ¹¹	VERY LOW
Te Water Randomis Allocation Blinding a Analysis of 'Weight fo their tuber Interventio Outcome ² Data is gu ¹ Differenc ² Total num ³ In additio on the day ⁴ GRADE	concealment un bsent or unclear did not follow the r age' and the 'r culosis was less on and compara is a substitute fo iven as medians not the medians nber of participa n to the use of o v of medication of rule of thumb ev	priate: randomis inclear r a intent-to-treat bumber who we is severe than the tor vary by more or the outcome and interquartile int provided b ints not stated different treatme collection ent number <30	principle re culture positive' le 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		
Odds rati	nfidence interval io and 95% conf	s ïdence intervals	s not provided by a	uthors; calculated	d by reviewer					

¹⁷ Treatment period

		Quali	ty assessment			Number of	patients	Effe	ct	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness		Daily (Monday-Friday) (unsupervised) dosing		Relative (95% CI)	Absolute (95% CI)	Quality
Abbreviation	ns: CI, confidend	ce interval; DO	T, directly observed	d therapy; OR, odd	ds ratio					

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

Comparator: daily (unsupervised) dosing

Site of tuberculosis: **pulmonary**

		Quali	ity assessment			Num	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 -	disease resolu	tion (number of pa	rticipants to comp	letely 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 -	radiologic imp	rovement (number		show radiologic in	mprovement; follow-u	ıp 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 -	time to clinical	response (therap	y period for an ear	ly clinical response	se; better indicated by	y lower values; follow-up 12 m	nonths ¹)		
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	improvement -	weight gain (n	umber to experience	ce weight gain; fol	low-up 12 months	¹ ; better indicated by	higher values)			
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	ience clinical or	radiological recurr		nths 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 se	rum aspartate am	inotransferase and a	anine aminotransferase; follo	w-up 12 months ¹)		
1 ²	randomised trial	very serious ^{3,4,5,6,}	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	ow-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	er of patients	Ef	fect	
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
	ment completior	ו								
² Kansoy et	al, 1998 randomisation ι	inclose								
	concealment un									
⁵ Blinding u		loicai								
	id not follow the	intent-to-treat	principle							
⁷ Loss to fol	low-up varied be	etween the two	arms: 3 of 18 patie	ents were exclude	d from the analys	is in the daily followed	by twice-weekly group for "p	oor compliance",	none were exclu	ided from the
ູ daily grou										
°Interventio	n and comparat	or vary by more	e than dosing frequ	ency; that is, the i	ntervention studi	ed does not precisely r	match the intervention of inte	rest		
	s a substitute to ule of thumb eve	r the outcome	of interest (cure, tre	eatment success a	nd treatment faill	ure)				
			onot provided by a	uthors: calculated	hy roviowor					
¹² Wide con	fidence intervals		s not provided by a		by reviewer					
			tervals not provide	d by authors: calcu	lated by reviewe	r: mean difference = (n	mean _{daily+twice-weekly} – mean _{daily})			
¹⁴ Outcome	not clearly defin	ed - thresholds	s for 'elevated' aspa	artate aminotransfe	erase and alanine	e aminotransferase not	t given			
¹⁵ Outcome	definition not pr	ovided					-			
Abbreviation	ns: Cl, confidend	ce interval; DO	T, directly observed	d therapy; MD, me	an difference; Ol	R, odds ratio				

Intervention: twice-weekly (DOT) dosing

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

Site of tuberculosis: cross-site

		Quali	ty assessment			Number of patients		Effect		
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% CI)	Quality
Mortality (n	umber of deaths		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 treatm	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				eatment12; 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

		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
Response	to treatment - p	oor response				follow-up <12-24 moi	nths)			
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 experie	ence clinical or	radiological recurre	ence; follow-up <12						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/35 (0%) ⁸	0/35 (0%) ⁸	OR 1.00 (0.02 to 51.81) ⁹	-	VERY LOW
Adverse ev	vents - side effe	ects requiring	modification of tre	eatment (number of	of participants that	t experienced side eff	ects that required modification	on of treatment; fol	low-up <12-24 m	nonths)
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 - hyperse	nsitivity reacti	ons (number of pa	rticipants that expe	erienced a hypers	ensitivity reaction; foll	ow-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 - haemato	ologic effects (number of participa	ants that experience	ed 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
¹ Kumar et ² Allocation ³ Blinding u	concealment ur Inclear	nclear								

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 ⁵ Follow-up varied considerably between participants ⁶ GRADE rule of thumb event number <300

⁷ Wide confidence intervals

⁸ Data for pulmonary tuberculosis, lymph node tuberculosis and disseminated tuberculosis was pooled by reviewer
 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	umber of deaths	s during the stud	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}	1/20 (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 t	to treatment - n	narked respons	se (number of patie	ents with marked r	esponse to treatn	nent ¹¹ ; follow-up <12-24 mo	onths)			
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 t	o treatment - n	noderate respo	onse (number of pa	atients with modera	ate response to tr	eatment ¹¹ ; follow-up <12-24	1 months)			
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	1/20 (5%)	0/23 (0%)	OR 3.62 (0.14 to 93.85) ⁸	-	VERY LOW
Response t	to treatment - p		(number of patient	s with poor respon	se to treatment ¹¹ ;	follow-up <12-24 months)				
1 ¹	randomised trials	very serious ^{2,3}	very serious ^{4,5,9}	serious ¹⁰	very serious ^{6,7}	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	ence; follow-up <12	2-24 months)					
1 ¹ ¹ Kumar et a	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

Numar et al, 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			Number of patients		Effect		
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
Mortality (n	umber of death	s during the stu	dy; follow-up 15-24	months)						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/15 (0%)	0/12 (0%)	OR 0.81 (0.01 to 43.60) ⁸	-	VERY LOW
Response t	o treatment - r	narked respon	se (number of pati	ents with marked i	esponse to treatm	nent ¹¹ ; follow-up 15	-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 t	o treatment - r	noderate respo		atients with moder		eatment11; follow-u	p 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 t	o treatment - p	oor response	(number of patient	s with poor respor	se to treatment ¹¹ ;	follow-up 15-24 m	onths)		,	
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 (nu	umber to experie		radiological recurre	ence; follow-up 15-						
1 ¹	randomised trials	serious ^{2,3}	very serious ^{4,5}	no serious indirectness	very serious ^{6,7}	0/15 (0%)	0/12 (0%)	OR 0.81 (0.01 to 43.60) ⁸	-	VERY LOW
¹ Kumar et a	al, 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: disseminated

		Quali	ity assessment			Number of patients		Effect		
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	to treatment - r	narked respon	se (number of patie	ents with marked r	esponse to treatm	nent ¹¹ ; follow-up <12	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 moder	ate response to tre	eatment ¹¹ ; follow-up	o <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	to treatment - p	boor response		with poor respon	se to treatment ¹¹ ;	follow-up <12-24 m	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	al, 1990 concealment ur	nclear								

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

A.6 RQK

People coinfected with tuberculosis and HIV A.6.1

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% CI)	Absolute		
Iortality	(follow-up 6 m	nonths; assess	ed with: number of	of deaths during	the study period)							
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	s 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	undergo sputum cor uction)	version, defined a		tive negative	sputum sm	ears and
1	randomised trials	no serious risk of bias⁴	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	
Substitu Odds ra Patients	s were able to a	onfidence inter see the differe		ts, but they were	not informed ab	out their content; s	tudy nurses and phy			quest inform	ation about	medicatio

from patients and remained blind to treatment throughout the study; the only individuals administering care not to be blinded were the drug dispensers 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		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	nonths (6 mor			sessed with: nun	nber of patients to	experience culture-	confirmed relapse)	1			
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	e to treatmen	t – culture co	nversion (follow-	up 12 months (6	months after trea	atment completion)	measured with: tim	ne to first negative	test results;	better indicat	ted 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	
² Unblind	ly et al 1996 led, except for	the radiograph		aloor if the math			vas valid and reliah	1-		J		

³ Precise definition of outcome not provided, and it is unclear if the method used to determine the outcome was valid and reliable
 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	Effect			
	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
I	' Wide co	nfidence inter	val										
	⁸ GRADE	rule of thumb	: <300 events										
			onfidence inte	rval not provided l	by authors; calcu	lated by reviewe	r						
	¹⁰ Substit	ute outcome											
	¹¹ Unable	¹¹ Unable to calculate confidence interval; insufficient data											
			provided by au	thors; calculated l	by reviewer								
	13 n - 0.0	003			-								

p = 0.0003

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

			Quality asse	essment			No of p	atients	Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-rifampicin- containing regimens	Rifampicin- containing regimens	Relative (95% Cl)	Absolute	Quality	Importance	
Mortality	Mortality (univariate analysis) (follow-up 1 years; assessed with: number of deaths during 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			sessed with: nun	nber of deaths de	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		
¹ HIV/TB ² Prosper	Study Writing G	roup, 2009											

Prospective

³ Unclear if method of allocation to treatment groups is related to potential confounding factors

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

No of Other containing	f patients	Ef	fect		
studies Design Risk of bias Inconsistency Indirectness Imprecision considerations phase	Standard recommended		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 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
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	
	· •		HRZE7/4HR7) (foll	ow-up 12 months	s after treatment	completion; assess		· · ·				
1 ¹	randomised trials ²	serious⁴	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	
		ompared to 2H	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	ompared to 2H	RZE/6HR) (follow			per 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 (2HRZ	ZE/6HE compar	ed to 2HRZE/6HF		(follow-up 2 yea	ars; assessed with:	number of patier	nts to experience t	reatment fail	ure)		
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	
	nt failure (2HRZ	ZE/6HE compar	ed to 2HRZE/6HF		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	fined as the	developmer	nt of active t	uberculosis
after suc 1 ¹⁶			ourse of treatmer	t during 24 mont			00/405	00/440	00.000	10		
1	observational studies ²	very serious ^{3,4,5}	very serious ^{6,7,8,9}	serious ^{10,11}	serious ¹²	none	23/136 (16.9%)	30/413 (7.3%)	OR 2.60 (1.45 to 4.65) ¹³	10 more per 100 (from 3 more to 19 more)	VERY LOW	
						er of patients to exp	erience relapse,	defined as the dev	velopment o	f active tuber	culosis afte	r successful
completio			ent during 24 mon	ths of follow-up a serious ^{10,11}			00/400	4.4/000		10		
1	observational studies ²	very serious ^{3,4,5}	very serious ^{6,7,8,9}	serious	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 Effect					
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
Pospon	a to tractment	unfoyourobl	a autooma (24P		75 /645 00000	red to 2HRZE ₇ /4HF) (follow up 12	months ofter treat	7.38) ¹³	(from 4 more to 24 more)	od with: pur	nhor of
patients 1	to have an unfav	ourable outcom	ne, defined as fail	2^{22} or relapse ²³	$2 = \frac{3}{6} = \frac{1}{7} = $	llea lo znkze7/4nr low-up)	(10110w-up 12	months after treat	nent comple	assess	ea with: hur	
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	
		- culture conv	ersion (2HRZE/6	HE compared to 2	2HRZE/6HR or 2	HRZE/4HR) (follow	-up 2 years; ass	essed with: numbe	er of patients	to be culture	e-negative a	after 2 months
of treatm 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	
		• •	HRZE/6HE compa	red to 2HRZE/6H		R) (follow-up 2 year						
1 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	
			HRZE/6HE compa		IR) (follow-up 2 y	/ears; assessed wit	h: number of pat	ients to complete t	herapy)	,		
1 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 Prosper ³ Unclear ⁴ Unclear ⁵ Attemp ⁶ Groups higher ⁷ Groups was dir ⁸ Groups 2HRZE ⁹ Groups 65% cc ¹⁰ Popula 	r if method of allor 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 not comparable ompleted treatme tion appears to	gh unlikely e within the des arable at baselin cell counts the same care a for an equal an for treatment c ent in the 2HRZ match the popu	ign or analysis to ne - 2HRZE/4HR apart from the inte ad appropriate leng ompletion and ava E/6HE group lation of interest.	balance the grou group were signif ervention(s) studie gth of time - med ailability of outcom although unclear	ups for potential c iicantly older, 2Hi ed - rifampicin re ian follow-up in ti me data - 83% co if there was any	ors - allocation was confounders RZE/6HR group had gimens (2HRZE/4H he 2HRZE/4HR gro ompleted treatment drug resistance at J requency and the us	d significantly hig IR and 2HRZE/6 up was 512 day in the 2HRZE/4 baseline	gher levels of haen HR) were self-adn s, 533 days in the 2 HR group, 73% co	ninistered, no 2HRZE/6HR mpleted trea	on-rifampicin group, and o atment in the	regimen (2 661 days in 2HRZE/6H	HRZE/6HE) the R group, and

¹² GRADE rule of thumb: <300 events

			Quality asse	ssment			No of	patients	Eff	Effect		
No of studies	Design		Inconsistency		Imprecision	Other considerations	Ethambutol- containing continuation phase	Standard recommended regimen	Relative (95% Cl)	Absolute	Quality	Importance
¹³ Odds ra	³ Odds ratio and 95% confidence interval not provided by authors; calculated by reviewer ⁴ Study did not provide a precise definition of the outcome											
¹⁵ Substit	ute outcome	precise demini		7								
¹⁶ Okwera	a et al, 2006											
¹⁷ Unclea	r if groups were	comparable at	baseline as basel	line characteristic	s not reported by	y HIV status						
¹⁸ Groups	s had comparabl	e rates of attriti	on, though rates w	vere high in both	groups							
¹⁹ Popula	tion may not exa	actly match the	population of inte	rest: some drug r	esistance at bas	eline, although uncl	lear if any within	the HIV subgroup	as baseline	characteristi	cs not repoi	ted by HIV
status												
²⁰ Interve	ntion may not ex	actly match the	e intervention of ir	nterest: intervention	on varies by mor	e than the combina	tion of antituberd	culosis drugs – reg	imens with a	n E-continua	tion phase	were 2

months longer than those with an R-continuation phase, and some patients receiving an E-continuation phase had an initial dosing schedule of 3-times weekly and some had a daily dosing schedule, whereas all

 ²¹ Wide confidence interval
 ²² Failure was defined as a culture of 20 or more colonies at month 6 or 8, or a change of treatment by the local investigator owing to treatment failure
 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

People with tuberculosis and liver disease A.6.2

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	IZEO/10HEO co	mpared with 2HR	E/7HR) (follow-u		treatment was stop	oped; 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/7F	IR) (follow-up 3 r	months after treatm	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	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 - hepate	otoxicity (HRb/	AOL compared wit	h HRZS/E) (follo	w-up unclear; as	sessed with: numb	er of patients to expe	erience liver dys	function, de	efined as ALT	Г >1336 IU	/L 2-3 months

			Quality asses	sment			No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone -containing regimen	containing	Relative (95% CI)	Absolute	Quality	Importance
after initia	ter initiation of antituberculosis chemotherapy)											
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 RQL

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	fect			
								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		with: number of a	mear-positive cul	ture-positive patie	nts to achieve a f	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 relaps	e ⁹)				
Relapse (follow-up 5 to 8 years after treatment initiation; assessed with: number of smear-positive culture-positive patients to experience relapse ³) 1 ¹ randomised trials very serious ^{2,3} serious ^{4,10} serious ^{5,6} very serious ^{7,11} 20/131 3/138 OR 8.11 (2.35) 13 more per 100 (from 3) more to 36 more) 1 ³ Singapore TB Service / British Medical Research Council, 1979/86 1979/86 1979/86 1979/86												
 ² Blinding unclear ³ Analysis is not inter ⁴ Unclear if the loss to ⁵ Intervention does not ⁶ Population does not 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, con 	t-to-treat of ollow-up was si ot exactly match th ervals of confidence inter for the full definiti follow-up period mb: <300 events	imilar in the 2 grou he intervention of e population of in vals calculated by on was the same in t	ups interest: did not c terest: unclear if c reviewer	ontain all of or jus hildren are includ	t the 4 standard re ed	ecommended dru	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 assessment mber of studies Design Risk of bias Inconsistency Indirectness Imprecise						Number of patients Effect					
							Relative	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 ass	sessment			Numbe	r 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	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 treatm reatment)	ent - culture st	atus (among tho	se that completed	treatment) (ass	essed with: numbe	er of smear-posi	itive, culture-positiv	e patients to be cu	Iture-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 an appearance 6 months	nd symptoms -	- deterioration in	radiographic stat	us (assessed wit	th: number of sme	ar-positive, cultu	ure-positive patients	s to experience det	terioration in radio	ographic
	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 an 6 months after treatm		no change in ra	diographic status	(assessed with:	number of smear-	· · /	· · /		ange in radiograp	ohic appearance
1 ¹	randomised trials	serious ^{2,3,4}	serious⁵	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				r aphic status (a	ssessed with: num	ber of smear-po	ositive, culture-posi	tive patients to exp	,	e improvement i
adiographic appeara	randomised	serious ^{2,3,4}	serious ⁵	serious ^{6,12}	serious ⁹	31/91	39/89	OR 0.66 (0.36	10 fewer per	VERY LOW
	trials					(34.1%)	(43.8%)	to 1.21) ¹⁰	100 (from 22 fewer to 5 more)	
Changes in signs ar adiographic 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 ar adiographic appeara				phic status (ass	essed with: numbe	er of smear-posi	tive, culture-positiv	e patients to exper	ience marked im	provement in
aulographic appeara 1 ¹	randomised trials	serious ^{2,3,4}	serious ⁵	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 ar adiographic appeara				phic status (ass	essed with: numbe	er of smear-posi	tive, culture-positiv	e patients to exper	,	provement in
	randomised	serious ^{2,3,4}	serious ⁵	serious ^{6,12}	serious ⁹	20/91	16/89	OR 1.29 (0.62	4 more per	VERY LOW
	trials					(22%)	(18%)	to 2.68) ¹⁰	100 (from 6 fewer to 19 more)	
dverse events lead									treatment interrup	
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	er 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 – treatm	nent default (ass	sessed with: numb	er of smear-positiv	e, culture-positive	e patients to defau	ult ¹³)				
1 ¹	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 treatr		ssessed with: num		sitive, culture-posi	tive patients to	experience relapse	3)		
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
 Allocation concealr Blinding unclear Although not statist (24%) Intervention does n Outcome is a subsi Wide confidence in GRADE rule of thui Odds ratio and 95 	tically significant, not exactly match titute for an outco tervals mb: <300 events	the intervention of one of interest	f interest: did not c					t the 3-month grou	np (36%) than the	9 4.5-month grou

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		
								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	ose)		
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious ^{6,7}	serious ⁸	1/97 (1%)	3/96 (3.1%)	OR 0.32 (0.03 to 3.16) ⁹	2 fewer per 100 (from 3	VERY LOW

		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)	
 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, con 	ent unclear nicludes childre t exactly match t nb: <300 events confidence inter tom treatment initi	n the intervention of vals calculated by ation; therefore, a	reviewer			0	nt 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	ent - culture stat	us (assessed with	n: number of initia	lly smear-positive	patients who wer	e smear-negative	after 8 weeks of t	reatment to be cu	lture-negative at t	he end of
treatment)										
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 a						r of initially smear	-positive patients	who were smear-	negative after 8 w	eeks of
treatment to experien		Ŭ			· · · · ·	. .				
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 o	of initially smear-p	ositive patients wh	no were smear-ne	gative after 8 wee	ks of treatment

		Quality ass	sessment			Numbe	er of patients	Ef	ffect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	6 months	Relative (95% CI)	Absolute (95% CI)	Quality
1 ¹	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 an 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 an experience deteriorate					th: number of initia	ally smear-positi	ive patients who w	ere 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: n	umber of initially	smear-positive pa		•			. ,
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 Committee Method of randomis Allocation concealm Blinding unclear Analysis is not inter Comparability of pa Number of patients Intervention does n Outcome is a subst GRADE rule of thu Wide confidence in Codds ratio and 955 Follow-up began fn Population does no 	sation unclear nent unclear tients at baseline lost to follow-up ot exactly match itute for an outco imb: <300 events ntervals % confidence inte om treatment ini	e unclear in each group is t the intervention c ome of interest s ervals calculated i tiation; therefore,	unclear of interest: did not o by reviewer as different duratio	ons of treatment v	vere used, follow-	up was for diffe	rent lengths			

¹⁵ Doses used are inconsistent with those recommended in the British National Formulary Abbreviations: CI, confidence interval; OR, odds ratio

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
ure (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)		
1	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
reatment failure (a	ssessed with: nu		mear-positive patie	ents to be smear-	positive at 5 mont	hs or later during	treatment)			
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
acteriological rela	pse (assessed w	ith: number of spu	tum-smear-positiv	e patients to exp	erience bacteriolo	gical relapse)				
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
Ziaullah et al, 2004 Method of randomis Allocation concealn Blinding unclear	sation unclear									

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% CI)	Quality
Treatment failure (a										
1 ²	randomised trials	serious ^{3,4,5}	no serious inconsistency	very serious ^{6,7}	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		tive patients with o	avities >2 cm to b	e considered alive	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		of culture-positive	patients with cavit	ties >2 cm to expe	erience relapse ¹)				
1 ²	randomised trials	serious ^{3,4,5}	serious	very serious ^{6,7}	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 Sou ³ Method of randomis ⁴ Allocation concealn ⁵ Radiographer blind ⁶ Intervention does no ⁸ Wide confidence in 	ciety, 1975/80 sation unclear nent possible - "ra ed to treatment al ot exactly match th t exactly match th	andom allocations llocation, but unclo the intervention of	ear if to prognostic interest: does not	factors or if other contain all of or ju	r investigators wer ust the 4 standard	recommended d		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

gn Risk of bias ad with: number of culture	Inconsistency	Indirectness	Imprecision			Relative	Absolute	1
ed with: number of culture		Indirectness	Imprecision					
	nositive natients wit		imprecision	6 months	12 months	(95% CI)	(95% CI)	Quality
345	poontro patiento mi			cm to experience	treatment failure ¹			
omised serious ^{3,4,5}	no serious inconsistency	very serious ^{6,7}	very serious ^{8,9}	1/214 (0.47%)	0/217 (0%)	OR 3.06 (0.12 to 75.45) ¹⁰	-	VERY LOW
with: number of culture-po	sitive patients witho	ut HIV or cavities	or no cavity >2 cn	n to be considere	alive and well aft	er 54 months of fo	ollow-up ¹)	
omised 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
ths; assessed with: numb	er of culture-positive		HV or cavities or r	io cavity >2 cm to	experience relaps	se ¹)		
omised 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
v 5 tl	mised serious ^{3,4,5} hs; assessed with: numbe	with: number of culture-positive patients witho mised serious ^{3,4,5} serious ¹¹ hs; assessed with: number of culture-positive mised serious ^{3,4,5} serious ¹¹ <i>full definition</i>	with: number of culture-positive patients without HIV or cavities mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} hs; assessed with: number of culture-positive patients without H mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} hs; assessed with: number of culture-positive patients without H mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7} full definition	with: number of culture-positive patients without HIV or cavities or no cavity >2 cm mised serious ^{3,4,5} serious ¹¹ very serious ⁹ hs; assessed with: number of culture-positive patients without HIV or cavities or no mised serious ^{3,4,5} serious ¹¹ very mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} very serious ⁹ hs; assessed with: number of culture-positive patients without HIV or cavities or no very serious ^{6,7} very serious ^{8,9} full definition serious serious ¹¹ very serious ^{6,7} very serious ^{8,9}	with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to be considered mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} serious ⁹ 129/214 (60.3%) hs; assessed with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7} very serious ^{8,9} 9/214 (4.2%) full definition	with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to be considered alive and well after mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} serious ⁹ 129/214 140/217 (60.3%) (64.5%) hs; assessed with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to experience relaps mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7} very serious ^{8,9} 9/214 2/217 (0.92%) full definition	with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to be considered alive and well after 54 months of for mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} serious ⁹ 129/214 140/217 OR 0.83 (0.57 to 1.23) ¹⁰ hs; assessed with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to experience relapse ¹) mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7} very serious ^{8,9} 9/214 2/217 OR 4.72 (1.01 to 22.11) ¹⁰	with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to be considered alive and well after 54 months of follow-up ¹) mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7,12} serious ⁹ 129/214 (60.3%) (64.5%) OR 0.83 (0.57 to 1.23) ¹⁰ 100 (from 14 fewer to 5 more) hs; assessed with: number of culture-positive patients without HIV or cavities or no cavity >2 cm to experience relapse ¹) mised serious ^{3,4,5} serious ¹¹ very serious ^{6,7} very serious ^{8,9} 9/214 (4.2%) (0.92%) OR 4.72 (1.01 to 22.11) ¹⁰ 100 (from 0 more to 16 more)

² British Thoracic Society, 1975/80

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	er 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
esponse to treatm	ent - culture sta	tus (assessed wit				egative after 6 n	nonths of treatmer	nt)		
1	randomised trials	very serious ^{2,3,4,5}	serious ^{6,7,8}	very serious ^{9,10}	serious ¹¹	287/287 (100%)	157/157 (100%)	OR 1.83 (0.04 to 92.44) ¹²	-	VERY LOV
elapse (follow-up a	minimum of 3 ye	ears after treatmer			er of culture-posi	tive patients to e	experience 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 LOV
Adverse events req reatment)	uiring modificat	ion or withdrawa	I of treatment (as	sessed with: nun	nber of culture-po	sitive patients to	experience an ac	lverse event requiri	ng modification o	r withdrawal c
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 LOW
dverse events - he	patic (assessed	with: number of c		ents 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 LOV
dverse events - ra	sh (assessed wit	h: number of cultu	re-positive patient	s to experience r	ash)					
1	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 (assesse	ed with: number o			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 LOV
dherence - treatme	ent default (asse		r of culture-positiv							
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 LOV

		Quality ass	essment			Number	of patients	Ef	fect	
								Relative	Absolute	
		Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Adherence - isoniaz	id metabolites (a	assessed with: nu	mber of urine sam	ples from culture	-positive patients	that were positive	for isoniazid met	abolites ¹⁴)		
1 ¹	randomised	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 folli ⁶ Unclear if groups ref ⁷ Unclear if the groups ⁸ High attrition rate w ⁹ Intervention does ne ¹⁰ Outcome is a subs ¹¹ Wide confidence in ¹² Odds ratio and 959 ¹³ GRADE rule of thu ¹⁴ See evidence table 	ent ow the intent-to-tr ceived the same s were comparab ith regards to the ot exactly match t titute for an outco tervals % confidence inte mb: <300 events	care except for th le for treatment c number of partici, he intervention of me of interest rvals calculated b	ompletion pants for whom da interest: did not c		t the 4 standard n	ecommended dru	igs, and the 2 reg	imens vary by mol	re than duration	

Abbreviations: CI, confidence interval; OR, odds ratio

SMEAR-NEGATIVE, MIXED/UNSPECIFIED CULTURE

<6 vs 6 months

Age: mix

HIV status: not specified – negative?

Disease status: smear-megative

Site of disease: pulmonary

Drug sensitivity: susceptible / unclear (pooled)

		Quality ass	sessment			Number	of patients	Ef	fect	
	Destina	Disks(hiss		In Providence		0 m m th a	0 m an tha	Relative	Absolute	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	<6 months	6 months	(95% CI)	(95% CI)	Quality
Relapse (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	5 years after treatm	nent initiation; asse	ssed with: numbe	er of smear-negati	ive 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	th: number of sme			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	uiring withdrav	val of one or mor			mear-negative pa				rawal of one or n	
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	per of smear-nega	tive patients to e	xperience an adv	verse event leading	to a temporary ir	terruption in
treatment)			. 6	. 80						
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	utaneous (asses	ssed with: number	of smear-negative		ience a cutaneou	s adverse reaction	n)			
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	gative patients to	experience a gast	trointestinal adve	rse 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		ence a vestibular	adverse reaction)			
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
		d with: number of	smear-negative pat	tients to experience	ce a hepatic adve	rse reaction)				
Adverse events - he	epatic (assessed		oniour nogunio pu	very serious ^{8,9}		,				

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
Method of randomisa	ation unclear									
³ Allocation concealment unclear										
⁴ Blinding unclear										
⁵ Analysis did not follow intent-to-treat principle										
⁶ Unclear if loss to follow-up was the same in the 2 groups										
⁷ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths										
Intervention does not										
⁹ Population does not exactly match the population of interest: includes some children (inclusion criteria = 15 to 75 years), and some cases were possibly 'inactive'										
¹⁰ Wide confidence intervals										
¹¹ Odds ratio and 95% confidence intervals calculated by reviewer										
¹² GRADE rule of thur	nb: <300 events									

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% CI)	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		

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 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	
Number of studies	Docian	Risk of bias	Inconsistancy	Indirectness	Imprecision	4 months	6 months	Relative (95% CI)	Absolute (95% CI)	Quality
Freatment failure (a			Inconsistency			4 11011115	omonuis	(95% CI)	(95% CI)	Quality
¹²	randomised	serious ³	serious ⁴	serious ^{5,10}	very serious ^{6,7}	0/59	1/54	OR 0.30 (0.01	1 fewer per	VERY LOV
I	trials	3611003	361003	3611003	very senous	(0%)	(1.9%)	to 7.52) ⁸	100 (from 2 fewer to 11 more)	VERTEO
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 o
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 LOV
	nd symptoms -	- <50% radiograp	hic clearing (asse	ssed with: numbe	er of smear-negati	ve patients to e	xperience less that	an 50% radiographic	clearing at the e	nd of treatme
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 LOV
	nd symptoms -	- >50% radiograp	hic clearing (asse	ssed with: numbe	er of smear-negati	ve patients to e	xperience more th	an 50% radiographi	c clearing at the	end of treatm
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 LOV
	nd symptoms -	 complete radiog 	raphic clearing (a		umber of smear-ne	gative patients	to demonstrate ra	diographic clearing	at the end of trea	itment)
2	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 LOV
Relapse (follow-up 6	60 months after t				egative patients to	experience rel	apse 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 LOV
See evidence table Teo et al, 2002 Blinding unclear Comparability of pa Intervention does r GRADE rule of thu Wide confidence in Odds ratio and 959 Follow-up began fr	atients at baselin hot exactly match mb: <300 events htervals % confidence inte	e was unclear a the intervention c s ervals calculated b	y reviewer			-		vary by more than d	uration alone	

¹⁰ Population does not exactly match the population of interest: unclear if children are included 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 asse	essment			Number of	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		n: number of sme	ar-negative patien	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 tre	eatment initiation;		mber of smear-ne	egative patients to	experience bacte	riological, radiogr	aphic or clinical re	elapse 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				nber of smear-neg	ative patients to e	experience bacter	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 (ang	y) (assessed with		r-negative patient		ny adverse reaction	on during chemoth	nerapy)			
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 withdrawa		by (assessed with	: number of smea	ar-negative patient	s to experience a	ny adverse reacti	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)	VERY LOW
 ¹ Hong Kong Chest S ² Method of randomis ³ Allocation concealn ⁴ Blinding unclear ⁵ Population does no ⁶ Intervention does no ⁷ Outcome is a subst 	sation unclear nent unclear t exactly match th ot exactly match t	e population of ini the intervention of	terest: some case	s were drug resisi	tant, and the popu	lation may include	e some children (i gs	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	Risk of bias	Inconsistency		Imprecision	2 months	3 months	(95% CI)	(95% CI)	Quality
¹³ note: most adverse	, ,	thors to be "trivial	or mild cutaneous	s, vestibular or ga	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	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 months	6 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Response to treatm	ent - culture stat	us (assessed with	n: number of smea	ar-negative patien	ts with 1 or more	initial culture posi	ive to be culture-	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 treatm	nent initiation; ass			tive patients with '	l or more initial cu	Iture positive to e	xperience relapse)	
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		osis Research Ce	ntre, Madras / Brit	tish Medical Rese	arch Council, 198	9				

³ Allocation concealment unclear

⁴ Blinding unclear

⁵ Analysis is not intent-to-treat

⁶ Number of patients lost to follow-up in each group is unclear

⁷ Intervention does not exactly match the intervention of interest: did not contain all of or just the 4 standard recommended drugs

⁸ Population does not exactly match the population of interest: includes some children (inclusion criteria = 15-75 years), and some cases were possibly '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	iect	
								Relative	Absolute	
Number of studies	•	Risk of bias	Inconsistency		Imprecision	4 months	6 months	(95% CI)	(95% CI)	Quality
¹² Follow-up began fr Abbreviations: CI, co	om treatment initi nfidence interval;	ation; therefore, a OR, odds ratio	s different duratio	ns of treatment w	ere used, follow-u	o was for different	lengths			

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 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
Response to treatm	ent - culture stat		n: number of smea	ar-negative patien	ts with 1 or more	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		assessed with: nu		egative patients wi	th 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'	randomised trials	serious ^{2,3,4}	serious ¹²	very serious ^{5,6}	serious [®]	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	VERY LOW

more)

		Quality asse	essment			Number o	of patients		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 / Tubercule	osis Research Ce	ntre, Madras / Brit	tish 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 c	ontain all of or jus	t the 4 standard re	ecommended drug	gs			
⁷ Outcome is a substi		ne of interest								
్లి GRADE rule of thun										
⁹ Wide confidence int										
¹⁰ Odds ratio and 95%			reviewer							
¹¹ See evidence table										
¹² Follow-up began fro Abbreviations: Cl, col			s different duratio	ns of treatment w	ere used, follow-u	o was for different	t lengths			

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 asse	essment			Number o	of patients	Eff	ect	
								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		n: number of smea	ar-negative patien	ts with all initial cu	ltures negative to	be culture-negati	ve at the end of tr	eatment)	
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			tive patients with a	all initial cultures r	negative 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	ose (assessed wit				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 asso	essment			Number o	of patients	Ef	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4 months	Relative (95% CI)	Absolute (95% CI)	Quality
 ² Method of randomis ³ Allocation concealn ⁴ Blinding unclear ⁵ Unclear if loss to for ⁶ Population does no ⁷ Intervention does no ⁸ Outcome is a subst ⁹ Wide confidence int ¹⁰ Odds ratio and 959 ¹¹ Follow-up began fr ¹² GRADE rule of thu Abbreviations: CI, co 	sation unclear nent unclear llow-up was simila t exactly match th ot exactly match th itute for an outcor tervals % confidence inter om treatment initi mb: <300 events	e population of in he intervention of ne of interest rvals calculated b ation; therefore, a	terest: may includ interest: did not c y reviewer	ontain all of or jus	íinclusion criteria = st the 4 standard r	ecommended drug	gs			

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	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 trea	tment - culture sta	atus (assessed wi	th: number of sme	ar-negative patier	nts with all initial c	ultures negative to	be culture-negat	tive 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-u relapse ¹¹)	o 60 months after tr		assessed with: no	umber of smear-ne	egative patients w	ith all initial cultur	es negative to exp	perience bacteriolo	ogical, radiograph	ic or clinical
11	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 re relapse ¹¹)	elapse (follow-up 6	0 months after trea	atment initiation; a	ssessed with: nur	nber of smear-neg	ative patients wit	h all initial cultures	s negative to expe	rience bacteriolo	gically confirme
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 ass	essment			Number o	of patients	E	ffect	
Number of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisio n	2 months	3 months	Relative (95% CI)	Absolute (95% Cl)	Quality
 ¹ Hong Kong Chest S ² Method of randomi. ³ Allocation concealner ⁴ Blinding unclear ⁵ Population does not ⁶ Intervention does not ⁷ Outcome is a substance of the substance o	sation unclear nent unclear of exactly match th of exactly match th titute for an outco mb: <300 events tervals % confidence inte e for the full defini rom treatment init	ne population of ir the intervention of me of interest ervals calculated b ition iation; therefore, a	nterest: may incluc f interest: did not o ny reviewer	le some children (contain all of or jus	íinclusion criteria = st the 4 standard n	: 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 asso	essment			Number	of patients	Eff	ect	
								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 sta	tus (assessed wit	h: number of patie	ents to be culture-	negative the end o	of treatment)	•	•		•
2 ^{1,2}	randomised trials	very serious ^{3,4,5,6}	very serious ^{7,8}	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 	ervice / Tubercu ation unclear pent unclear	losis Research Ce		tish Medical Rese	earch Council, 198	9				

² Research Committee of the Tuberculosis Association of India, 1984: comparability of patients at baseline was unclear

⁸ Unclear if loss to follow-up was the same in the 2 groups

		Quality asse	essment			Number o	of patients	Eff	ect	
								Relative	Absolute	
Number 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 advigs, 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 asse	essment			Number	r of patients	Ef	fect	
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	to 8 years after the	reatment initiation	; assessed with: n	umber of patients	s to experience re	lapse)			•	
3 ^{1,2,3}	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 LOW
 ¹ Hong Kong Chest S ² Singapore TB Servi ³ Teo et al, 2002 ⁴ Method of randomis ⁵ Allocation concealing ⁶ Blinding unclear ⁷ Analysis is not inter ⁸ Follow-up began frc ⁹ Teo et al, 2002: cor ¹⁰ Hong Kong Chest of patients lost to fc ¹¹ Intervention does r ¹² Unclear if population ¹³ Teo et al, 2002: inter ¹⁴ Wide confidence introduces the 4-mor ¹⁵ GRADE rule of thu ¹⁶ Pooled odds ratio at ¹⁷ Point estimates values and the following the stimates values and the stimates value of the stimates values and the stimates values and the stimates values and the stimates value of the stimates values and the stimates values and the stimates values and the stimates values and the stimates value of the stimates values and the stimates value of the stimates values and the stimates value of the stimates values and the stimates values and the stimates value of the stimates values and the stimates and the stimates and the stimates values and the stimates and the stimate	ce / British Medic sation unclear nent unclear off tro-treat off tro-treat off tro-treat off tro-treat off tro-treat off tro-treat service / Tubercu off of the service / Tubercu off tro-treat off tr	al Research Cour ation; therefore, as ents at baseline u losis Research Co group is unclear the intervention o en (inclusion crite ot exactly match th faily throughout	acil, 1979/86 s different duration nclear entre, Madras / Br f interest: did not o ria = 15 years or n re intervention of i lated by reviewer	is of treatment we itish Medical Res contain all of or ju nore)	ere used, follow-u earch Council (19 ist the 4 standard	p was for differe 89) and Singapo recommended c	ore TB Service / B Irugs			

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	of patients	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	3 months	4 or 4.5 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Response to treatme	ent - culture stat	us (assessed with	n: number of patie	nts to be culture-	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	se)		
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 Service / Tuberculosis Research Centre, Madras / British Medical Research Council, 1989

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 of	of patients	Eff	iect	
								Relative	Absolute	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	>6 months	(95% CI)	(95% CI)	Quality
Treatment failure (a	ssessed with: nur		experience treat	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 af	ter treatment initia	ation; assessed wi	th: number of pati	ents to experienc	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 Sou	ciety 1975/80									

British Thoracic Society, 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

⁶Ziaullah 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 asse	essment			Number	of patients	Eff	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	minimum of 18 m	onths after treatn	nent completion; a		mber of patients to		ose)			
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
 ² Ziaullah et al, 2004 ³ Method of randomis ⁴ Allocation concealn ⁵ Blinding unclear ⁶ Analysis did not foll ⁷ British Thoracic Soc ⁹ British Thoracic Soc ⁹ British Thoracic Soc ¹⁰ British Thoracic Soc ¹¹ Ziaullah et al, 2004 ¹² Wide confidence ir ¹³ GRADE rule of thu ¹⁴ Pooled odds ratio at ¹⁵ Forest plot (relapsed) 	sation unclear nent ciety, 1981/2/4: ur ciety, 1981/2/4: ur ciety, 1981/2/4: in pociety, 1981/2/4: in t: population does tervals mb: <300 events and 95% confiden	nclear if groups re Inclear if the group gh attrition rate wi Intervention does r Inot exactly matc.	s were comparabl ith regards to the l not exactly match h the population o	le for treatment co number of particip the intervention o f interest: include	ompletion pants for whom da f interest: did not o	contain all of or ju			igs, and the 2 reg	imens vary by

Abbreviations: CI, confidence interval; OR, odds ratio

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	Eff	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 24	4 to 36 months a	after treatment initi	ation: assessed wi	th: number of pat	ients with HIV to e	experience relaps	e)			
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
 ² Perriens et al, 1995. ³ Perriens et al, 1995. ⁴ Perriens et al, 1995. ⁵ Suring the part of all 	: allocation conc	ealment unclear d, but investigators		istering care were	e not					

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 assessment						of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Mortality (all cause)	(follow-up 36 mo	nths after treatme	nt initiation; asses	ssed with: number	of patients with H	IIV 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	Number of patients Effect		fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Cure (assessed with	number of patie	nts with HIV to ac	hieve a 'favourable		e end of treatmen	t ⁶)				
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
reatment failure (a	ssessed with: nu	mber of patients w	vith HIV to experie	nce treatment fai	lure ⁶)					
,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; as	ssessed with: nur	mber of patients w	ith HIV to expe	rience 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	y) (assessed with	: number of patie	nts with HIV to exp	perience any adve	erse event resultir	ng from drug tox	(icity)			
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	r of patients with H	HIV to default trea	atment)					
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

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

fortality (follow-up 36	Design 6 months after tre	Risk of bias	Inconsistency							
fortality (follow-up 36	•		Inconsistency					Relative	Absolute	
	6 months after tre		Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
1 r		eatment initiation;	assessed with: no	umber of drug su	sceptible patients	with HIV to die ((all cause))			
tı	randomised trials	very serious ^{2,3}	serious⁴	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 LO
Cure (assessed with: n	number of drug s		ts with HIV to ach		e response' by the	end of treatment	nt ⁸)			
	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ^{5,11}	serious⁵	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 LO
reatment failure (ass	sessed with: nun		eptible patients wi			ure ⁸)				
	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ^{5,11}	serious ⁶	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 LO
dverse events (any)	(assessed with:	: number of drug s	susceptible patien	ts with HIV to exp	perience any adve	rse event result	ing from drug toxi	city)	,	
	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ^{5,11}	very serious ^{6,7}	1/100 (1%)	0/97 (0%)	OR 2.93 (0.12 to 73.05) ⁹	-	VERY LO
Adherence - treatmen	nt default (asses		of drug susceptil	ole patients with I	HIV to default trea	tment)				
	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ^{5,11}	serious ⁶	5/100 (5%)	4/97 (4.1%)	OR 1.22 (0.32 to 4.7) ⁹	1 more per 100 (from 3 fewer to 13 more)	VERY LO

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 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
Cure (assessed with:	number of cultur	e-positive patients	s with HIV to achie		response' by the e	nd of treatment ¹)				
1 ²	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 experience	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 (any	y) (assessed with	: number of cultur	e-positive patients		rience any advers	e event resulting	from drug toxicity)		
1 ²	randomised trials	very serious ^{3,4}	no serious inconsistency	serious ^{5,9}	very serious ^{6,8}	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 im ⁹ Doses used are inc. Abbreviations: CI, co 	2010 ow intent-to-treat t exactly match th nb: <300 events 6 confidence inten tervals onsistent with tho	principle e population of ini vals calculated by se listed in the Bri	reviewer	·	v be some childrer	n (inclusion = 15 y	ears and above)			

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	iect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	12 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Mortality (follow-up 2	4 months after tre	eatment initiation;	assessed with: n	umber of smear-	and culture-positiv	e patients with HI	V to die from tube	erculosis)		
1 ¹	randomised trials	very serious ^{2,3,4}	serious ^{5,6}	no serious indirectness	very serious ^{7,8}	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	ind culture-positive	patients with HIV	to experience re	lapse)		
1 ¹	randomised	very	serious ^{5,6}	no serious	serious	1/123	9/124	OR 0.10 (0.01	6 fewer per	VERY LOW

		Quality asse	essment			Number o	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	12 months	Relative (95% CI)	Absolute (95% CI)	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 culture	e-negative patient	ts with HIV to achi	eve a 'favourable	response' by the	end of treatment ¹)			
1 ²	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: nun	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 serious ^{6,8}	0/34 (0%)	0/38 (0%)	OR 1.12 (0.02 to 57.77) ⁷	-	VERY LOW
Adverse events (ang	y) (assessed with		e-negative patient	ts with HIV to exp		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 asse	essment			Number o	of patients	Ef	fect						
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)							
See evidence table Swaminathan et al, 2		ion													
³ Unblinded ⁴ Analysis did not follo	w intent-to-treat	principle													
⁵ Population does not ⁵ GRADE rule of thun		e population of in	terest: some DR-	ГВ, and there may	/ be some childrer	n (inclusion = 15 y	ears and above)								
Odds ratio and 95%	confidence inter	vals calculated by	reviewer												
⁸ Wide confidence inte ⁹ Doses used are inco		se listed in the Br	itish National Forr	nulary											
Abbreviations: CI, cor	nfidence interval;	OR, odds ratio													

A.8 RQ M

Duration of treatment in children with respiratory tuberculosis A.8.1

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 to experience clinical or radiological recurrence in the 12 months after treatment completion; follow-up 12 months after treatment completion)													
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 - he	patotoxicity (nur	mber to experienc	e elevated levels			e and alanine am	inotransferase)						
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	E	Effect	
Number of studies Design Risk of bias Inconsistency Indirectness Imprecision 9 months 12 months Relative (95% CI) Absolute (95% CI) Qual 9										
 ⁹ Wide confidence internet ¹⁰ Odds ratio and 95% ¹¹ Outcome not clearly ¹² Substitute for outco ¹³ Prescribed doses of Abbreviations: CI, cor 	6 confidence inte / defined - thresh me of interest (n f isoniazid and s	holds for 'elevated' elapse) treptomycin are ab	" aspartate aminot			-				

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% Cl)	Quality	Importance
	(follow-up 1	to 3 years; as	sessed with: nun	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			onth (assessed	with: number of	of patients to have	e a sputum culture	negative for M. tube	erculosis af	ter 1 month	of treatme	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 have	ve a sputum culture	e negative for M. tul	perculosis a	after 2 mont	hs of treat	ment)
2 ^{2,10}	randomised trials		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	
			onversion at 3 mo	onths (assessed	l with: number	of patients to have	ve a sputum culture	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 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% CI)	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 adn	hission but	disappeare	d by the e	nd of
1 ¹⁰	randomised trials		serious ¹³	very serious ^{14,15}	serious ⁸	none	103/245 (42%)	88/250 (35.2%)	OR 1.34 (0.93 to 1.92) ⁹	7 more per 100 (from 2 fewer to 16 more)	⊙OOO VERY LOW	
		symptoms - ra	adiographic impr	ovement (asses	sed with: num	ber of patients to	achieve moderate	or greater radiogra	phic improv	ement after	2 months	s of
treatmer 1 ¹⁰	randomised trials	serious ^{11,12}	serious ¹³	very serious ^{14,15}	serious ⁸	none	130/261 (49.8%)	107/269 (39.8%)	OR 1.50 (1.06 to 2.12) ⁹	10 more per 100 (from 1 more to 19 more)	⊙OOO VERY LOW	
		symptoms - le	essening of cavita	ation (assessed	with: number	of patients in who	om the cavitation th	at was present on a	admission	had lessene	d by the e	nd of
treatmen	randomised	aaria.ua ^{11,12}	serious ¹³		serious ⁸		97/245	111/250	OR 0.82	5 fewer	0000	
	trials	senous	senous	very serious ^{14,15}	senous	none	(39.6%)	(44.4%)	(0.57 to 1.17) ⁹	per 100 (from 13 fewer to 4 more)	VERY LOW	
			endobronchial les	ions (assessed	I with: number	of endobronchial	lesions identified	using bronchoscop	y before tre	atment to h	ave impro	ved after 2
1 ¹⁷	of treatment ¹⁶ 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	
	in signs and s	symptoms – p	oulmonary lesion	s (assessed wit	h: number of I	esions identified	using chest-x-ray b	efore treatment to h	nave improv	ved after 2 n	nonths of	treatment ¹⁶)
1 ¹⁷	randomised trials	serious ^{11,12}	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	
	• •	<i>.</i>	to 3 years; asse		ber of patients	1	apse during follow					
2 ^{1,10}	randomised trials	very serious ^{3,4,11,} 12	serious ^{5,13}	serious'	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 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% Cl)	Quality	Importance
placebo 7 Bilacen 8 GRADI 9 Odds n 10 Tubero 12 Unclea 13 Tubero 14 Outcon 15 Tubero 16 See en 17 Park e 18 Follow 19 Wide o 20 Forest	po oglu et al, 1998 E rule of thumb atio and 95% c culosis Resear reculosis Resear re is a substitu- culosis Resear vidence table fut t al, 1997 -up not for the polit (mortality) plot (response	9: antituberculo 9: <300 events onfidence inte ch Centre (Ma is follows the ir ch Centre (Ma ute for an outco ch Centre (Ma or full definition full treatment p rval): a to treatment -	osis regimens do n rval calculated by i dras), 1983 dras) (1983) and F ntent-to-treat princi dras), 1983: unclea ome of interest dras), 1983: antitu n	ot use all of or ju reviewer Park et al (1997): ple ar if the groups v berculosis regim pon at 1 month):	nst the 4 standa method of rand	rd recommended c domisation and use	Irugs e of allocation concea npletion and availabi	ive prednisolone tha alment and blinding is lity of outcome data led drugs; in particul	s unclear			

²³ Forest plot (relapse):

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

			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% CI)	Quality	Importance
Mortality	(HIV-positive) (follow-up 1	to 3 years; asse	ssed with: num	ber of deaths)							
1 ¹	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	
Event- fr	ee survival (H	IV-positive) (follow-up 1 to 3 y	ears; assessed	with: number	of patients to sur	vive to 36 months v	vithout significant a	adverse eve	ent)		
1 ¹	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	
Treatmen	nt failure (HIV	-positive) (as	sessed with: nun	nber of patients	to experience	treatment failure	²)					

			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% CI)	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	
Respons		t – sputum co	onversion at 1 m	onth (HIV-posit	ive) (assessed	with: number of p	atients to have a sp	outum culture nega	tive for M. t	uberculosis	s after 1 m	onth of
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	
						rrence within 2 yea	ars of initiating trea	tment⁵)				
1 ¹	randomised trials	risk of bias	serious ²	serious⁵	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	
				per of patients t	o experience a	iny 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	
		t – sputum co	onversion at 2 m	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
treatmen 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)	0000 VERY LOW	
								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)	0000 LOW	

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 service and the service service interval calculated by reviewer

⁷ Wide confidence interval

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

			Quality asses	ssment			No of	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% CI)	Absolute (95% CI)	Quality	Importanc
Mortality	(HIV-negative	e) (follow-up	1 to 3 years; asse	essed with: nur	nber of deaths)						
1 ¹	randomised trials		serious⁴	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 was initia	ated)		in bacillary count	(HIV-negative)	(follow-up 50	days; assessed w	ith: number of to ex	operience a drop in l	/	ount 50 days	after pred	dnisolone
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	
	se to treatmen plone was initi		ecrease in bacilla	ry count (HIV-n	egative) (follow	w-up 50 days; ass	essed with: numbe	r of to experience a	marked dro	op in bacilla	ry count 5	0 days after
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	
Change i			ever (HIV-negativ	e) (measured w	ith: change in	temperature with	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 - v	veight (HIV-negati	ive) (measured	with: weight c	hange during trea	tment; better indica	ated by lower values	5)			
1 ¹	randomised trials		serious ⁴	serious⁵	serious ¹⁰	none	91	87	-	MD 1.4kg higher ¹¹		
Change i predniso	in signs and solone initiation	symptoms - n 1 ¹²)	narked radiograp	hic improveme	nt (HIV-negativ	ve) (assessed with	: number of patient	s to experience mar	ked radiog	raphic impre	ovement 5	50 days after
1 ¹	randomised trials	serious ^{2,3}	serious ⁴	serious⁵	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 prednisc			ovement (HIV-n	egative) (asse	ssed with: numbe	r of patients to exp	erience radiographi	c improven	nent (marke	d, modera	te or slight)
1 ¹	randomised trials		serious⁴	serious⁵	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	

Bilaçeroglu et al, 1999: method of randomisation and use of allocation concealment is unclear

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	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% CI)		Importance
⁶ Wide confidence interval ⁷ GRADE rule of thumb: <300 events												

⁸ Odds ratio and 95% confidence interval calculated by reviewer
 ⁹ Outcome is a substitute for an outcome of interest
 ¹⁰ Authors did not provide sufficient data to calculate a confidence interval
 ¹¹ Mean difference calculated by reviewer
 ¹² See evidence table for full definition

PLEURAL TUBERCULOSIS

Dexamethasone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	patients	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 –				ight at the end of t		dicated by higher va	lues)			
1 ¹	non- randomised trials	very serious ^{2,3,4}	serious ^{5,6}	serious'	serious ⁸	none	30	20	-	MD 1.6kg higher ⁹	⊙OOO VERY LOW	
Changes	in signs and	symptoms -	weight change (f	ollow-up uncle	ar; measured v	with: change in me	ean weight from bas	seline to the end of t	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: time	e to relief of coug	h; better indicated k	by 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 –		ision (follow-up	o unclear; mea	sured with: time ta	aken for complete a	bsorption of a large	pleural eff	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 o	effusion (follow	-up unclear; m	neasured with: tim	e taken for complet	e absorption of a m	edium pleu	ral effusion	; better ind	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 asse	ssment			No of p	patients	Efi	iect		
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	p unclear; mea	sured with: time t	aken for complete a	absorption of a sma	II 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 -		w-up unclear; n	neasured with	time to relief of c	hest pain; better inc	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	
	in signs and	symptoms -		ath (follow-up i		ured with: time to	relief of shortness of	of breath; better ind	icated by lo	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 (fol	low-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	sessed 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 bline ⁵ Unclear ⁶ Unclear ⁷ Antitube ⁸ Authors ⁹ Mean d ¹⁰ GRAD 	r if the groups w r if the groups i perculosis regim	ment vere compara received the s iens do not us e sufficient da lated by revie c <300 events	e all of or just the ta to calculate a c wer s	4 standard recor	nmended drugs	etails provided are s; of particular note	limited is that rifampicin is n	ot used, and that onl	y a 2-drug re		used	

¹¹ Odds ratio and 95% confidence intervals

Prednisolone vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			No of p	atients	Eff	ect	
No of studies	s Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	plus	chemotherapy alone or plus	Relative	Absolute (95% Cl)	Importance

			Quality asse	ssment			No of j	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency			Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importanc
						s (follow-up uncle	ear; measured with:	time to disappeara	nce of clini	cal signs an	d symptor	ns
11	randomised trials	very serious ^{2,3,4}	spnea); better ind no serious inconsistency ⁵	serious ⁶	no serious imprecision	none	21	19	-	MD 6.8 days lower (14.3 lower to 0.07 higher) ⁷	0000 VERY LOW	
						I with: time to clea dicated by lower v		usion (as defined b	y roentgen	ologic evide	nce of clea	aring of the
1 ¹	randomised trials		no serious inconsistency ⁵	serious ⁶	serious ⁸	none	21	19	-	MD 68.7 days lower ⁷	⊙OOO VERY LOW	
			fever (follow-up			tion of fever at 46		icated by lower value	ues)			
9	randomised trials	serious ²	no serious inconsistency⁵	serious ⁶	serious ⁸	none	57	60	-	MD 0.83 days lower ⁷	⊙OOO VERY LOW	
						ed with: number o	f patients to experi	ence pleural adhesi	ons)			
1	randomised trials	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	
Analysi Blinding Unclear Antitube Mean o Authors Galarza ⁰ GRAD ¹ Wide o ² Wyser	of randomisat s did not follow g is unclear r if the groups r erculosis regim lifference calcu s did not provid a et al, 1995 E rule of thumk confidence inte. et al, 1996	v the intent-to- received the s lens do not us lated by revie le sufficient da b: <300 events rvals	ame care apart fro e all of or just the wer ta to calculate a c	m the interventi 4 standard reco onfidence interv	on(s) studied; a mmended drugs al		is that Galarza et al	(1995) used only a 2 pulmonary tuberculo.				

(21.2%) (21.2%) 14 Odds ratio and 95% confidence interval calculated by reviewer

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

			Quality asse	ssment			No of p	oatients	Effe	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% CI)	Absolute (95% Cl)	Quality	Important
	•	<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 treatment	nt)			
1 ¹	randomised trials	risk of bias	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	
				sitive) (measur		t after 24 weeks o	f treatment; better		values)			
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁵	none	99	98	-	MD 3kg higher ⁶	©©©O MODERATE	
Changes	in signs and		- cough (HIV-pos	sitive) (assesse	d with: numbe	of patients with	a cough after 24 we	eeks 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	
	in signs and	symptoms -	 pleural effusion 	n (HIV-positive)		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)	OOO MODERATE	
	ce (HIV-posit	ive) (measu	red with: recurre	nce rate; better	r indicated by	lower values)						
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious'	no serious imprecision	none	99	98	-	recurrenc e rate 2.3 higher (0.6 to 9 higher)	⊙⊙⊙O MODERATE	

			Quality asse	essment			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% Cl)	Quality	Importance
	events requir	•	nt discontinuatio	on (HIV-positive	e) (assessed w	ith: number of pat	ients to experience	an adverse event t	hat required	discontinua	tion of	
1 ¹	randomised trials	no serious risk of bias	inconsistency	no serious indirectness	serious ³	none	9/99 (9.1%)	2/98 (2%)	OR 4.80 (1.01 to 22.82) ⁴	7 more per 100 (from 0 more to 30 more)	©⊙⊙O MODERATE	
							: number of patient					
1 ¹	randomised trials	risk of bias	inconsistency	no serious indirectness	very serious ^{2,3}	none	9/99 (9.1%)	2/98 (2%)	OR 13.70 (0.76 to 246.52) ⁴	20 more per 100 (from 0 fewer to 82 more)	©⊙⊖⊖ LOW	
	events - incid	ence of HIV	-related disease:	cryptococcal		/-positive) (asses	sed with: number o			coccal menin		
1 ¹	randomised trials	risk of bias	inconsistency	no serious indirectness	serious ²	none	3/99 (3%)	5/98 (5.1%)	OR 0.58 (0.14 to 2.5) ⁴	2 fewer per 100 (from 4 fewer to 7 more)	©⊙⊙ MODERATE	
Adverse	events - incid	ence of HIV	-related disease:	oesophageal	candidiasis (H	V-positive) (asses	ssed with: number of	of patients to exper	ience oesop	hageal cand	idiasis)	
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	35/99 (35.4%)	23/98 (23.5%)	OR 1.78 (0.96 to 3.32) ⁴	12 more per 100 (from 1 fewer to 27 more)	©⊙⊙ MODERATE	
Adverse	events - incid	ence of HIV	-related disease:	herpes zoster	(HIV-positive)	(assessed with: r	number of patients	o experience herpe	es zoster)			
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	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 more)	⊙⊙⊙ MODERATE	
Adverse	events - incid	ence of HIV	-related disease:	oral or genital	herpes simple	ex (HIV-positive) (assessed with: num	ber of patients to e	experience o	ral or genital	herpes simp	lex)
1 ¹	randomised trials	no serious risk of bias		no serious indirectness	serious ²	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 more)	©⊙⊙ MODERATE	
Adverse	events - incid	ence of HIV	-related disease:	oral thrush (H	IV-positive) (as	ssessed with: nur	nber of patients to e	experience oral thru	ısh)			
1 ¹	randomised trials	risk of bias	inconsistency	no serious indirectness	serious ²	none	31/99 (31.3%)	31/98 (31.6%)	OR 1.43 (0.79 to 2.56) ⁴	8 more per 100 (from 5 fewer to 23 more)	©⊙⊙ MODERATE	
	events - incid	ence of HIV	-related disease	gastroenteritie) (assessed with:	number of patients		roenteritis)			
1 ¹	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious ²	none	34/99 (34.3%)	28/98 (28.6%)	OR 1.32 (0.72 to	6 more per 100	OOO MODERATE	

			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% CI)	Absolute (95% CI)	Quality	Importance
		bias							2.39)4	(from 6 fewer to 20 more)		
 ² GRADE ³ Wide co ⁴ Odds ra ⁵ Authors ⁶ Mean di 	did not provid ifference calcu	vals onfidence int le sufficient d lated by revie	erval calculated by ata to calculate a	y reviewer confidence inter	val							

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

			Quality asse	essment			No of p	oatients	Eft	fect		
No of studies Changes	Design	Risk of bias symptoms -	Inconsistency	Indirectness		Other considerations unclear; measure	Antituberculosis chemotherapy plus prednisolone d with: Index of rea	Antituberculosis chemotherapy alone or plus placebo bsorption of pleura	Relative (95% CI) I hemithora	Absolute (95% CI) ix at 12 mon	Quality	Importance indicated
by lower			•		, , , , , , , , , , , , , , , , , , ,	·						
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 -	 pleural thicken 			ssessed with: nun	nber of patients wit	n residual pleural th	ickening, a		using a ch	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 -			• •) (assessed with: I	number of patients	with residual pleura	I thickening	g, as assess	•	a CT scan)
1'	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	serious'	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 thicken 	ing on x-ray (HI	V-negative) (m	easured with: ple	ural thickening at 2	4 weeks, as assesse	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 J	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
										higher) ⁹		
	in signs and er indicated b			ing on x-ray (H	V-negative) (m	easured with: cha	ange in pleural thicl	kening from baselin	e to 24 wee	ks, as asse	ssed using	g a chest x-
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 val		symptoms	 pleural thicken 	ing on CT scan	(HIV-negative)) (measured with:	pleural thickening	at 24 weeks, as asse	essed using	g a CT scan;	better ind	licated by
1	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	⊙OOO VERY LOW	
dverse	events (HIV-r	negative) (as	sessed with: nur	mber of patients	s to experience	e an adverse even	t)			0 /		
¹	randomised trials	very serious ^{2,3}	serious ^{4,5}	serious ⁶	serious ⁷	none	17/34 (50%)	21/36 (58.3%)	OR 1.47 (0.3 to 7.1) ⁸	9 more per 100 (from 29 fewer to 33 more)	⊙OOO VERY LOW	

³ Analysis did not follow the intent-to-treat principle 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 J	oatients	Ef	fect	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy plus		Relative		Importance

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

			Quality asse	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 or plus placebo	Relative (95% CI)	Absolute (95% CI)	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 in 	n radiological s	tatus (prednise	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	atus (predniso	olone; children) (a	ssessed with: numl	ber of patients who	se radiolog	cal 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	
			 bronchoscopy 	score (prednis	olone; childrer	n) (measured with:	change in broncho	oscopy score from I	baseline to		st-treatmer	nt ⁹ ; better
	l by higher va		. 4	· ·								
1 ¹	randomised trials		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	
						Iren) (assessed wi		ents to require >2 br				
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	⊙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 of a 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 p	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% CI)	Absolute (95% Cl)	Quality	Importance
Mortality	(dexamethas	one) (follow	-up 3 months to	5 years; assess	ed with: numb	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	
			cin-containing a					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	one; non-ra	ndomised) (follow			number of deaths	5)					
1 ¹⁵	non- randomised trials	very serious ^{16,17}	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	
	e to treatmen	t - full or par	tial recovery (de	xamethasone)		n: number of patie		I or partial recovery				
1 ⁴	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	e to treatmen	t - poor outo	ome (dexametha	isone) (assesse	ed with: numbe	er of patients to e	xperience a poor οι	Itcome (death or su	rvival with	major seque	lae (persister	nt vegetative
			rocephalus, mod	lerate-to-sever		npairment, severe		ty (totally depender	nt), or unco	ntrolled seiz	ures)))	
1 ⁴	randomised trials		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	
								utcome (survival w	ith minor (r	nild intellect	ual impairme	nt, mild-to-
moderate	e functional d randomised				serious ²¹		ance)) or no sequel	ae)) 13/23	OR 1.28	6 moro	0000	
	trials		no serious inconsistency	very serious ^{24,25}		none	(62.5%)	(56.5%)	(0.4 to 4.12) ¹⁴	6 more per 100 (from 22 fewer to 28 more)	VERY LOW	
	-				red with: time	-		ng patients; better i	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 asse	ssment			No of J	patients	Ei	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% CI)	Absolute (95% Cl)	Quality	Importanc
Changes	s in signs and	symptoms -	fever (dexameth	asone) (measu	red with: time	to fever clearance	e (days from randoi	nisation to observa	tion of a m	aximal daily	temperature	of less than
			tive days); better		,							
1 ²	randomised trials	risk of bias	inconsistency	no serious indirectness	serious ²⁷	none	274	271	-	difference between the medians 2 days lower	©⊙⊙O MODERATE	coore of 15
			/s); better indica			e to coma clearant	e (median, days fro	om randomization u	ntii observ	ation of a Gia	asgow coma	score of 15
1 ²	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²⁷	none	274	271	-	difference between the medians 2 days lower	©⊙⊙O MODERATE	
							1 · · · · · · · · · · · · · · · · · · ·	sis at baseline to re				
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 treatmer		symptoms -	hemiparesis (de	examethasone)	(assessed wit	h: number of patie	ents without hemipa	aresis at baseline to	be experie	encing hemip	aresis after s	9 months of
1 ²	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)	©⊙⊙O MODERATE	
Changes	s in signs and	symptoms -	paraparesis (de	xamethasone)	(assessed with	n: number of patie	nts with parapares	is at baseline to res	olve after 9	months of t	reatment)	
1 ²	randomised trials	no serious risk of bias	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)	©⊙⊙ MODERATE	
•	•	symptoms -	paraparesis (de	xamethasone)	(assessed with	n: number of patie	nts without parapa	resis at baseline to	be experie	ncing parapa	resis after 9	months of
treatmer 1 ²	randomised	no serious	no serious	no serious	serious ²¹	none	11/246	11/260	OR 1.06	0 more	0000	
I	trials	risk of bias		indirectness	Senous	none	(4.5%)	(4.2%)	(0.45 to 2.49) ¹⁴	per 100 (from 2 fewer to 6 more)	MODERATE	
						1 · · · · · · · · · · · · · · · · · · ·		a tuberculoma durii	•			
1 ²	randomised trials	no serious risk of bias	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)	©⊙⊙ MODERATE	

	Quality assessment							No of patients				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus dexamethasone	Antituberculosis chemotherapy alone or plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Changes	_	symptoms -	hydrocephalus	(dexamethasor	ne) (assessed v	with: number of p	atients to experience	e a hydrocephalus			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)	©⊙ÓO MODERATE	
	in signs and	symptoms -	good disability	status (dexame		essed with: numb	per of patients in a g	ood disability statu	s 5 years a	fter randomi	sation)	
2 ^{2,5}	randomised trials		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	
	in signs and domisation)	symptoms -	 intermediate or 	severe disabil	ity status (dexa	amethasone) (ass	sessed 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	s (dexamethaso	one) (measured	l with: time to imp	provement in mini-m	nental score among	st surviving	g patients ²⁸ ;	better indicat	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 ring treatment)	normalities du	ing 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	
	s in signs and hemiparesis			ogical abnorma	lities (dexame	thasone) (assess	ed with: number of	patients to with per	manent res	,	ogic abnorma	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	
						time to recovery	of headache among	st surviving patient	ts; better in	dicated by lo		
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	vith: time to improve	ment in Barthel sco	ore amongs	st 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 J	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% CI)	Absolute (95% CI)	Quality	Importance
										higher	LOW	
			ed with: number			apse ²⁸)						
1 ²	randomised trials		no serious 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 O O O O O O O O O	
Adverse	events - ocula	ar (dexameth	nasone; non-rand			assessed with: nu		ith ocular complica	tions)			
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	
		re (dexamet	hasone) (assesse	ed with: numbe	er of patients to	o experience a sev	vere event (any eve	nt causing or threa	tening to ca	ause prolong	jed hospital s	stay,
	y, or death))				, 21.27			1 - 10 - 1				
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)	OOO MODERATE	
	events - hepa	ititis (dexam	ethasone; HIV-ne	egative) (asses		ber of patients to		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	bleeding (dexame	ethasone; HIV-	negative) (asse	essed with: of pat	ients to experience	gastrointestinal ble	eding ²⁹)	,		
1 ⁵	randomised trials	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	
			rculoma (dexame	ethasone; HIV-		essed with: numb		perience paradoxica	al 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 	e et al, 1969 es et al, 2004/7 et al, 1991 velu et al, 1994 ra et al, 2009		2011							22 more)		

⁶ Unclear if analysis followed the intent-to-treat principle
 ⁷ Malhotra et al, 2009: unclear if alloctation concealment used, and blinding not used
 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 p	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% CI)	Absolute (95% Cl)	Quality	Importance
¹¹ Follow-	up varied wid	ely between g	groups				<u></u>					
¹² Estima	tes of effect ve	ery widely acr	oss the studies									
¹³ O'Toole	e et al (1969),	Girgis et al (1	1983 and 1991), K	umarvelu et al (*	1994): antituber	culosis regimens a	o not use all of or jus	st the 4 standard reco	ommended	drugs; of part	icular not is t	he lack of
rifampic	in in O'Toole	et al (1969) a	nd Girgis et al (198	33 and 1991)								
¹⁴ Odds r	atio and 95%	confidence in	terval calculated b	y reviewer								
¹⁵ Girgis e	et al, 1983											
			ternately assigned	to receive antitu	iberculosis che	motherapy plus de	kamethasone or antil	tuberculosis chemoth	nerapy alone	9		
	cation concea blinding uncle											
¹⁹ Author	s state that an	ai None were coi	mnarahla with rosi	port to and sex	and dispase se	verity on admission	to hospital: howeve	r, although not statis	tically signif	icant more n	ationts in the	
								- that is, the conditio				
	ered to be mor		c comatosc on ad			osis enemenerapy					andsone grou	
²⁰ Unclea	r if aroups rea	eived the san	ne care except for	the intervention	(s) studied: limi	ted information ava	ilable					
²¹ GRADI	E rule of thum	b: <300 event	ts		c) claalea,		indiana a					
²² Kumar	velu et al, 199	4: use of alloc	cation concealmen	t and blinding is	unclear							
²³ Authors	s do not provie	de a definition	1	Ŭ								
24 Kumar	velu et al, 199	4: antitubercu	Ilosis regimens do	not use all of or	just the 4 stand	dard recommended	l drugs					
²⁵ Outcon	ne is a surroga	ate for an outo	come of interest				-					
²⁶ Some o	data was only	available for p	patients with either					ce the authors do no			patients with	either 'severe'
_or 'mild-	-to-moderate'	disease on ac	dmission who were	randomised to	each interventi	on, this data could	not be analysed in a	ccordance with the ir	ntent-to-trea	t principle		
² / ₂ Insuffic	eient data to ca	alculate confic	lence intervals									
² ° For full	definition, see	e evidence tal	ble									

- ²⁹ 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	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% CI)	Absolute (95% CI)	Quality	Importance
	(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	patients to r	equire vent	ricular shu	nting, as
1 ²	randomised	-	very serious ⁶				5/29	4/30	OR 1.35	4 more	0000	
	trials	very serious ¹²		very serious ^{8,13}	very serious ^{9,10}	none	(17.2%)	(13.3%)	(0.33 to 5.64) ¹¹	per 100 (from 9 fewer to 33 more)	VERY LOW	
								ed (severely or mild	• •			
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	
	n signs and s eatment)	symptoms - n	eurological abno	ormalities durin	g treatment (p	rednisolone; HIV-	negative) (assesse	d with: number of p	atients to d	levelop 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	
Changes months)	in signs and	symptoms -	hearing (prednis	olone; children) (assessed w	ith: number of pat	ients with deterior	ation in their hearin	g (decrease	ed hearing, t	hough not	deaf) at 6
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	
Changes	-		severe disability			sessed with: numb		e severely disabled		s)		
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 J	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% CI)	Absolute (95% CI)	Quality	Importance
Changes	s in signs and	symptoms -	tuberculoma (pr	ednisolone; chi	ldren) (assess	ed with: number	of patients to devel	op tuberculomas in	the first me	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	
								ss than 75 at 6 mon				
1 ¹	randomised trials	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	
	s in signs and	symptoms -			· _	n: number of patie	ents with visual det	erioration (decreas	ed vision or	blindness)		hs)
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 with	n: 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 wi	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 pation	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	

			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 alone or plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1 ²	randomised trials	very serious ¹²	serious ⁶	serious ⁸	serious ¹⁸	none	29	30	-	MD 3.7 days lower ¹¹	⊙OOO VERY LOW	
	nce (predniso	lone; HIV-ne		o 18 months; as	sessed with: r	number of patients		urrence of meningi		ollow-up)		
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 (0.02 to 53.83) ¹¹	-	⊙OOO VERY LOW	
	events - hype	erglycaemia			llow-up 18 mo	nths; assessed wi		ents to experience I		mia)		
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 (0.02 to 53.83) ¹¹	-	⊙OOO VERY LOW	
	events - gast	rointestinal I	bleeding (prednis	olone; HIV-neg	ative) (follow-u	up 18 months; ass	sessed with: numbe	er of patients to exp		strointestina		1)
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 (0.02 to 53.83) ¹¹	-	⊙OOO VERY LOW	
 ⁵ Unclean ⁶ Chotmo statistic weaknet weaknet ⁷ Follow-¹⁸ ⁸ Chotmo ⁹ GRADE ¹⁰ Wide of ¹⁰ Wide of ¹¹ Odds r ¹² Chotm ¹³ Outcor ¹⁴ Blindes profess ¹⁵ Follow ¹⁶ Antitub 	if analysis foll ongkol et al, 19 ally significant ses than in the the placebo gr up varied wide ongkol et al, 19 atio and 95% of ongkol et al, 19 ne is a surroga d = clinical psy ionals were bli -up only 3 mor	owed the inte 96: groups no , more patien placebo grou roup, although ly between gr 96: antitubero : <300 events rvals confidence int 996: method ate for an out chologist ass inded ths after trea mens do not u	ts in the prednisolo p (10%); additiona n again this was no roups culosis regimens d s terval calculated b of randomisation a come of interest	aseline - clinical one group (17%) Illy, there were n ot statistically sig lo not use all of c y reviewer nd use of alloca , clinician testing	had motor wea nore patients wi nificant or just the 4 star tion concealment tion concealment the hearing, ophth	akness than in the p th severe (stage 3) ndard recommende nt is unclear nalmologist testing v	placebo group (3%), disease and fewer p ed drugs	tion and comparator and more patients ir patients with less sev therapist testing mot	h the prednis vere (stage 1	olone group) disease in	(17%) had the prednis	motor solone 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)	
		nisolone; HIV				after 6 months of t					
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
hanges eatmen		symptoms -	severe disability	y (methylpredni	isolone; HIV-ne	egative) (assessed	l with: number of pa	atients to experienc	e severe d	isability afte	r 6 months of
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
hanges f treatm		symptoms -	intermediate dis	sability (methyl	prednisolone;	HIV-negative) (ass	essed with: numbe	r of patients to expe	erience inte	ermediate di	sability after 6 mo
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
hanges reatmen		symptoms -	good disability	status (methylp	orednisolone; H	HV-negative) (asso	essed with: number	of patients to achie	eve a good	disability s	tatus after 6 montl
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
dverse	events - hepa	atitis (methyl	orednisolone; HI	V-negative) (as	sessed with: n	umber of patients	to experience clinic	cal or subclinical he	epatitis⁵)		
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
	events - gast	rointestinal b	leeding (methyl	orednisolone; H	IIV-negative) (a	assessed with: nu		experience gastroir		• •	
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 paradox			
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 more)	⊙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
³ Unblinde	allocation conc ed ' rule of thumb											
ຼິ For full o	tio and 95% co definition, see nfidence inter	evidence table	rval calculated by es	reviewer								

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo

			Quality asses	ssment			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% CI)	Absolute (95% Cl)	Quality	Importa
Mortality ((follow-up 3 n	nonths to 5 y	ears; assessed v	vith: number of	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	
Mortality (•	year) (follow	-up 3 to 10 mont			deaths)						
3 ^{1,6,7}	randomise d trials	very serious ^{8,9,10}	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	
	· ·		-up 18 months to									
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 anti	ituberculosis reg	imens only) (fo	llow-up 3 mon	ths to 5 years; as	sessed with: numbe	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	
	n signs and sy		eurological abno			nonths; assessed	with: number of pa	tients to develop ne	urological	abnormaliti	es during	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)	⊙OOO VERY LOW	
					picin-containir	ng antituberculosi	s regimens only) (fo	ollow-up 18 months	; assessed	with: numb	er of patie	nts to
develop n 1 ²	eurological a randomise d trials	bnormalities serious ⁸	during treatmen serious ¹²	t) 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	

⁶ Kumarvelu et al, 1991
 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	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
 ⁹ Schoema patients ¹⁰ Unclear ¹¹ Malhotra ¹² Chotmo statistica weaknes than in til ¹³ O'Toole ¹⁴ Kumarva ¹⁵ Follow-L ¹⁵ Follow-L ¹⁶ Estimate ¹⁷ Chotmo. ¹⁸ Odds ra ¹⁹ GRADE 	an et al, 1997: or other health if analysis follo a et al, 2009: b ngkol et al, 19 nlly significant, ss than in the p he placebo gro et al, 1969: ur elu et al, 1994. up varied widen as of effect ver ngkol et al (19	blinded = clin n professional owed the inter- blinding not us 96: groups no more patients blacebo group oup, although nclear if group to follow-up on by between gra y widely acro- 96), O'Toole e onfidence inter- < <300 events	ical psychologist a s were blinded nt-to-treat principle ed t comparable at b s in the prednisolo (10%); additional again this was not s were comparabl ly 3 months after t oups ss the studies et al (1969), Girgis rval calculated by	assessing intellig aseline - clinical ne group (17%) ly, there were m 's statistically sigr e at baseline, or reatment initiation et al (1991), Ku	pence, clinician presentations a had motor weal ore patients wit nificant r if they were co on	testing hearing, opl and staging were si kness than in the pi h severe (stage 3) omparable for treatm	milar in the interventi lacebo group (3%), a disease and fewer pa nent completion and	vision, and physical t ion and comparator g and more patients in th atients with less seven availability of outcom use all of or just the 4	roups at rar he predniso re (stage 1) ne data	ndomisation; Ione group (disease in ti	however, (17%) had i he prednis	although not motor
²¹ Forest p	lot (mortality;	follow-up subg	groups):									
²² Forest p	lot (mortality;	rifampicin-con	ntaining antituberc	ulosis regimens	only):							
²³ Forest p	lot (change in	signs and syr	mptoms - neurolog	ical abnormalitie	es):							

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% CI)	Quality	Importance
Mortality	(HIV-negative)) (follow-up [•]	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; asso	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 p	patients	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% CI)	Quality	Importance
		mptoms - n	eurological abno	rmalities durin	g treatment (H	IIV-negative) (asse	essed with: number	of patients to deve	lop neurolo	gical abnor	malities du	uring
treatment	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 ities after trea		eurological abno	rmalities after	treatment (HIV	/-negative) (follow	-up 18 months; ass	essed with: numbe	r of patients	to develop	neurologi	cal
1 ¹	randomised trials	very serious ³	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	
Change ir								tter indicated by low	ver values)			
1'	randomised trials	very serious ³	serious ⁶	serious'	serious ¹²	none	29	30	-	MD 2.6 days higher ⁹	⊙OOO VERY LOW	
Change ir	n signs and sy	mptoms - s	evere disability (HIV-negative) (a	assessed with	: number of patie	nts to experience se	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 ir	n signs and sy	mptoms - ir	ntermediate disal	oility (HIV-nega	tive) (assesse	d with: number of	patients to experie	nce intermediate di	sability afte	r 6 months	of treatme	nt ¹³)
1 ²	randomised trials	very serious ^{4,5}	no serious inconsistency	no serious indirectness	serious [®]	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	
			o disability (HIV-		essed with: nu	mber of patients w		e after 6 months of				
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	
Change ir						normalisation of		better indicated by	lower value			
1'	randomised trials	very serious ³	serious ⁶	serious ⁷	serious ¹²	none	29	30	-	MD 3.7 days lower ⁹	⊙OOO VERY LOW	
	ce (HIV-negati	ve) (follow-	up 18 months; as	sessed with: n	umber of patie	ents to experience	recurrence of men	ingitis during follow	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	patients	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% CI)	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	perience gastroint	estinal bleeding)		, í		
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	loxical tuber	culoma (HIV-neg	ative) (assesse	d with: numbe	er of patients to ex	cperience 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	

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 (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	Eff	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% CI)	Absolute (95% CI)	Quality	Importance
Mortality	(prednisolone	; children) (i	follow-up 3 mont	hs to 6 months	; assessed wit	th: number of dea						
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 -	disability (predni	solone; childre	n) (assessed v	with: number of pa	atients to be disable	ed (severely or mild	,	nths)		
1 ¹	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 -				essed with: numb	er of patients to be	severely disabled	at 6 months	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 - t	tuberculoma (pre	dnisolone; chi	ldren) (assess	ed with: number o	of patients to develo	op tuberculomas in	the first mo	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 -		; children) (ass	essed with: nu	umber of patients	to have an IQ of les	s than 75 at 6 mont	hs)			
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	
		symptoms -				ssed with: numbe		experience hemiple				
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 -			(assessed with	n: number of patie	nts with visual dete	erioration (decrease	d vision or	blindness)	at 6 month	is)
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	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid nts to be blind at 6	Antituberculosis chemotherapy alone or with placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
	randomised	very	serious ¹¹	serious ¹²	serious ⁹	none	3/70	3/71	OR 1.01	0 more	0000	
	trials	serious ^{4,5,6}	3611003	Senous	3611003	none	(4.3%)	(4.2%)	(0.2 to 5.21) ¹⁰	per 100 (from 3 fewer to 14 more)	VERY LOW	
Changes months)	in signs and s	symptoms - I	nearing (predniso	olone; children)	(assessed wi	th: number of pati	ients with deteriora	tion in their hearing	g (decrease	d hearing, t	hough not	deaf) at 6
1 ¹	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 pati	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	

Schoeman 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 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
Mortality	(dexamethas	one; stage 1) (measured with	: survival rate	at 5 years amo	ngst those classi	fied as stage 1 on a	dmission; better in	dicated by	higher value		
1 ¹	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)	©⊙⊙ MODERATE	
					ber of deaths	amongst those cl	assified as stage 1					
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			severe disability		I) (follow-up 10) months; assess	ed with: number of	deaths amongst the	ose with sta	age 1 CNS T	B on admissi	on)
1 ⁴	randomised trials		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 Chotmon Malhotra Chotmon Chotmon Analhotra Chotmon Statistica than in t placebo Chotmon GRADE Wide co Chods ra Malhotra Malhotra 	does not follo ngkol et al, 199 a et al, 2009 ngkol et al, 2009 a et al, 2009: un a et al, 2009: un ngkol et al, 199 ally significant, he placebo group, althoug group, althoug Frule of thumb onfidence inter titio and 95% c a et al, 2009: u	w intent-to-tr 96: method o se of allocatii nblinded 96: groups no more patien oup (10%); ac gh again this 96: antitubero : <300 event vals onfidence int use of allocat 196), Malhotra	eat principle f randomisation ar on concealment u ot comparable at b ts in the prednisol dditionally, there w was not statistical culosis regimens of s erval calculated b ion concealment i	nclear aseline - clinical one group (17%, vere more patien ly significant lo not use all of o y reviewer s unclear; blindir	presentations a had motor wea ts with severe (or just the 4 star	and staging were s akness than in the j (stage 3) disease a ndard recommende	placebo group (3%), nd fewer patients wit	tion and comparator and more patients ir th less severe (stage nded drugs	the prednis	olone group	(17%) had mo	tor weaknes

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

			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 plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Mortality	y (stage 2) (fol	low-up 6 to 1	8 months; assess	ed with: numb	er of deaths an	nongst those with	stage 2 CNS TB or	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	16/98 (16.3%)	14/82 (17.1%)	OR 0.70 (0.28 to 1.77) ^{16,22}	4 fewer per 100 (from 12 fewer to 10 more)	©OOO VERY LOW	
			ining antitubercu					mber of deaths amo				admission)
3 ^{1,2,4}	randomised trials	very serious ^{5,6,7,8}	very serious ^{9,11,12,13}	serious ¹⁴	serious ¹⁵	none	7/75	7/73	OR 0.91 (0.28 to 2.99) ¹⁶	1 fewer per 100 (from 7 fewer to 14 more)	©000 VERY LOW	
			(measured with:	survival rate at	5 years amon	gst those classifie		mission; better indi	cated by hi			
1 ¹⁷	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	122	125	-	differenc e in survival rates 0.02 lower (0.15 lower to 0.11 higher)	©⊙⊙ MODERATE	
	y (prednisolor	ne; stage 2) (fe			ed with: numb	er of deaths amor	gst those classifie	d as stage 2 on adm	ission)			
2 ^{1,2}	randomised trials	serious ^{6,7,19}	very serious ^{9,12}	serious ²⁰	very serious ^{15,21}	none	2/57 (3.5%)	1/56 (1.8%)	OR 1.61 (0.19 to 13.49) ^{16,2}	1 more per 100 (from 1 fewer to 18 more)	⊙OOO VERY LOW	
						months; assessed		eaths amongst thos				on)
14	randomised trials		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	
² Chotmo ³ O'Toole ⁴ Malhoti	man et al, 1997 ongkol et al, 19 e et al, 1969 ra et al, 2009 man et al (1997	996	nakol et al (1996):	method of rando	misation and u	se of allocation cor	cealment is unclear					

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
placebo	group, althou	gh again this	was not statistically	significant		U ,		less severe (stage 1	•	the predniso	olone group t	han in the
¹⁰ O'Toole	e et al, 1969: L	inclear if group	os were comparabl	e at baseline, or		mparable for treatn	nent completion and	availability of outcom	ne data			
¹² Follow-	up varied wide	ely between g	roups	eaunent milialio	11							
¹³ Estima	tes of effect ve prakol et al (1)	ery widely acro 996) O'Toole	oss ['] the studies et al (1969) Girais	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 druas	
¹⁵ GRAD	E rule of thuml	b: <300 events	5		naiveia et ai (i				r olandara r	coominando	u urugo	
	atio and 95% (es et al, 2004/		erval calculated by	reviewer								
¹⁸ Analys	is does not foll	low intent-to-ti	eat principle									
²⁰ Chotm	l of randomisa ongkol et al (1	tion and use o 996). Malhotra	of allocation concea a et al (2009): antitu	ilment is unclear iberculosis regin	nens do not use	all of or just the 4	standard recommend	ded drugs				
²¹ Wide c	onfidence inte	rvals		0		,		Ū				
	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)		Quality	Importance
	y (stage 3) (fol	low-up 6 to 1	8 months; assess			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	
	y (stage 3; rifa	mpicin-conta	ining antitubercu	losis regimens	only) (follow-u	p 6 to 18 months;	assessed with: nur	mber of deaths amo	ongst those	with stage	3 CNS TB on	admission)
3 ^{1,2,4}	randomised trials	very serious ^{5,6,7,8}	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	Indirectness		Other considerations		Antituberculosis chemotherapy alone or plus placebo	Relative (95% Cl)	Absolute (95% Cl)	Quality	Importance
	(dexamethas	sone; stage 3)) (measured with:	survival rate a	5 years amon	gst those classifie	ed as stage 3 on ad	mission; better indi	cated by hi			
1 ¹⁷	randomised trials		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	
							•	as stage 3 on adm				
2 ^{1,2}	randomised trials	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	
	<u> </u>				(follow-up 10	months; assessed	with: number of de	eaths amongst thos	se with stag	je 3 CNS TB		on)
1 ⁴	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	
Malhotr Schoen or othe Unclear Malhotr Chotmo	nan et al, 1997 r health profes r if analysis foli ra et al, 2009: I ongkol et al, 19 cally significant	7: blinded = clir ssionals were b lowed the inter blinding not us 996: groups no t, more patient	nical psychologist a blinded nt-to-treat principle ed t comparable at ba s in the prednisolo	assessing intellig aseline - clinical µ ne group (17%)	ence, clinician t presentations ar had motor weal	testing hearing, oph nd staging were sim kness than in the pl	ilar in the interventio	vision, and physical t n and comparator gr nd more patients in t	oups at ran	domisation; h	nowever, altho	·
than in placebo O'Tool Kumar Follow Estima Chotm GRAD Odds r Thwait	o group, althou le et al, 1969: u velu et al, 199 -up varied wide tes of effect ve ongkol et al (1 E rule of thum	igh again this unclear if group 4: follow-up or ely between gi ery widely acro 996), O'Toole b: <300 events confidence inte 7 / Török et al.	was not statistically os were comparab ly 3 months after t oups oss the studies et al (1969), Girgis s erval calculated by 2011	y significant le at baseline, oi reatment initiatio s et al (1991), Ku	if they were co n	mparable for treatm	d fewer patients with nent completion and	less severe (stage 1 availability of outcorr use all of or just the 4) disease in ne data	the prednisc	olone group th	or weakness

			Quality asses	ssment			No of p	oatients	Eff	fect		
No of studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy alone or plus placebo	Relative	Absolute (95% Cl)	Quality	Importance
²³ Wide c ²⁴ Forest	onfidence inte plot (mortality)	rvals :										
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% CI)	Quality	Importance
Mortality	(dexamethas	one; culture-p	ositive) (follow-u	ip 2 years; ass	essed with: nu	mber of deaths a	mongst those class	ified as culture-pos	sitive on ad	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	
	•		•		U (,	• • • •	low-up ; assessed		per of patien	ts to deve	lop
								re-positive on admi			000	
1 ¹	randomised trials	serious	no serious inconsistency	serious	serious ⁴	none	4/75 (5.3%)	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		ith: number of pati	ents to wit	h permanen	t residual	neurologic
1 ¹	randomised trials	serious ²	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	
			ever (dexamethas r indicated by lo		ositive) (meas	ured with: time to	become afebrile (c	lefined as a temper	ature of <3	7.5'C) amon	gst those	classified as
1 ¹	randomised trials	serious ²	no serious inconsistency	serious	no serious imprecision	none	75	85 e fully alert amongs	-	MD 3.0 days lower (6.9 lower to 0.9 higher) ⁶	©©O O LOW	

admission⁷; better indicated by lower values)

			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	000 0 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- randomised trials	very serious ^{10,11,12}	serious ^{13,14}	serious ³	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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Girgis et al. 1991

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

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

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% CI)	Quality	Importance
Mortality	(dexamethas	one; cultu	re-negative) (follo	ow-up 2 years;	assessed with	: number of death	s amongst those cl	assified as culture-r	egative 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	

itment (dexamethasone; culture-negative) (follow-up ; Changes in signs and symptoms - net

			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% CI)	Quality	Importance
neurolog	gic abnormali	ties (fundu	s, hemiparesis o	hydrocephalu	s) during treat	ment amongst the	ose classified as cu	Iture-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	
							e-negative) (assesse ative on admission)	d with: number of p	atients to w	ith permane	ent residua	l neurologic
1 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	se to treatmer	nt – need fo	r additional surg	ical interventio	n (assessed w	ith: number of pa	tients requiring sur	rgery due to insuffic	ient shrink	age of the s	wollen joiı	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			s – 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 assessment						No of p	oatients	Effect				
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	Iortality (follow-up 1 to 10 years; assessed with: number of deaths)												
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		
	Response to treatment - favourable (assessed with: number of patients to be considered in a favourable status after 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 asses	ssment			No of	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% CI)	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			•		with: number o			ntion (pericardector	• • •			
3 ^{1,3,4}	randomised trials	very serious ^{5,7,8}	serious ¹⁰	very serious ^{12,15}	13	none	31/220 (14.1%)	29/220 (13.2%)	OR 1.12 (0.6 to 2.09) ^{14,19}	1 more per 100 (from 5 fewer to 11 more)		
						1 · · · · · · · · · · · · · · · · · · ·		I physical activity at			• •	
2 ^{3,4}	randomised trials	very 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 pl	nysical activity	(assessed with:	number of patients	to be 'out and abou	t' but with	restricted p	hysical ac	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	
	s in signs and	symptoms -			tivity (assesse	d with: number o	f patients to confine	ed to home or hosp	ital after 10	/	llow-up)	
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 intrapel ⁶ Hakim ⁷ Analysi ⁸ Strang ⁹ Hakim ¹⁰ Strang ¹¹ Follow ¹² Strang ¹³ GRAD ¹⁴ Odds ¹⁵ Outcol 	ricardial steroic et al, 2000: use is does not folk et al (1987/200 et al, 2000: uni et al, 1988/20 -up periods va et al (1987/20 E rule of thum ratio and 95% of	04 andomisation of ls/placebo was e of allocation ow the intent-t 04 and 1988/2 clear if the gro 04: unclear if ried widely 104 and 1988/2 b: <300 events confidence inte ate for an outco	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 a	treatment comp e baseline	letion and availabi	or the study subjects lity of outcome data ard recommended dr	until completion of th	he study; hc	wever, phys	ician admir	istering the

			Quality asses	ssment			No of p	patients	Ef	fect		
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy	Relative (95% Cl)	Absolute (95% Cl)	Quality	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	sment			No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency to 10 years; asse	Indirectness	•	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
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	
Respons	e to treatmen	t - favourable	e (effusive TB) (fo	ollow-up 10 yea	rs; assessed w	vith: 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 interventi	on (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	
	s in signs and follow-up)	symptoms -	unrestricted phy	sical activity (e		llow-up 10 years;	assessed with: nur	nber of patients to	with 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 asses	ssment			No of	patients	Ei	ifect		
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% CI)	Quality	Importance
Changes	in signs and	symptoms -	'out and about' b	out restricted pl	nysical activity	(effusive TB) (fo	llow-up 10 years; as	ssessed with: numb	er of patie	more) nts to be 'ou	t and abou	ut' but with
1 ³	randomised trials	very serious ^{6,7}	years of follow-u 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	0 years; assessed w	vith: number of pation	ents to con	fined to hor	ne or hosp	oital after 10
1 ³	randomised trials	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	
							ber of patients to ex					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 ⁹ Strang e ¹⁰ Follow ¹¹ Strang ¹² GRAD ¹³ Odds r ¹⁴ Wide c 	ricardial steroid et al, 2000: use s does not folld et al, 1988/200 et al, 2000: uno et al, 1988/200 -up periods va et al, 1988/20 E rule of thuml	andomisation of ds/placebo wa e of allocation bw the intent-t 24: quasi-rand clear if the gro 04: unclear if the ried widely 04: antitubero b: <300 event confidence int rvals	as unblinded concealment uncl to-treat principle lomised oups were compara he groups were co sulosis regimens de	ear able in terms of a omparable at the o not use all of c	treatment comp baseline		or the study subjects ility of outcome data ed drugs	until completion of t	he study; ho	owever, phys	ician admir	nistering the
¹⁶ Forest	plot (response	e to treatment	- need for surgical	l intervention):								

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

Quality assessment No of patients Effect	Quality Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% CI)	Absolute (95% CI)		
						ith: number of dea			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
1 ¹	randomised trials	very serious ^{2,3}	no serious inconsistency	serious ⁴	serious⁵	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	
Respons	se to treatmen	t - favourabl	e (constrictive tu	berculous peri	carditis) (asse	ssed with: numbe	r of patients to be c	onsidered in a favo	urable stat	us after 24 r	nonths of f	follow-u
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	
		it - need for s	surgical intervent	tion (constrictiv	e tuberculous	pericarditis) (Cop	y) (assessed with:	number of patients	to require a	surgical inte	ervention	
(pericard	dectomy)) 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)	⊙OOO VERY LOW	
Changes	s in signs and	symptoms -	unrestricted phy	sical activity (onstrictive tub	perculous pericar	ditis) (follow-up 10 y	vears; assessed wit	h: number		to with unr	estricted
	activity after											
1 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	ars; assess	ed with: nur	mber of pa	tients to
			physical activity				07/70	00/70	00444		0000	
1 ¹	randomised trials	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	
				cted physical ac	tivity (constric	tive tuberculous	pericarditis) (follow	-up 10 years; asses	sed with: n	umber of pa	atients to c	onfined
nome or 1 ¹	hospital after randomised		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 Analysi ³ Quasi-r ⁴ Antitub ⁵ GRADE	andomised erculosis regim E rule of thumb	ow the intent- nens do not us : <300 events	to-treat principle se all of or just the s ervals calculated b		mmended drug	s						

⁷ Outcome is a surrogate for an outcome of interest

	Quality assessment						No of p	oatients	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy		Absolute (95% CI)	Importance

⁸ Wide confidence interval

Any corticosteroid vs antituberculosis chemotherapy alone or plus placebo

lo of				ssment			No of p	patients	Ef	fect		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus any corticosteroid	Antituberculosis chemotherapy plus placebo	Relative (95% CI)	Absolute (95% Cl)	Quality	Importance
	(follow-up 1	to 10 years; a	ssessed with: n									
	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	
	e to treatmen	nt - need for s	urgical intervent		1 to 10 years; a	ssessed with: nur	nber of patients to	require surgical inte	ervention (pericardecto	omy))	
t	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)
	randomised trials	serious ⁵	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	
Strang et Reuter et intraperio Hakim et Analysis Strang et Hakim et ⁰ Strang e ¹ Follow-u	t al, 2000 t al, 1987/200 t al, 1988/200 t al (2006): ra cardial steroic t al, 2000: use does not follo t al, 1987/200 t al, 2000: un et al, 1988/20 up periods va et al (1987/20)4 andomisation c ds/placebo wa e of allocation ow the intent-to 04 and 1988/2 clear if the gro 04: unclear if tried widely 04 and 1988/2 b: <300 events	s unblinded concealment uncl p-treat principle 004): quasi-rando ups were compara the groups were c 2004): antitubercu	ear mised able in terms of omparable 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

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	Quality	Importance

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% CI)		
	(effusive TB)) (follow-up 1	to 10 years; ass)						
3 ^{1,2,3}	randomised trials	very serious ^{4,5,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	31/179 (17.3%)	43/176 (24.4%)	OR 0.69 (0.4 to 1.17) ^{13,14}	6 fewer per 100 (from 13 fewer to 3 more)	⊙OOO VERY LOW	
	se to treatmer	nt - need for s	urgical intervent	tion (effusive TE	3) (follow-up 1	to 10 years; asses	sed with: number of	of patients to requir	e surgical i	ntervention	(pericarde	ctomy))
2 ^{1,3}	randomised trials	very serious ^{4,6,7}	very serious ^{8,9,10}	serious ¹¹	serious ¹²	none	13/150 (8.7%)	7/147 (4.8%)	OR 1.85 (0.73 to 4.73) ^{13,15}	4 more per 100 (from 1 fewer to 14 more)	⊙OOO VERY LOW	
 ³ Strang ⁴ Reuter intrape ⁵ Hakim ⁶ Analysi ⁷ Strang ⁸ Hakim ⁹ Strang 	ricardial steroi et al, 2000: use s does not folle et al, 1988/200 et al, 2000: une et al, 1988/200 -up periods va	andomisation c ds/placebo wa e of allocation ow the intent-to 04: quasi-rando clear if the gro 04: unclear if th ried widely	s unblinded concealment uncl o-treat principle omised ups were compar he groups were co	lear able in terms of t omparable at the	treatment comp	letion and availabili	r the study subjects ty of outcome data	until completion of th	ne study; ho	wever, physic	cian admini.	stering the

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

Prednisolone vs triamcinalone

			Quality asse	ssment			No of p	oatients	Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Antituberculosis chemotherapy plus triamcinalone	Relative (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 asse	ssment			No of p	atients	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus triamcinalone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Respons	se to treatmer	nt – need for a	additional interve	ntion (effusive	TB) (follow-up	1 years; assessed	I 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	-	⊙OOO VERY LOW	
Changes	s in signs and	l symptoms –	activity levels (e	ffusive TB) (foll	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	serious ²	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	

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% CI)	Quality	Importance
Mortality) (follow-up 18 m	onths; assesse	d with: numbe	r 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			constrictive perio	carditis (HIV-po	sitive; effusive	TB) (follow-up 18	months; assessed	with: number of pa	atients to ex	xperience 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	

			Quality asse	ssment			No of p	oatients	Effect			
No of studies	Design	Risk of bias	Inconsistency		Imprecision	Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% Cl)	· · ·	Quality	Importance
Adheren	ce (HIV-positi	ive; effusive 1	TB) (follow-up 18	months; asses	sed with: num	ber of pill counts s	showing that >90%	of tablets had been	consumed	l)		
1 ¹	randomised trials	serious ^{2,3}	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	
² Use of ³ Unclear		lows the intent	-to-treat principle	atment completic	on and availabil	ity 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	iect		
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	symptoms – i	mprovement (ass	essed with: nu	mber of patien	ts in whom sympt	toms improved or w	vere resolved after 4	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	atients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Antituberculosis chemotherapy plus prednisolone	Antituberculosis chemotherapy plus placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Change							oms deteriorated a					
1'	randomised trials	serious ²	serious ³	no serious indirectness	serious ⁵	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	th: number of pat	ients whose chest I	adiographs improv	ed or were	resolved af	ter 4 week	s⁴)
1 ¹	randomised trials		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		deterioration of c	hest radiograph		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	s to experienc	e adverse drug re	actions)					
1 ¹	randomised trials	serious ²	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	sed with: numbe	r of patients to	experience info	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 OPT 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

..10.1 Duration of treatment in people with non-respiratory tuberculosis

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% CI)	Absolute (95% CI)	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 LOV
⁶ Unclear if the gi ⁷ Regimens do no ⁸ All patients rece ⁹ GRADE rule of	roups were compa roups were followe ot contain all of/jus eived corticosteroid thumb: <300 even I 95% confidence i	ed up for the same at the 4 standard r ds ts ntervals calculate	ecommended drug d by reviewer							

Change in signs and symptoms

		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
Change in signs (hydrocephalus, c	and symptoms - cerebral palsy with	- neurological se mental retardatio	n, hemiparesis, lo	only; antituberc ng-term seizures,	ulosis chemother or behavioural ch	apy + corticoste	roids) (number of	patients to experie	nce 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} Very serious ^{7,8,11} Serious ⁹ 11/45 serious ⁹ 11/45 (24.4%) (50%) Very serious ^{2,3,4,6} Very serious ^{7,8,11} Very to 2.58) ¹⁰ Very to 2.58) ¹⁰ Very to 2.58) ¹⁰ Very to 2.58) ¹⁰ Very serious ¹⁰ Very ser										
¹ Jacobs et al, 1992 ² No randomisation or blinding ³ Allocation concealment unclear ⁴ No blinding										

		Quality as	sessment			Numbe	r of patients	Effect				
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality		
	oups were compa											
	Unclear if the groups were followed up for the same length of time, or if follow-up was for an appropriate length of time Regimens do not contain all of/just the 4 standard recommended drugs											
			ecommended drug	IS								
	eived corticosteroid											
	thumb: <300 even											
	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	l, confidence inter	val; 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
Change in signs (median months)	and symptoms – ne IQR)) = 13 (4–36); as	eurological sequ	elae (antitubercu	losis chemothe	rapy + corticoste	roids) (follow-up	8 months (mediar	n months (IQR)) =	10 (6–24); 12–16	months
imbalance, sense	or hearing loss))				_					
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 attem ⁴ No randomisatio ⁵ Retreatment and ⁶ Differences betw ⁷ Wide variations ⁸ Intervention doe ⁹ GRADE rule of ¹⁰ Odds ratio and 	assed upon the centre ots were made within on, and blinding uncle d default cases exclue veen groups in the co in duration of follow-u s not exactly match to thumb: <300 events 95% confidence interval;	the study design ar ded from 8-month rticosteroid regim p he intervention of vals calculated b	or analysis to bal group but not the pens used interest: does not	ance potential col 12-to-16-month (nfounders group				han duration alone	9
Relapse										
		Quality asse	essment			Number of	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

Delence (follow up: 9 month aroun (modion months $(I(DP)) = 10$ (6, 24): 12 to 16 months aroun (modion months $(I(DP)) = 12$ (4, 26): accessed with number of potients to experience rely	2000)
Relapse (follow-up: 8-month group (median months (IQR)) = 10 (6–24); 12-to-16-month group (median months (IQR)) = 13 (4–36); assessed with: number of patients to experience relations and the second	apse)
41	DVLOW
1^{1} non-randomised serious ^{2,3,4} very serious ⁸ very serious ^{9,12} 0/100 0/100 OR 1.00 (0.02 - VE	RY LOW

		Quality ass	essment			Numbe	r of patients	E	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 attent ⁴ Blinding unclear ⁵ Retreatment ar ⁶ Differences bet ⁷ Wide variations ⁸ Intervention do ⁹ GRADE rule of ¹⁰ Odds ratio and ¹¹ Unclear if the 1 ¹² Wide confident ¹³ It is unclear hor rate in each gr 	nd default cases exclu- ween groups in the co is in duration of follow-t es not exactly match t thumb: <300 events 1 95% confidence inter 2 arms were compara- ce intervals w many patients in ea	the study design ded from 8-mont pricosteroid regin p he intervention o rvals calculated t ble for the availan 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 nta	nfounders group just the 4 standar	d recommendea	drugs, and the 2	2 arms vary by more		

Adverse events

		Quality asse	essment			Number o	of patients	Effe	ect	
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 even	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								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Mortality (antituberculosis chemotherapy + surgery) (follow-up 60 months; number of deaths associated with spinal tuberculosis)										
1 ¹	randomised	very serious ^{2,3,4}	serious ¹⁰	very serious ^{5,6}	very serious ^{7,8}	0/24	0/26	OR 1.08 (0.02	-	VERY LOW
	trials					(0%)	(0%)	to 56.64) ⁹		
¹ Darbyshire, 19										
² Allocation conc										
³ Blinding unclea										
	not follow the inten									
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										
	is chemotherapy									
$rac{6}{2}$ Population does not exactly match the population of interest: 6 of the 43 patients tested had single or combined drug resistance										
	thumb: <300 even	nts								
⁸ Wide confidence										
⁸ Odds ratio and	95% confidence ir	ntervals calculated	l 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

3	ne ana eympi										
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	
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	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious9,13	25/25	26/26	011 0.00 (0.02	-	VERY LOW	
	trials					(100%)	(100%)	to 50.35) ¹⁰			
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-											
	ed 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 m	and symptoms - onths)	 kyphosis (antitu 	iberculosis chem	otherapy + surg	ery) (number of pa	atients with improv	ement in their ang	le of kyphosis (red	duction of 11° or m	nore) from	
1 ²³	randomised	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious ^{9,13}	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 sigr 60 months)	is and symptoms	– kyphosis (antit	uberculosis chen	notherapy + surg	ery) (number of p	atients with no c	change in their angle	e of kyphosis (withi		ine 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 n		– kyphosis (antit	uberculosis chen	notherapy + surg	ery) (number of p	atients with dete	erioration in their and	gle of kyphosis (inc	rease of 11° or m	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
	nin 0.24 vertebrae)		(antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; r	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
	and symptoms (n 0.25 vertebrae))	- vertebral loss	(antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; r	number of patients w	vith 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
	and symptoms (n 0.25 vertebrae))	- vertebral loss	(antituberculosis	chemotherapy +	surgery) (follow-	up 60 months; r	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
					surgery) (mean	vertebral loss fro	om treatment initiation	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
	is and symptoms ved during follow-u		iberculosis chem	otherapy + surge	ery) (follow-up 36	months; numbe	r of patients with sin	us and/or clinically		s on admission
1 ¹¹	randomised trials	very serious ^{5,6,7}	serious ²⁴	very serious ^{8,12}	very serious ^{9,13}	4/5 (80%)	2/2 (100%)	OR 0.60 (0.02 to 20.98) ¹⁰	-	VERY LOW
Change in sigr resolved during	is and symptoms	 sinuses (antitu 	iberculosis chem	otherapy + surge	ery) (follow-up 36	· · /	r of patients with ne		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
	is and symptoms in had resolved duri	ing follow-up)	•	ntituberculosis c	hemotherapy + s	urgery) (follow-	up 36 months; num	per of patients with	nervous system i	volvement 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

Number of studies Design Risk of bias Inconsistency Indirectness Imprecision 6 months 9 months Relative (95% Cl) Absolute (95% Cl) Quality * For full definition, see evidence tables in the appendices (100%) (100%) (00%) to 49.45) ¹⁰ • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • • <td< th=""><th colspan="7">Quality assessment</th><th colspan="5">Number of patients Effect</th></td<>	Quality assessment							Number of patients Effect				
For full definition, see evidence tables in the appendices For full definition, see evidence tables in the appendices For full definition, see evidence tables in the appendices For full definition, see evidence tables in the appendices For full definition concealment unclear For full definition concealment unclear For full definition concealment unclear For full definition 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 For full definition 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 For full definition does not exactly match the population of interest: for full exactly and the population of interest: for the 43 patients tested had single or combined drug resistance (Medical Research Council Working Party on Tuberculosis of the 5pine (Griffiths et al), 1986 For full definitis et al) (1986) and Darbyshire (1999), or some patients also had respiratory TB (Upadhyay et al (1986)) For full definition to receiving antituberculosis chemotherapy For full definition to receiving antituberculosis chemotherapy For full definition to receiving antituberculosis of the Spine (Griffiths et al) (1986) underwent surgery in addition to receiving antituberculosis chemotherapy For full definition and the population or standard errors of the means; reviewer could not assess imprecision For Authors did not give standard deviations or standard errors of the means; reviewer could not calculate 95% confidence intervals For full definition and differences in the change from baseline to 36 months are unlikely to be due to the different durations of treatment because they occurred mainly in the first 6 months - that is, when there was no difference intervals calculated by reviewer Fore that is, when there was n		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months			Quality	
 ⁴ Method of randomisation unclear ⁵ Allocation concealment unclear ⁶ Blinding unclear ⁶ Blinding unclear ⁷ Analysis does not follow the intert-to-treat principle ⁸ 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 ⁹ GRADE rule of thumb: <300 events ¹⁰ Odds ratio and 95% confidence intervals calculated by reviewer ¹¹ Medical Research Council Working Party on Tuberculosis of the Spine (Griffiths et al), 1986 ¹² 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 Wide confidence intervals ¹⁴ Patients in Medical Research Council Working Party on Tuberculosis of the Spine (Griffiths et al) (1986) and Larbyshire (1999)), or some patients also had respiratory TB (Upadhyay et al (1986)) ¹³ Wide confidence intervals ¹⁴ Patients in Medical Research Council Working Party on Tuberculosis of the Spine (Griffiths et al) (1986) underwent surgery in addition to receiving antituberculosis chemotherapy ¹⁵ Individual point estimates vary widely ¹⁶ Authors did not give standard deviations or standard errors of the means; reviewer could not assess imprecision ¹⁷ Authors did not give standard deviations or standard errors of the means; reviewer could not calculate 95% confidence intervals ¹⁸ Mean difference calculated by reviewer ¹⁹ The authors state that the differences in the change from baseline to 36 months are unlikel		trials					(100%)	(100%)	to 49.45) ¹⁰			
²⁴ Follow-up began from treatment initiation; therefore, as different durations of treatment were used, follow-up was for different lengths	 ⁴ Method of ran ⁵ Allocation con ⁶ Blinding uncle ⁷ Analysis does ⁸ Intervention of antituberculo ⁹ GRADE rule ¹⁰ Odds ratio a ¹¹ Medical Res ¹² Population of Spine (Griffiti ¹³ Wide confide ¹⁴ Patients in N ¹⁵ Individual populations of Authors did In ¹⁶ Authors did In ¹⁷ Authors did In ¹⁸ Mean difference ¹⁹ Calculated b ²⁰ The authors that is, when ²¹ Upadhyay end ²² Mean difference ²³ Darbyshire, 	ndomisation uncle ncealment unclea ear s not follow the in- loes not exactly in- sis chemotherap of thumb: <300 end 95% confiden earch Council Wi- loes not exactly in- hs et al) (1986) a ence intervals fedical Research int estimates var not give standard not give	ear ar htent-to-treat principle match the interventio by events ice intervals calculate forking Party on Tube match the population and Darbyshire (1999 Council Working Pa y widely deviations or standed deviations or standed y reviewer ferences in the chang ference between the nfidence intervals cal	e n of interest: regime ed by reviewer erculosis of the Spir of interest: 6 of the p)), or some patient inty on Tuberculosis and errors of the me and errors of the me ge from baseline to regimens of the tw lculated by reviewe	ne (Griffiths et al), 43 patients teste 5 also had respira of the Spine (Gri ans; reviewer cou ans; reviewer cou 36 months are un o groups r	1986 Ind had single or co atory TB (Upadhy iffiths et al) (1986 uld not assess im uld not calculate s nlikely to be due t	ombined drug res ay et al (1986))) underwent surg precision 95% confidence i to the different du	sistance (Medical I lery in addition to r ntervals urations of treatme.	Research Council receiving antituber	Working Party on culosis chemothei	Tuberculosis of the apy	

Response to treatment

		Quality as	sessment			Number of	of patients	Eff	iect		
Number of								Relative	Absolute		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality	
Response to treatment – favourable response (antituberculosis chemotherapy + surgery) (follow-up 60 months; number of patients who had a 'favourable' response to treatment 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	
				chemotherapy +	surgery) (number	r of patients who h	ad an unfavourab	le response to trea	atment that require	ed additional	
hemotherapy an	d/or surgery during										
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	

⁴ Allocation concealment unclear

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

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 o	of patients	Eff	iect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Recurrence (ant	tuberculosis che	motherapy + sur	gery) (follow-up n	ninimum 10 years		ts to experience re	ecurrence or react	vation of tubercul	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
 Intervention doe antituberculosis Substitute for ou GRADE rule of 1 Odds ratio and 2 Population doe Wide confidence Unclear if follow Substitute for ou 	omisation unclear calment unclear of follow the intent s not exactly matc chemotherapy tcome of interest thumb: <300 even 95% confidence in s not exactly matcl	th the intervention ts tervals calculated h the population o in each group (relapse)	of interest: regime by reviewer f interest: some pa			andard recommer	nded drugs, and al	l patients underwe	ent surgery in addi	tion to receiving

Adverse events

		Quality as	sessment			Number o	f patients	Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% Cl)	Absolute (95% Cl)	Quality
Adverse events			(antituberculosis	s chemotherapy	surgery) (follow	up for the full trea	tment period; num	ber of patients to	experience advers	e events that
led to modification	n of the allocated r	egimen)								
1 ¹	randomised trials	serious ^{3,4}	no serious inconsistency	very serious ^{6,11}	very serious ^{7,8}	2/31 (6.5%)	0/29 (0%)	OR 5.00 (0.23 to 108.68) ⁹	-	VERY LOW
Adverse events	- any (antitubercu	losis chemother			10 years; numbe	r of patients to exp	erience 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
¹ Medical Resear	ch Council Working	g Party on Tuberc	ulosis of the Spine	e (Griffiths et al), 1	986				,	

² Method of randomisation unclear

³ Allocation concealment unclear 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	of patients	Eff	iect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
¹⁴ The authors no Abbreviations: Cl	te that the inciden , confidence interv	ce of drug reaction val; OR, odds ratio	ns is not related to	the duration of cl	hemotherapy beca	use most of the ac	lverse events wer	e observed in the	earlier period of a	rug therapy

LYMPH NODE TB

6 MONTHS vs 9 MONTHS

Treatment success or failure

		Quality as	ssessment			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 s	success after 5 ye	ars of follow-up (5	-year actuarial rer	mission 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						
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 uncles ⁶ Analyses did n ⁷ Regimens doe ⁸ GRADE rule on ⁹ Odds ratio and ¹⁰ Wide confider ¹¹ Doses not cord 	lomisation unclear cealment unclear ar ot follow the intent s not contain all of f thumb: <300 even 95% confidence in nce intervals	-to-treat principle or just the 4 stand nts ntervals calculated listed in the Britisi	dard recommended d by reviewer h National Formula	-						

Change in signs and symptoms

		Quality as	sessment			Numbe	er 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
	•	– residual nodes					3 months	(3378 01)		Quanty
1 ¹	randomised trials	very serious ^{2,3,4}	serious ¹⁰	serious ⁵	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 of	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		mber of patients v	with new sinuses)					
1 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 w	ith new glands)					
11	randomised trials	very serious ^{2,3,4}		serious⁵	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
 ³ Blinding uncleat ⁴ Analyses did n ⁵ Intervention dc ⁶ GRADE rule of ⁷ Data for multip ⁸ Odds ratio and ⁹ Wide confident ¹⁰ Follow-up beg 	domisation unclear ar ot follow the inten- oes not contain all f thumb: <300 eve le groups pooled l l 95% confidence i ce intervals gan from treatment	t-to-treat principle of/contains drugs onts	l by reviewer e, as different dura		-	v-up was for diff	erent lengths			

Relapse

		Quality as	sessment			Number	of patients	Effect		
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 c	luring 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			Number	of patients	Ef		
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 o ¹¹ Odds ratio and 	ot follow the intent es not contain all (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 st npbell et al (1993)		-					
Abbreviations: C	I, confidence inter	val; OR, odds rati	0							

Adverse events

		Quality as	sessment			Number of patients Effect			ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Adverse events	leading to treatm	nent modificatior	(number of patier	nts to experience	adverse events that	at led to modificati	on 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
¹ Yuen et al, 199 ² Method of rand	lomisation unclear									

³ Allocation concealment unclear ⁴ Blinding unclear

⁵ Analyses did not follow the intent-to-treat principle ⁶ Intervention does not contain all of/contains drugs other than the 4 standard recommended 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	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
Treatment defau	ult (follow-up for th	ne full treatment pe	eriod; number of p	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	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
 ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and ¹⁰ Doses not con 	thumb: <300 ever e intervals 95% confidence ii	nts ntervals calculated listed in the Britisl	h National Formula		ded drugs					

9 months vs >9 months

Adverse events

		Quality as	ssessment			Number of	of patients	Ef	fect	
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 he	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 Car ⁷ Intervention do ⁸ GRADE rule of ⁹ Odds ratio and ¹⁰ Forest plot (he 	1985 Iomisation unclear ealment unclear r npell et al (1985) o es not contain all o thumb: <300 ever 95% confidence ii	did not follow the in of/contains drugs of hts htervals calculated			ded drugs					

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% CI)	Absolute (95% Cl)	Quality
Response to tre	eatment - favoura	ible 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 serious ^{6,7,8}	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			Numbe	r of patients		Effect	
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 cond ⁴ Blinding uncleas ⁵ No clear definiti ⁶ Intervention do ⁷ Different comb ⁸ Substitute for a ⁹ GRADE rule of ¹⁰ Odds ratio and 	lomisation unclear cealment unclear ar tion of the outcome	e of/contains drugs n each arm rest nts intervals calculate		andard recommer	nded drugs					

Adverse events

		Quality as	ssessment			Number o	of patients	Eff	fect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	12 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Adverse events	- hepatotoxicity (n		to experience hep	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 cond ⁴ Blinding uncleat ⁵ Intervention do ⁶ Different comb ⁷ GRADE rule of ⁸ Wide confident ⁹ Odds ratio and 	lomisation unclear realment unclear ar es not contain all (inations of drugs ii thumb: <300 evel	of/contains drugs n each arm nts ntervals calculated		andard recommen	ded drugs					

9 MONTHS vs 18 MONTHS

Response to treatment

		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
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	I nodes during foll	ow-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 (nu	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	s during follow-up)			
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹⁰	serious⁵	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			ent (number of pa	tients with nodes		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	er 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
									to 26 more)	
Change in signs	s and symptoms	- node enlargem	nent (follow-up 36	months; number o	of patients with noo	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 signs	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	serious⁵	serious'	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 signs	s and symptoms	- sinuses (follow	-up 36 months; nu	mber of patients w	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 conce ⁴ Blinding uncleas ⁵ Analysis did no ⁶ Intervention do ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and 	lomisation unclear realment 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	other than the 4 st d by reviewer re, as different dura		J	v-up was for diff	erent lengths			

Abbreviations: CI, confidence interval; OR, odds ratio

Response to treatment

		Quality as	ssessment			Number	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
Response to tre	eatment - need fo	r surgical interve	ention (number of	patients needing	surgical interventio	n (e.g. aspiration	of pus) during trea	tment)		
1 ¹	randomised trials	very serious ^{2,3,4,5}	no serious inconsistency	very serious ^{6,7}	serious ⁸	4/56 (7.1%)	6/57 (10.5%)	OR 0.65 (0.17 to 2.45) ⁹	3 fewer per 100 (from 9 fewer to 12 more)	VERY LOW
Response to tre	eatment - need fo	r surgical interve	ention (follow-up 3	6 months; numbe		ng surgical interve	ntion (e.g. aspirati	on of pus) during f	ollow-up)	
1 ¹	randomised trials	very serious ^{2,3,4,5}	serious ¹¹	very serious ^{6,7}	very serious ^{8,10}	4/56 (7.1%)	6/57 (10.5%)	OR 0.65 (0.17 to 2.45) ⁹	3 fewer per 100 (from 9 fewer to 12 more)	VERY LOW

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	r of patients	Ef	fect	
Number of	_ ·	B : 1 (1)					10 11	Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	indirectness	Imprecision	9 months	18 months	(95% CI)	(95% CI)	Quality
⁶ Intervention doe	es not contain all o	of/contains drugs (other than the 4 st	andard recommer	nded drugs					
⁷ Substitute for a	n outcome of inter	rest			-					
⁸ GRADE rule of	thumb: <300 ever	nts								
⁹ Odds ratio and	95% confidence i	ntervals calculated	d by reviewer							
¹⁰ Wide confiden	ce intervals									
¹¹ Follow-up bega	an from treatment	initiation; therefor	re, as different dura	ations of treatmen	t were used, follow	v-up was for diffe	erent lengths			
Abbreviations: C	l, confidence inter	val; OR, odds rati	0				-			

Relapse

		Quality as	ssessment			Number o	of patients	Eff	iect	
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	18 months	(95% CI)	(95% CI)	Quality
Relapse (follow-	up 5 years; numbe	er of patients to ex	perience clinical o	r microbiological r		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 do ⁷ GRADE rule of ⁸ Wide confidence ⁹ Odds ratio and ¹⁰ Follow-up bega 	omisation unclear ealment unclear r t follow the intent- es not contain all o thumb: <300 ever e intervals 95% confidence ii	to-treat principle of/contains drugs nts ntervals calculated initiation; therefor	e, as different dura		Ũ	v-up was for differe	ent lengths			

Adverse events

		Quality as	sessment			Number of	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 conc ⁴ Blinding unclear ⁵ Analysis did no 	lomisation unclear cealment unclear	to-treat principle	sther then the det		and drives					

⁶ Intervention does not contain all of/contains drugs other than the 4 standard recommended drugs ⁷ GRADE rule of thumb: <300 events</p>

		Quality as	sessment			Number o	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
⁸ Wide confidence			meensistemey	mancounces	Imprediction	o montino	To months			Quanty

⁸ 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								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Response to tre	eatment - comple	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
	eatment - need fo		ment (follow-up fo			f patients to need			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 tr	eatment - need fo	r additional treat	ment (follow-up fo	r the full treatmen	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 serious ^{6,7}	0/45 (0%)	0/45 (0%)	OR 1.00 (0.02 to 51.49) ⁸	-	VERY LOW
	ons, see evidence	tables in the appe	ndices							
² Park et al, 200										
	cealment unclear ot blinded, unclear	if others were hlir	adad							
	an outcome of inter		lueu							
	f thumb: <300 ever									
⁷ Wide confiden										
	95% confidence in									
	sistent with those I			У						
Abbreviations: C	CI, confidence inter	val; OR, odds ratio	0							

Relapse

		Quality as	sessment			Number of	of patients	Eff		
Number of								Relative	Absolute	
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 months	9 months	(95% CI)	(95% CI)	Quality
Recurrence (foll	ow-up 1 year after	r treatment comple	tion; number of pa	atients to experien	ce recurrence duri	ing follow-up ¹)				
1 ²	randomised trials	serious ^{3,4}	no serious inconsistency	very serious ^{8,9}	very serious ^{5,6}	1/45 (2.2%)	0/45 (0%)	OR 3.07 (0.12 to 77.33) ⁷	-	VERY LOW
¹ For full definitio	ns, see evidence i	tables in the anne				(2.270)	(078)	(077.55)		

		Quality as	ssessment			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
² Park et al, 2009										
³ Allocation conc	ealment unclear ot blinded, unclear	r if others were blu	nded							
	thumb: <300 ever		lueu							
⁶ Wide confidence	e intervals									
⁷ Odds ratio and	95% confidence in	ntervals calculated	d by reviewer							
⁸ Doses not cons	sistent with those I	isted in the British	National Formula	У						
⁹ Substitute for a	n outcome of inter	rest (relapse)								
Abbreviations: C	l, confidence inter	val; OR, odds rati	0							

Adverse events

		Quality as	sessment			Number of	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
Adverse events	leading to treat	nent 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 discontin	uation)
1 ¹	randomised trials	serious ^{2,3}	no serious inconsistency	serious ⁶	serious⁴	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
 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	sessment			Number o	of patients	Eff	ect	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	15 months	Relative (95% CI)	Absolute (95% Cl)	Quality
Response to tre	eatment - comple	te response (follo	w-up 23-34 month		ents to achieve a c	omplete response	during follow-up ¹)		
1 ²	randomised trials	serious ^{3,4}	serious⁵	serious ^{6,11}	very serious ^{7,8}	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	er 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 confidend ⁹ Odds ratio and ¹⁰ Mean differend ¹¹ Doses not cond 	ealment unclear icipants and those equal utcome of interest thumb: <300 ever	a administering car nts ntervals calculated lence intervals cal listed in the Britisl	re unclear I by reviewer culated by reviewe n National Formula	ary						

Relapse

		Quality as	sessment			Number	of patients	Eff	ect				
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	9 months	15 months	Relative	Absolute (95% CI)	Quality			
						9 11011115	15 monuts	(95% CI)	(95% CI)	Quality			
Recurrence (follow-up 23-34 months; number of patients to experience recurrence during follow-up1) 1^2 randomisedserious3.4serious5very serious9.10very serious6.70/220/18OR 0.82 (0.02-VERY LOW													
1	randomised trials	serious ^{3,4}	serious	very serious ^{3,10}	very serious ^{0,7}	0/22 (0%)	0/18 (0%)	OR 0.82 (0.02 to 43.48) ⁸	-	VERY LOW			
 ⁵ Follow-up not e ⁶ GRADE rule of ⁷ Wide confidence ⁸ Odds ratio and ⁹ Doses not cons ¹⁰ Substitute for a 	ealment unclear icipants and those qual thumb: <300 ever	nts ntervals calculated isted in the British prest (relapse)	l by reviewer National Formula	у									

RQs O, R and X **\.11**

.11.1 Adjunctive surgery in the treatment of active PULMONARY 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	patients	Ef	fect		
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
(follow-up uncle	ar; assessed w	ith: number of dea	aths)								
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	
low-up unclear; a	assessed with:	number of patients	s to be classified	l as a cure)							
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	
nt failure (follow	-up unclear; as	sessed with: numl	ber of patients w	ho still had acti	ive tuberculosis)						
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	
ality - return to	work (follow-u	ip unclear; assess	ed with: numbe	r of patients wh	o still had active tu	berculosis)					
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	
	 (follow-up uncle observational studies² low-up unclear; a observational studies² nt failure (follow observational studies² nality – return to observational 	(follow-up unclear; assessed w observational studies ² very serious ^{3,4,5,6,7} low-up unclear; assessed with: observational studies ² very serious ^{3,4,5,6,7} nt failure (follow-up unclear; as observational studies ² very serious ^{3,4,5,6,7} nality – return to work (follow-u observational studies ² very serious ^{3,4,5,6,7}	DesignRisk of biasInconsistency(follow-up unclear; assessed with: number of dearobservationalveryverystudies2serious3,4,5,6,7veryserious2serious3,4,5,6,7veryobservationalveryveryobservationalveryserious3,4,5,6,7observationalveryverystudies2serious3,4,5,6,7veryserious2serious3,4,5,6,7veryserious2serious3,4,5,6,7veryserious2serious3,4,5,6,7serious3,4,5,6,7studies2veryserious3,4,5,6,7serious3,4,5,6,7serious2serious3,4,5,6,7serious3,4,5,6,7serious2serious3,4,5,6,7serious3,4,5,6,7serious2serious3,4,5,6,7serious3,4,5,6,7serious2serious3,4,5,6,7serious3,4,5,6,7serious2serious3,4,5,6,7serious3,4,5,6,7	(follow-up unclear; assessed with: number of deaths)observational studies2very serious3.4.5.6.7very serious8.9.10.11very serious12.13low-up unclear; assessed with: number of patients to be classified observational studies2very serious3.4.5.6.7very very serious8.9.10.11very serious12.13low-up unclear; assessed with: number of patients to be classified observational studies2very serious3.4.5.6.7very very serious8.9.10.11very serious12.13nt failure (follow-up unclear; assessed with: number of patients w observational studies2very serious3.4.5.6.7very serious8.9.10.11very serious12.13nality - return to work (follow-up unclear; assessed with: number observational studies2very serious3.4.5.6.7very serious8.9.10.11very serious12.13studies2serious3.4.5.6.7very serious8.9.10.11very serious12.13very serious12.13	DesignRisk of biasInconsistencyIndirectnessImprecision(follow-up unclear; assessed with: number of deaths)observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13serious14low-up unclear; assessed with: number of patients to be classified as a cure) observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13serious14low-up unclear; assessed with: number of patients to be classified as a cure) observational serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16nt failure (follow-up unclear; assessed with: number of patients who still had act observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16nality - return to work (follow-up unclear; assessed with: number of patients who observational serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16nality - return to work (follow-up unclear; assessed with: number of patients who observational serious3,4,5,6,7very serious8,9,10,11very serious12,13,17very serious14,16	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerations/ (follow-up unclear; assessed with: number of deaths) observational studies2very serious3.4.5.6.7very very serious8.9.10.11very very serious12.13serious14none/ (ow-up unclear; assessed with: number of patients to be classified as a cure) observational studies2very very serious3.4.5.6.7very very serious8.9.10.11very very serious12.13serious14.16/ (follow-up unclear; assessed with: number of patients to be classified as a cure) very serious12.13very very serious14.16none/ (follow-up unclear; assessed with: number of patients who still had active tuberculosis) observational studies2very very serious3.4.5.6.7very very serious8.9.10.11very very serious12.13none/ (follow-up unclear; assessed with: number of patients who still had active tuberculosis) observational studies2very very serious3.4.5.6.7very very serious8.9.10.11very very serious12.13very very serious14.16/ (follow-up unclear; assessed with: number of patients who still had active tub serious14.16none/ (bservational studies2very serious3.4.5.6.7very very serious8.9.10.11very very serious12.13very very serious14.16/ (bservational studies2very serious3.4.5.6.7very very serious8.9.10.11very 	Design PlasingRisk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy plus surgery(follow-up unclear; assessed with: number of deaths) observational studies2very serious3,4,5,6,7very very serious8,8,9,10,11very serious12,13serious14none6/184 (3.3%)low-up unclear; assessed with: number of patients to be classified as a cure) observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16none175/184 (95.1%)low-up unclear; assessed with: number of patients to be classified as a cure) observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16none175/184 (95.1%)none175/184 (95.1%)very serious12,13very serious14,16none3/184 (1.6%)atility - return to work (follow-up unclear; assessed with: number of patients who still had active tuberculosis) observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13very serious14,16none3/184 (1.6%)atility - return to work (follow-up unclear; assessed with: number of patients who still had active tuberculosis) observational studies2very serious3,4,5,6,7very serious8,9,10,11very serious12,13,17very serious14,16none3/184 (1.6%)	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneAntituberculosis chemotherapy alone(follow-up unclear; assessed with: number of patients to be classified as a cure) observational studies²very serious ^{3,4,5,6,7} very serious ^{8,9,10,11} very very serious ^{12,13} serious ^{14,16} none6/184 (3.3%)3/48 (6.3%)low-up unclear; assessed with: number of patients to be classified as a cure) very serious ^{12,13} very very serious ^{14,16} none175/184 (95.1%)3/48 (72.9%)low-up unclear; assessed with: number of patients who still had active tuberculosis) very serious ^{3,4,5,6,7} very serious ^{8,9,10,11} very very serious ^{12,13} none3/184 (10/48 (20.8%)10/48 (20.8%)observational studies²very serious ^{3,4,5,6,7} very serious ^{8,9,10,11} very serious ^{12,13} very serious ^{14,16} none3/184 (1.6%)10/48 (20.8%)ality - return to studies²very serious ^{3,4,5,6,7} very serious ^{8,9,10,11} very serious ^{12,13,17} very serious ^{14,16} none3/184 (1.6%)10/48 (20.8%)	Design (follow-up unclear; assessed with: number of patients who still had active tuberculosis) studies2Antituberculosis chemotherapy plus surgeryAntituberculosis chemotherapy aloneRelative (g9% CI)(follow-up unclear; assessed with: number of deaths) observational studies2very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7very serious3,4,5,6,7v	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapy aloneAntituberculosis chemotherapy aloneRelative (95% CI)Absolute(follow-up unclear, assessed with: number of deaths; observational studies²very serious ^{3,4,5,6,7} serious ^{3,4,5,6,7} very serious ^{3,4,5,6,7} serious ^{3,2,1,11} very serious ^{1,2,13} serious ^{1,2,13} none175/184 serious ^{1,4,16} serious ^{1,4,16} 3/184 none10/48 serious ^{3,4,5,6,7} OR 0.06 serious ^{1,2,13,17} 10/48 serious ^{1,4,16} OR 0.06 serious ^{1,4,16} 10/	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerationsAntituberculosis chemotherapyAntituberculosis chemotherapyRelative (95% CI)AbsoluteQuality(follow-up unclear, assessed with: number of deaths)very serious ^{3,4,5,6,7} very serious ^{1,1,10} none(175/184 (16,6%)10/48 (20,8%)OR 0.06 (0,02 to 0,24) ¹⁵ 19 fewer per 100 (from 15 fewer to 20 fewer)VERY LOWobservational studies ² very serious ^{3,4,5,6,7} very serious ^{1,2,1,17} very serious ^{1,4,16} none3/184 (1,6%)10/48 (20,8%)OR 0.06 (0,02 to 0,24) ¹⁵ 19 fewer per 100 (from 15

Jaworski, 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	ment	No of p	oatients	Ef	fect			
No of studies Design	Risk of bias	Inconsistency	Indirectness		chemotherapy		Relative (95% CI)		Quality	Importance

^b attempts do not appear to have been made to balance confounders

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	patients	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
			nprovement in e educed) or healed				itiation of treatment;	assessed with: num	per of patier	nts in whom I	esions we	e improved
11	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 patien	ts in whom l	esions had	deteriorated
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 s of follow-up)	ymptoms - re	ecurrence of end	lobronchial les	ions (follow-up	9 months after initia	ation of treatment; as	ssessed with: numbe	r of patients	in whom les	ions and re	ecurred after
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	
¹ Jin et a ² 'historic	l, 2013 al controlled trial	l': retrospectiv	ve observational						,			

³ allocation was based upon the time at which the patient was treated

⁴ blinding unclear, though unlikely

⁵ attempts do not appear to have been made to balance confounders ⁶ may have been some drug resistant cases were included (only patients with disease resistant to a combination of rifampicin, isoniazid or ethambutol were excluded)

⁷ GRADE rule of thumb: <300 events

⁸ wide confidence intervals

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 = 0Trachea 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	patients	Eff	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	se to treatment	- good outcom	e (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 unclease ⁶ definitio ⁷ significa ⁸ groups ⁹ unclear ¹⁰ groups ¹¹ antitub ¹² 'good c ¹³ GRADI 	s do not appear ar length of follo n of 'good outco ant variation in a received differer if groups were f appear to be co erculosis regime	w-up was appro- me' not provide ge, size and loc nt combinations followed for an e omparable for tr ans did not use bstitute for cure <300 events	ed cation of the chest of antituberculosi equal period eatment completic all of or just the 4	wall mass, radic s drugs for treati n and availabilit standard recomi	ment periods of y of outcome da mended drugs, a	different duration Ita and the interventior	ge involvement, and i n and comparator arm mptoms of disease		an the prese	ence or abse	nce of sur	gery

POST-OPERATIVE COMPLICATIONS

Hsu et al, 1995

No details provided

Adjunctive surgery in the treatment of active BONE AND JOINT tuberculosis .11.4

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	atients	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
Changes	in signs and s	ymptoms – bor	ny fusion (follow		s ¹ ; assessed w	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	
				-up mean 29.3 mo	onths ¹⁷ ; assess	sed with: number	of patients to exper	ience fusion of the	sacroiliac j	oint, as asso	essed usir	ng plain
1 ¹⁸	phs and confiri	•					0/40	0/4			0000	
1	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 n	nean 29.3 months	¹⁷ ; assessed w	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 n	nean 29.3 months	¹⁷ ; measured v	with: time to healing	ng ²² ; better indicate	d by lower values)	,			
1 ¹⁸	observational studies ³	very serious ^{5,6,7,8,19}	VOTV	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 r	mean 15 years ¹	; assessed with:	number of patien	ts to experience	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	

³ retrospective - review of clinical records and collection of additional data via interview
 ⁴ unclear if allocation to treatment groups related to potential confounding factors
 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 assessment							oatients	Ef	fect		
No o							chemotherapy		Relative			
studi	es 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

.11.5 Adjunctive surgery in the treatment of active SPINAL tuberculosis

RANDOMISED CONTROLLED TRIALS

			Quality asse	essment			No of	patients	E	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	Importanc
/lortality	/ - TB-related	(follow-up 10	years; assessed	with: number of	deaths associa	ted with spinal tube	erculosis)					
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	very serious ^{6,7}	none	4/100 (4%)	0/204 (0%)	OR 19.07 (1.02 to 357.83) ⁸	-	VERY LOW	
Changes assesse	d with: numbe	r of patients to	complete bony	fusion (antitube plete bony fusio	rculosis chemo n within 10-yea	therapy alone = 6 i r follow-up)	months or 9 months;	antituberculosis cher	notherapy i	n surgery gro	up = 6 moi	nths)
1	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious	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 fusio			therapy alone = 6 r	months; antituberculo	osis chemotherapy in	surgery gro	oup = 6 montl	ns) (assess	ed with:
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁶	none	64/100 (64%)	61/101 (60.4%)	OR 1.17 (0.66 to 2.06) ⁸	4 more per 100 (from 10 fewer to 15 more)	VERY LOW	
			partial bony fus			erapy alone = 6 mor	nths or 9 months; an	tituberculosis chemot	herapy in s	urgery group	= 6 months	s) (assessed
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious	none	5/100 (5%)	21/204 (10.3%)	OR 0.46 (0.17 to 1.25) ⁸	5 fewer per 100 (from 8 fewer to 2 more)	VERY LOW	
			 partial bony fus fusion within 10- 		losis chemothe	erapy 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		s chemotherapy	alone = 6 months	or 9 months; antitub	erculosis chemothera	py in surge	/	months) (a	ssessed with
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious ⁵	serious ⁶	none	2/100 (2%)	5/204 (2.5%)	OR 0.81 (0.15 to 4.26) ⁸	0 fewer per 100 (from 2 fewer to 7 more)	VERY LOW	

patients to have no bony fusion within 10-year follow-up)

			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
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious [€]	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 be o experience spor 				= 6 months or 9 mon	ths; antituberculosis	chemothera	py in surgery	group = 6	months)
Ì 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	
							ionths; antituberculos dicated by lower valu	sis chemotherapy in s	surgery grou	up = 6 months	s) (measui	ed with: mean
1 ¹	randomised trials	serious ^{2,3,4}	no serious inconsistency	serious⁵	serious ⁹	none	28	79 rapy in surgery group	-	MD 3 lower (0 to 0 higher) ¹⁰		n angle of
						s; better indicated b		apy in surgery group		s) (measured		In angle of
11	randomised trials			serious ⁵	serious ⁹	none	28	41	-	MD 6 lower (0 to 0 higher) ¹⁰	VERY LOW	
								ths; antituberculosis (chemothera		group = 6	months)
(follow-up 1 ¹¹	5 5 years; asse randomised trials		umber of patients no serious inconsistency	to experience ar serious⁵	n improvement very serious ^{6,7}	of 11° or more in th none	neir angle of kyphosis 1/100 (1%)	;) 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	
								culosis chemotherap	y in surgery	,	onths) (fol	low-up 5 years
assessed 1 ¹¹	d with: number randomised		o experience an in no serious	nprovement of 1 serious ⁵		heir angle of kypho	osis) 1/100	0/101	OR 3.06		VERY	
	trials		inconsistency		very serious ^{6,7}	none	(1%)	(0%)	(0.12 to 76.03) ⁸		LOW	
							= 6 months or 9 mont eir angle of kyphosis	hs; antituberculosis o	chemothera	py in surgery	group = 6	months)
1 ¹¹	randomised trials		no serious inconsistency	serious⁵	serious ⁶	none	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	
								culosis chemotherap	y in surgery	group = 6 m	onths) (fol	ow-up 5 years
assessed	a with: number randomised		o experience an de no serious	eterioration of 11 serious ⁵	serious ⁶	eir angle of kyphosi none	is) 13/100	17/101	OR 0.74	4 fewer	VERY	
	trials	001000	inconsistency	001000	501003	none	(13%)	(16.8%)	(0.34 to 1.61) ⁸	per 100 (from 10 fewer to 8	LOW	

			Quality asse	essment			No of	patients	Ef	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	Importance
										more)		
								antituberculosis chem lesions; better indica			$p = 6 \mod 10^{10}$	ths) (measure
1	randomised trials		no serious inconsistency	serious⁵	serious ⁹	none	28	79	-	MD 0 higher (0 to 0 higher) ¹⁰	VERY LOW	
								sis chemotherapy in s			s) (measur	ed with: mea
1 rease	randomised			r follow-up amor serious⁵	igst patients wit serious9	h thoracic or thorac none	columbar lesions; bei 28	tter indicated by lowe 41	r values)	MD 2	VERY	
	trials	Senous	inconsistency	Senous	Senous	none	20	41		lower (0 to 0 higher) ¹⁰		
							lone = 6 months or 9 or more in their vertet	months; antitubercul	osis chemo	therapy in su	rgery group	p = 6 months
11 11	randomised		no serious	serious ⁵	very	none	5/100	0/204	OR	_	VERY	
	trials	Seneus	inconsistency	Seneus	serious ^{6,7}	hone	(5%)	(0%)	23.56 (1.29 to 430.36) ⁸		LOW	
								months; antitubercule	osis chemot	therapy in su	gery group	= 6 months
ollow-up	p 5 years; asse randomised			to experience a serious ⁵	deterioration of serious ⁶	0.25 vertebrae or none	more in their vertebra 24/100	al loss) 66/204	OR 0.66	8 fewer	VERY	
	trials	serious	inconsistency	senous	senous	none	(24%)	(32.4%)	(0.38 to 1.14) ⁸	o lewel per 100 (from 17 fewer to 3 more)	LOW	
								tuberculosis chemoth	nerapy in su	rgery group =	6 months) (follow-up 5
ears; as	sessed with: n randomised					rae or more in their	/	07/10/	00.055	101		
	randomised trials	serious	no serious inconsistency	serious ⁵	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 of	chemothera	py in surgery	group = 6	months)
measure	ed with: mean i randomised			baseline to 5 ye serious⁵	ars; better indic serious ⁹	ated by lower value	es) 75	157		MD 0.11	VERY	
	trials	senous	inconsistency	senous	senous	none	75	157	-	lower (0 to 0 higher) ¹⁰		
			- increase in vert baseline to 5 year				= 6 months; antitube	rculosis chemotherap	y in surgery	/ group = 6 m	onths) (me	easured with:
12 nean Inc	rease in verter randomised		no serious	serious ⁵	serious ⁹	none	75	75	-	MD 0.16	VERY	
	trials		inconsistency							lower (0 to 0 higher) ¹⁰	LOW	
			 myelopathy (an sidual myelopathy 			one = 6 months or 9	9 months; antitubercu	ulosis chemotherapy	in surgery g	group = 6 mor	nths) (asse	ssed with:
	randomised	serious ^{2,3,4}	no serious	serious ⁵	very	none	2/100	0/204	OR	-	VERY	
	trials	0011000	inconsistency	0011040	serious ^{6,7}		(2%)	(0%)	10.38		LOW	

			Quality asse	essment			No of J	patients	Ef	fect		
lo of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone		Absolute	Quality	Importance
`hango	e in eigne and	symptoms	- now sinusos an	d/or abscesse	s (antituberculo	sis chemotherany a	lone - 6 months or (9 months; antitubercu	218.3) ⁸	therapy in s	Irgen/ grou	in – 6 months
							luring 5-year follow-u				urgery grot	ар – 0 Шонць
13	randomised trials	serious ^{2,3,4}	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	nonths; antituberculo	sis chemoth	erapy in sur	gery group	= 6 months)
12	randomised			serious ⁵	very	none	0/100	0/204	OR 2.03	-	VERY	
	trials	5011045	inconsistency	5011003	serious ^{6,7}	none	(0%)	(0%)	$(0.04 \text{ to} 103.30)^8$		LOW	
					otherapy alone =	6 months or 9 mo	nths; antituberculosis	s chemotherapy in su	irgery group	= 6 months)	(assessed	l with: numbe
	ts to achieve a	favourable s	tatus during 10-ye		6				0.0.0.0			
1	randomised trials	serious ^{2,0,4}	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	
					otherapy alone =	6 months; antitube	erculosis chemothera	apy in surgery group :	= 6 months)	(assessed w	ith: numbe	er of patients
chieve a	a favourable st randomised	atus during 1	0-year follow-up ¹⁴		6		70/400	70/4.04		0 (
	randomised trials	serious 22	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	surgery gro	up = 6 mor	nths) (assess
/ith: nun			dditional chemoth				5/4.00	0/004	00474	0		
	randomised trials		no serious inconsistency	very serious ^{5,15}	serious ⁶	none	5/100 (5%)	6/204 (2.9%)	OR 1.74 (0.52 to 5.83) ⁸	2 more per 100 (from 1 fewer to 12 more)	VERY LOW	
			additional intervention and chemotherapy				nonths; antituberculo	sis chemotherapy in	surgery gro	up = 6 month	ns) (assess	ed with:
1	randomised trials	serious ^{2,3,4}	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	essment			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	Absolute	Quality	Importance
-	rule of thum		ts									
0	nfidence inter											
			tervals calculated b	by reviewer								
	ent data to as											
🦉 mean d	difference cald	culated by rev	viewer									
¹¹ Darbys	hire, 1999											
¹² Reetha	a et al, 1994											
13 Palacu	bromonion of	01 1001										

¹³ Balasubramanian et al, 1994
 ¹⁴ for full definition, see evidence table
 ¹⁵ outcome is a substitute for an outcome of interest

NON-RANDOMISED CONTROLLED TRIALS

			Quality asse	essment			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% CI)	Absolute	Quality	Importance
	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	onths; assessed with	n: number of	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 erm follo		symptoms	- sinuses (follow-	up 27 were follo	wed up for 5 ye	ars. 1 for 15 month	s and 1 for 12 month	ns; assessed with: nu	imber of pat	ients to deve	lop a sinus	during long-
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	
	in signs and follow-up)	symptoms	- abscesses (follo	ow-up 27 were fo	bllowed up for 5	years. 1 for 15 mo	nths and 1 for 12 mo	onths; assessed with		patients to d	evelop an a	abscess 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 ph				5 years. 1 for 15 mor	oths and 1 for 12 mor	nths; assess	ed with: num	ber of pation	ents to
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 er indicated by low		surgery at any t	ime) (follow-up 27	were followed up for	5 years. 1 for 15 mo	onths and 1 f	or 12 month	s; measure	d with: mean
1	randomised trials	very serious ^{2,3,4}	serious ⁵	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		or 5 years.	1 for 15 month
1 ¹	randomised		serious ⁵	very	serious ¹¹	none	18	8	-	MD 44	VERY	

			Quality asse	essment			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
	trials	serious ^{2,3,4}		serious ^{6,7}						higher (0 to 0 higher) ¹²	LOW	
	· ·	were followed		for 15 months a	nd 1 for 12 mor	ths; assessed with	: number of patients		0	ng-term follow	1 /	
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	
	isation (surge	ry at any time	e) (follow-up 27 we	ere followed up f	for 5 years. 1 fo	r 15 months and 1	for 12 months; meas	ured with: mean dur	ation of hos	pital stay; be	tter indicate	ed by lower
values) 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 (surger al stay; better in			ntituberculosis c	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 allocati ⁴ blinding ⁵ unclear ⁶ 3 cases ⁷ antitube ⁸ GRADE ⁹ wide cc ¹⁰ odds n ¹¹ insuffic ¹² mean 	on concealmer g unclear if groups were of drug resista erculosis regim E rule of thumb unfidence intervatio 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 terval calculated b sion	ugh all 3 patient oniazid and 1 to e 4 standard reco	isoniazid and ri	ifampicin)	re in the surgery grou	ηp				

OBSERVATIONAL STUDIES

Mortality

			Quality asse	ssment			No of p	oatients	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		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 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 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; assesse	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 (fo	ollow-up und	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	
	/ - treatment-rel	ated (follow	-up unclear; asse	essed with: numb	per of treatment	-related deaths)				, i		
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 assessment						patients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance

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 j	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness			Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance
		ymptoms ·			ow-up unclear;	assessed with: nur		neurological improve				
1 ¹	observational studies ²	very serious ³	very serious ⁴	serious⁵	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	
				· · ·		Ũ		with: number of patie			0	ally 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	s 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 ¹⁹	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	s in signs and s	ymptoms ·	- residual deform	ity (follow-up m	edian 24 month	ns; assessed with: r	number of patients to	experience residual				
122	observational studies ¹⁰		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		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	
	s in signs and s	ymptoms -		-up mean 20.2	years; measure	d with: mean angle	of kyphosis; better	ndicated 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	
Changes					least 24 month			osis at end of follow-u	up; better inc			
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	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
Changes values)	in signs and s	ymptoms ·	- kyphosis (adults	s) (follow-up at l	east 24 months	; measured with: m	ean angle of kyphos	is amongst the adult	s at end of fo	ollow-up; bet	ter indicated	by lower
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	ns; measured with:	mean angle of kypho	osis amongst the chil	dren at end		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 ky		baseline to	follow-up;
1 ⁹	observational studies ¹⁰	very serious ¹¹	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	nosis at end		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	
	in signs and s by lower values		- change in kyph	osis (adults) (fo	ollow-up at least	24 months; measu	ured with: change in r	mean angle of kypho	sis amongst	y ,	d of follow-u	ıp; better
1 ³⁰	observational studies ¹⁰	very serious ³¹	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 by lower values		- change in kyph	osis (children)	(follow-up at lea	st 24 months; mea	sured with: change ir	n mean angle of kypt	nosis among		end of follo	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	an improverr	nent (decreas	se) in their a	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 7	2 months; assesse	d with: number of pat	ients to experience r	noderate or	severe deter	ioration (an	increase of
1 ³⁴	observational studies ¹⁰	very serious ³⁵	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	essment			No of p	patients	Eft	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)		
•	s in signs and s e) in their angle		•	kyphosis (<16	Syears) (follow-	up at least 72 mon	ths; assessed with: n	umber of patients be	low the age	of 16 to expe	erience an i	mprovement
1 ³⁴	, 0	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			up at least 72 mont	hs; assessed with: n	umber of patients be	ow the age	of 16 to expe	rience moo	lerate or
1 ³⁴	observational studies ¹⁰	very serious ³⁵	very serious ³⁶	serious ³⁷	serious ⁶	none up at least 72 mon	3/7 (42.9%) ths; assessed with: n	17/30 (56.7%) umber of patients ag	OR 0.57 (0.11 to 3.02) ⁸ ed 16 and a	14 fewer per 100 (from 44 fewer to 23 more) bove to expe	VERY LOW	mprovement
decreas	e) in their angle	of kyphosis)		. , .	•		, ,				proronion
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			up at least 72 mont	hs; 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	•		•				ts with spinal fusion)	o /o	00 /5 00			
	observational studies ²	very serious ³	very serious ⁴	serious⁵	very serious ^{6,7}	none	22/22 (100%)	3/6 (50%)	OR 45.00 (1.89 to 1071.38) ⁸	48 more per 100 (from 15 more to 50 more)	VERY LOW	
Changes 1 ²⁶					1	1	ents to experience ra	v , ,	00.040			
I	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	
	s in signs and s	ymptoms -	fusion (all ages)	(follow-up at le	ast 24 months;	assessed with: nur	mber of patients to ex	perience intracorpor				
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	essment			No of p	patients	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 -	(/ (follow-up at leas	t 24 months; as	ssessed with: numb	per of adult patients t	o experience intraco	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	
	in signs and s	ymptoms -		(follow-up at lea	ast 24 months;	assessed with: nur	nber 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	
Changes	in signs and s	ymptoms -	pain (follow-up a	at 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	
	in signs and s	ymptoms -		pendence (follo	w-up unclear; n	neasured with: mea	in change in measur	e of functional indepe	endence; bet	ter indicated	by higher	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	ymptoms -		pendence (self-	care) (follow-up	o unclear; measure	d 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 ^{1/}	serious'	none	5	4	-	MD 5.5 lower (17.46 lower to 6.46 higher) ²⁹	VERY LOW	
	in signs and s	ymptoms -			ility) (follow-up	unclear; measured	d with: mean change	in mobility and trans	fer score; be		d by higher	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	
Changes	in signs and s	ymptoms -		pendence (loco	motion) (follow	-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	
	0	ymptoms -			ar; assessed wi	th: number of patie	nts able to walk on d					
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	patients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		Relative (95% CI)	Absolute	Quality	Importance
									8.95) ⁸	(from 67 fewer to 21 more)		

Richardson et al. 1976

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 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

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)

GRADE rule of thumb: <300 events

⁷ wide confidence interval

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

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 assessment						No of p	oatients	Effect			
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
group re ²⁶ Pun et ²⁷ unclear appropr ²⁸ insuffic. ²⁹ mean c ³⁰ Moon e ³¹ allocati attempt. ³² groups interven ³³ populat underta. ³⁴ Rajase. ³⁵ unclear appropr ³⁶ antitube if the gr availabi ³⁷ populat compan	eceived antitube al, 1990 r if allocation to a iate; outcome d ient data to asse lifference (and S et al, 2007 fon to treatment s were made to not comparable not comparable tion (s) studied; tion appears to r karan et al, 198 r if allocation to riate; outcome d erculosis chemo oups received the lity of outcome of tion appears to r ator differ by mo	rculosis chi reatment g efinitions w ess imprecia 5% confide groups was balance co at baseline unclear if g match the p ric rather the reatment g efinitions w therapy alco e same ca lata match the p re than the	emotherapy for 12 roups related to p ere valid and prec sion ence interval, when s related to potenti nfounders; length e (angle of kyphos roups were follow opulation of intere an therapeutic pul roups related to p ere valid and prec one has significant re apart from the i presence of abse	months; outcor otential confoun- ise al confounding t of follow-up was is higher in the ed up for an equ est, although det poses otential confoun- ise potential confoun- set, although det est, although det once of surgery (ne is not a subs ding factors; bli ulated by revie factors (decision s appropriate; c surgical group (al period; group ails were limited ding factors; bli <16 years of a tudied; unclear ails were limited some patients	stitute or surrogate inding unclear, thou wer n to operate was ba utcome definitions '13.2 vs 12.6; adult os appear to be co d; antituberculosis inding unclear, thou ge than the surger if the groups were d; the antituberculo in the chemotherap	outcome igh unlikely; unclear ased upon clinical sig were valid and precis s: 13 vs 9; children: mparable for treatme regimens do not use igh unlikely; unclear y group (no further de followed for an equal sis regimens do not	if attempts were mad gns and symptoms); i se 14 vs 12)); unclear if nt completion and av all of the 4 standard if attempts were mad etails are available fo I period; groups appe use all of the 4 stand red antituberculosis c	le to balance blinding unc groups rece railability of o recommend le to balance r the groups ear to be com lard recomm	e confounder lear, though ived the sam outcome data led drugs, an e confounder characteris nparable for vended drugs	s; length o unlikely; ur e care apa d some su s; length o tics at base treatment o ; and the i	f follow-up was nclear if art from the rrgeries were f follow-up was eline); unclear completion and ntervention and

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% CI)	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 ir	n the group th	at also un	derwent
1 ¹	observational studies ²	serious ³	very serious ⁴	very serious ⁵	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	onths; assesse	ed with: number of p	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 u	unclear; measure	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 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
										2		
Respons	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	
	¹ Arthornthurasook, 1983 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

 $^{\scriptscriptstyle 8}$ 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	Relapse (follow-up median 24 months; assessed with: number of patients to experience relapse)											
1 ¹	observational studies ²	very serious ³	serious ⁴	serious⁵	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:
 - \circ 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

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	atients	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
	(follow-up minir	num 1 year; as	sessed with: num	/								
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	
•	s in signs and s ent2, optic atroph	• •	• •	elae (follow-up 1	years; assesse	ed with: number of	patients to experienc	e neurological seque	elae, includi	ng neurologi	cal deficit,	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	s in signs and s	ymptoms – dis	sability (follow-up	minimum 1 yea	r; assessed wit	h: number of patie	nts to experience dis	ability)				
1 ¹	observational studies ²	very serious ^{3,4,5,6,7}		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	sessed 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					Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
			e (follow-up uncle				III) to have a 'poor of					
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	
		 poor outcom 	e (stage II) (follow	v-up unclear; as		umber of patients w	ith stage II disease t					ath))
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	
		 poor outcom 	e (stage III) (follo	w-up unclear; as		umber of patients w	vith stage III disease					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	th 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 retrosp ³ study of ⁴ it is unclear ⁵ unclear ⁶ exposu ⁷ unclear ⁸ unclear ⁹ it is unclear ¹⁰ unclear ¹¹ unclear ¹² GRAD ¹³ odds r ¹⁴ Kalita ¹⁵ prosperies 	id not explicitly re clear if the same if measures take re status measure if the main pote if the cases and clear if the 2 grou re if follow-up was re if follow-up was re if follow-up was re if the interventi E rule of thumb: atio and 95% con- ective	eport the quest exclusion criter en to prevent ki red in a standai ntial confounde l controls were ups were match s equal in the 2 on exactly matc <300 events nfidence interva	ia was applied to nowledge of prima rd, valid and reliat rs were identified taken from compa ed in terms of the groups	cases and contr ary exposure fro- ole way and taken into a arable population participation rai ntion of interest (rols; cases and m influencing ca account in the o ns, although the te	controls adequatel ase ascertainment lesign and analysis	r age and severity of	ⁱ disease				

¹⁷ 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 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	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% Cl)	Absolute	Quality	Importance

²⁴ unclear if length of follow-up was appropriate

²⁵ â€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 ٠
- intracerebral haematoma = 1 ٠

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	essment			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% CI)	Absolute	Quality	Importance
Response was requ		- need for a	additional interve	ention (follow-up	o median (maxi	mum), months = 34	(62); assessed with	number of patients	in whom rec	onstructive s	urgery or r	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	
	se to treatment	- need for	reconstructive su	urgery (follow-u	p median (maxi	mum), months = 34	(62); assessed with	: number of patients	in whom rec	constructive s	surgery wa	s required)
1 ¹	observational studies ²	very serious ³	serious ⁴	very serious ⁵	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	nephrectomy (fol	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 serious ⁵	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	surgery 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 (ablat	ive surgery			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 ¹⁴	very serious ^{6,9}	none	0/45 (0%)	0/18 (0%)	OR 0.21 (0.00 to 11.19) ⁸		VERY LOW	
		nstructive s			ery) (follow-up	16 to 60 months; as	sessed with: numbe	r of patients to exper		•	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

hdrawal of dru servational idies ¹¹ ents – drug to ing to withdraw servational	ug (without very serious ¹² xicity lead /al of drug (very	without change to	serious ¹⁴ ndrawal (ablativ	serious ⁶	Other considerations none	Antituberculosis chemotherapy plus surgery 9/74 (12.2%)	Antituberculosis chemotherapy alone 2/18 (11.1%)	Relative (95% Cl) OR 1.11 (0.22 to 5.64) ⁸	Absolute 1 more per 100 (from 8	Quality VERY LOW	Importance
servational udies ¹¹ ents – drug to ng to withdraw servational	very serious ¹²	serious ¹³ ling to drug with (without change to	serious ¹⁴ ndrawal (ablativ	serious ⁶	none			(0.22 to	per 100		
udies ¹¹ ents – drug to ng to withdraw servational	serious ¹² exicity lead val of drug (ling to drug with (without change to	ndrawal (ablativ		none			(0.22 to	per 100		
ng to withdraw servational	/al of drug (verv	without change to		e surgery con					fewer to 30 more)		
servational	verv				npared with no sur	rgery) (follow-up 9 to	60 months; assesse	ed with: num	ber of patien	ts to exper	ience drug
servational	very	13		.,		E / 4 E	0/40	00400	0 (
	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	
					ery compared with	no surgery) (follow	up 16 to 60 months;	assessed w	ith: number	of patients	to experience
servational udies 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	
any surgery of	compared	with no surgery	(follow-up 9 to	60 months; as	sessed with: numbe	er of patients to defau	ult treatment)				
servational udies 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	
ea se idi ar se idi	ts – drug to ading to with ervational ies ¹¹ hy surgery ervational	ts – drug toxicity lead ading to withdrawal of e ervational very ies ¹¹ serious ¹² hy surgery compared ervational very ies ¹¹ serious ¹²	ts – drug toxicity leading to drug with ading to withdrawal of drug (without cha ervational very serious ¹³ hy surgery compared with no surgery ervational very serious ¹³	ts – drug toxicity leading to drug withdrawal (reconstanting to withdrawal of drug (without change to duration ervational very serious ¹³ serious ¹⁴ hy surgery compared with no surgery) (follow-up 9 to serious ¹¹ serious ¹² serious ¹³ serious ¹⁴	ts – drug toxicity leading to drug withdrawal (reconstructive surged ading to withdrawal of drug (without change to duration of treatment)) ervational very serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} hy surgery compared with no surgery) (follow-up 9 to 60 months; as prvational ies ¹¹ serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9}	ts – drug toxicity leading to drug withdrawal (reconstructive surgery compared with ading to withdrawal of drug (without change to duration of treatment)) ervational ies ¹¹ very serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} none hy surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number relational ies ¹¹ very serious ¹² none	ts – drug toxicity leading to drug withdrawal (reconstructive surgery compared with no surgery) (follow-ading to withdrawal of drug (without change to duration of treatment)) ervational ies ¹¹ very serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} none 4/29 (13.8%) ny surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number of patients to defaure the serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} none 1/74 (1.4%)	ts - drug toxicity leading to drug withdrawal (reconstructive surgery compared with no surgery) (follow-up 16 to 60 months; ading to withdrawal of drug (without change to duration of treatment)) ervational ies ¹¹ very serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} none 4/29 (13.8%) 2/18 (11.1%) ny surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number of patients to default treatment) every serious ¹² none 1/74 1/18 (5.6%)	ts - drug toxicity leading to drug withdrawal (reconstructive surgery compared with no surgery) (follow-up 16 to 60 months; assessed we adding to withdrawal of drug (without change to duration of treatment)) 9.75)* ervational ies 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)* ny surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number of patients to default treatment) 13.17)* ervational ies ¹¹ very serious ¹² serious ¹³ serious ¹⁴ very serious ^{6,9} none 1/74 (1.4%) 0R 0.38 (0.02 to 6.34)*	ts - drug toxicity leading to drug withdrawal (reconstructive surgery compared with no surgery) (follow-up 16 to 60 months; assessed with: number adding to withdrawal of drug (without change to duration of treatment)) 9.75)* (from 10 fewer to 44 more) eading to withdrawal of drug (without change to duration of treatment) reconstructive surgery compared with no surgery) (follow-up 16 to 60 months; assessed with: number of treatment) 9.75)* (from 10 fewer to 44 more) ervational ies 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)* ger 100 (from 10 fewer to 51 more) ny surgery compared with no surgery) (follow-up 9 to 60 months; assessed with: number of patients to default treatment) 9.75)* GR 0.38 (0.12 to 13.17)* ger 100 (from 10 fewer to 51 more) ervational ies ¹¹ very serious ¹² serious ¹³ serious ^{6,9} none 1/74 (1.4%) 1/18 (0.02 to 16.9) (0.02 to 16.9) (0.02 to 16.9) (0.02 to 16.9) (0.02 to 16.34)* per 100 (from 5 fewer to 22 more)	$\frac{1}{1000} = \frac{1}{1000} + \frac{1}{10000} + \frac{1}{100000} + \frac{1}{10000000000000000000000000000000000$

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%)

.11.8 Adjunctive surgery in the treatment of active DRUG RESISTANT tuberculosis

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
Mortality			ear; assessed wit		· · ·							
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								
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	
	r - 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	
	- all-cause (foll	ow-up uncl	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 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	- all-cause (foll	low-up uncl	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	
	- all-cause (pa	tients ageo	d 40 years or you	nger) (follow-up	o 3 to 7 years af	ter treatment initiati	ion; assessed with: n	umber of deaths of a	ny cause ar	nong patient	s aged 40	years or
younger) 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	
•	- TB-related (p	atients age	ed 40 years or yo	unger) (follow-u	up 3 to 7 years	after treatment initia	ation; assessed with:	number of TB-relate	d deaths an	nong patients	s aged 40 y	ears or
younger) 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	
⁸ Karagöz ⁹ prospec ¹⁰ allocatii availabu unclear ¹¹ unclear ¹² some p by more ¹³ those th	e et al, 2009 tive cohort on to surgery wa ility of drugs with if length of follo f groups were atients had corr o than the prese	as based or h adequate w-up was a comparable norbidities to nce or abso gery were s	efficacy to cause appropriate at baseline; uncl hat may affect the ence of surgery - i selected due to a l	drug resistance rapid healing of ear if groups rec choice or mana in particular, the	the bronchial s eived the same gement of treat re is insufficient	tump); blinding uncl e 'other' care; unclea ment (12% had dial g detail around the p	lear, though unlikely; ar if follow-up was cc betes mellitus and 2 precise regimens of a	calized disease with a attempts do not appo omparable across the 1.8% had COPD); no ntituberculosis chem- le reduced incidence	ear to have groups females; it otherapy us	been made i is unclear if t ed in each g	to balance the 2 interv roup	confounders; rentions varied
 ¹⁴ Kwon e ¹⁵ retrospond ¹⁶ method lesion); ¹⁷ unclear ¹⁸ some p 	et al, 2008 ective cohort I of allocation to blinding unclea if groups were if groups were atients had a co	treatment g r, though u comparable comparable pmorbidity t	groups was related nlikely; attempts d at baseline; grou for treatment cor hat might affect th	o not appear to ps appeared to npletion and ava e choice or man	have been mad receive the san ailability of outco agement of ant	le to balance confol ne 'other' care, altho ome data ituberculosis treatm	unders ough details provideo nent (15% diabetes n	ry to at least 6 month I are limited; unclear nellitus, 5% chronic li	if follow-up ver disease,	was compar . 3% maligna	able betwe ancy); it is u	en the groups; unclear if the 2
interver ¹⁹ Leiman ²⁰ unclear	ntions varied by le et al, 2005 [.] if method of all	more than ocation to t	the presence or a	bsence of surge Inrelated to pote	ry - in particulai	r, there is insufficier	nt detail around the p	recise regimens of ar kely; attempts do not	ntituberculos	sis chemothe	erapy used	in each group

			Quality asse	essment		No of p	patients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	chemotherapy	Antituberculosis chemotherapy alone	Relative (95% CI)	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	Eff	iect		
No of		Risk of						Antituberculosis chemotherapy	Relative			
studies	Design		Inconsistency	Indirectness	Imprecision	considerations				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)

this posit	ive culture was i	onowed by	a minimum of 5 co	Insecutive nega	live cultures							
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	ients to achieve	a cure, defined	as a patient who h	as completed treatme	ent and consistently h	nad negative	e culture res	ults (with a	it least 5
negative	results) during th	he final 12 r	nonths of treatme	nt)		·			Ũ		,	
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	
treatmen	t)			ients to achieve	a cure, defined	as patients who co	mpleted treatment a	nd were <i>M. tuberculo</i>	<i>si</i> s culture r	negative 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 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
										fewer to 28 more)		
	low-up unclear; al 12 months)	assessed w	vith: of patients to	achieve a cure,	defined as com	pletion of treatment	and at least 5 conse	ecutive negative cultu	ires from sa	mples collec	ted at leas	t 30 days apa
1 ¹⁹	observational studies ¹¹ z et al. 2009	serious ²⁰	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 some p by mon GRADE wide co those th confound odds rational Kwond retrosp method retrosp method anclear groups some p intervei treatment treatment some p some p and confound and confound and confound some p treatment treatment and confound analysi 18.7 % surgery 	atients had com e than the prese Fule of thumb: Infidence interva- mat received sur- nding factor wer tio and 95% con- et al, 2008 bective cohort d of allocation to blinding unclear r if groups were ; unclear if group batients had a co- ntions varied by that received sur- ent); therefore it ne et al, 2005 r if method of all nders; unclear if batients had a co- v - in particular, t et al, 2007 ion to surgery w red lung, and on s	comparable orbidities the ence or abse- <300 events als gery were s e not prese fidence inter treatment g r, though ui comparable os were cor omorbidity t more than "gery were s is likely tha location to t i length of fo omorbidity t there is insu- as based on ly if they has a comorbid	at baseline; uncle nat 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 mparable for treatr hat might affect th the presence or a selected due to a t the higher incide t the higher incide low-up was appr hat might affect th ifficient detail arou n specific criteria (d relatively robust	choice or manage in particular, their high likelihood of by reviewer d to potential con- to not appear to pos appeared to ment completion the choice or man- basence of surgen high likelihood o nce of cure in the unrelated to pote opriate to choice or man- to the precise of tresistance to a l t cardiopulmonal	gement of treatr re is insufficient treatment failur nfounding facto have been mad received the sa and availability hagement of ant f treatment failu is group would ential confoundin hagement of ant regimens of anti high number of ry functions); bla	nent (12% had dial detail around the p e or relapse; theref rs (criteria for surge e to balance confou me 'other' care, alt of outcome data ituberculosis treatm tituberculosis treatm tuberculosis treatm tuberculosis treatm tuberculosis chemo drugs and therefore inding unclear, thou	etes mellitus and 21 recise regimens of a fore it is likely that the env: MDR-TB refractor inders hough details provide ment (15% diabetes n it detail around the p irming surgery: MDR is confounding factor unclear, though unlik ment; it is unclear if th therapy used in each e a high possibility of igh unlikely; attempts	kely; attempts do not he 2 interventions var h group relapse or treatment s appear to have bee if the 2 interventions	Females; it is otherapy us cure in this ins of medica in if follow-up intituberculos o chemother appear to h ied by more failure; con n made to b	ed in each g group would Il treatment v o was compa sis chemothe apy after at l ave been ma than the pre than the pre tinued localis alance confo	roup be even h with a prim arable betw ancy); it is erapy used east 6 mol ade to bala sence or a sed cavital bunders in	nigher if this ary localized ween the unclear if the in each grou nths of ance absence of y disease; the multivari

Treatment failure

			Quality asse	essment			No of p	oatients	Ef	fect		
o of tudies reatme	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery ilure, defined as patie	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	
	over at least a 3-					e microbiological la				Jonocounvo	nogutivo o	putum
1	observational studies ²	very serious ³	serious ⁴	serious⁵	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	
eatme	nt failure (follow	-up unclea	r; assessed with:	number of patien	nts 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 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	its to experience	e treatment failure,	defined as ≥2 positive	e culture results reco	rded during	the final 12	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					
19 19	observational studies ²			very serious ²¹		none	istently <i>M. tuberculos</i> 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 physician)
			r; assessed with: i final 3 cultures we		its to experience	e treatment failure,	defined as 2 or more	positive cultures am	ongst final s	5 samples co	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 5 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; 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 ass	essment			No of patients		Ef	fect		
No of studies De	Risk o Design bias	f Inconsistency	Indirectness	Imprecision	Other considerations	Antituberculosis chemotherapy plus surgery	Antituberculosis chemotherapy alone	Relative (95% CI)	Absolute	Quality	Importance
confoundin ⁸ odds ratio a ⁹ Karagöz et ¹⁰ prospective ¹¹ allocation t availability unclear if le ¹² unclear if g ¹³ some patie by more tha ¹⁴ wide confid ¹⁵ Kwon et al ¹⁶ method of lesion); blir ¹⁷ unclear if g groups; unc ¹⁸ some patie intervention ¹⁹ Leimane e ²⁰ unclear if r confoundel ²¹ some patie surgery - ir ²² Törün et al ²³ allocation t destroyed l ²⁴ 18.7 % of j	ng factor were not pr and 95% confidence t al, 2009 ve cohort to surgery was base v of drugs with adequ length of follow-up w groups were compar ients had comorbiditi han the presence or a idence intervals al, 2008 f allocation to treatma inding unclear, thoug groups were compar nclear if groups were ients had a comorbid ons varied by more the et al, 2005 method of allocation ars; unclear if length ients had a comorbid in particular, there is al, 2007 to surgery was base lung, and only if they patients had a comor in partients had a comorbid in particular, there is al, 2007	esent intervals calculated l ate efficacy to cause as appropriate able at baseline; unc s that may affect the bsence of surgery - nt groups was relate n unlikely; attempts c able at baseline; grou comparable for treati ty that might affect th an the presence or a to treatment groups of f follow-up was appr ty that might affect th nsufficient detail arou d on specific criteria had relatively robus	by reviewer (drug resistance rapid healing of lear if groups rec choice or mana- in particular, ther d to potential cor lo not appear to l ups appeared to ment completion he choice or man bsence of surger unrelated to pote opriate he choice or man und the precise re (resistance to a h t cardiopulmonar ect the choice or man	with high probat the bronchial stu- eived the same gement of treati e is insufficient nfounding factor have been made received the sai and availability agement of anti agement of anti egimens of antit high number of o y functions); blin management of	bility of failure or rel ump); blinding uncle 'other' care; unclea ment (12% had diab detail around the pr s (criteria for surgel e to balance confou me 'other' care, alth of outcome data tuberculosis treatm there is insufficient there is insufficient tuberculosis treatm tuberculosis chemo drugs and therefore nding unclear, thoug antituberculosis tre	apse, sufficiently loca ear, though unlikely; a r if follow-up was con betes mellitus and 21. ecise regimens of an ry: MDR-TB refractor	alized disease with a attempts do not appe mparable across the .8% had COPD); no tituberculosis chemo y to at least 6 month d are limited; unclear ellitus, 5% chronic liv ecise regimens of an ely; attempts do not a group relapse or treatment do not appear to hav if the 2 interventions	dequate ca par to have l groups females; it i otherapy use s of medica r if follow-up ver disease, tituberculos appear to ha ed by more failure; comi ve been ma	rdiopulmona been made t is unclear if t ed in each g I treatment v o was compa 3% maligna is chemothe ave been ma than the pre tinued localis de to balanc	ry reserve o balance he 2 interv roup vith a prim- rable betw ancy); it is rapy used ade to bala sence or a sed cavitar e confound	and the confounders; rentions varied ary localized reen the unclear if the 2 in each group nce ubsence of y disease; ders

Adherence

			Quality asso	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 (95% CI)	Absolute	Quality	Importance
Adheren	dherence (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						No of p	oatients	Ef	fect		
No of studie	s Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		Relative	Absolute	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	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
Adheren	ce - default (foll	ow-up uncl	ear; assessed with	n: number of pati	ents to be cons	idered a defaulter,	defined as failure to	complete treatment f	or any reaso	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				n: 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	•	treatment	(follow-up unclea	r; assessed with	: number of pat	ients to experience	incomplete treatmen	t, defined as treatme	ent interrupte	ed for 2 or m	ore consec	cutive months
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 fewer to 5	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

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						No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		chemotherapy	Antituberculosis chemotherapy alone	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	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	Importanc
						ients to experience	an initial favourable	response, defined as	patients wi	th at least th	ree consec	utive
negative			od of at least 3 m					1				
1.	observational studies ²	serious	serious	very serious ⁵	serious	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	o treatment	(follow-up unclea	r; assessed with	: number of pat	ients to experience	a favourable outcom	ne, 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	
								ponse, defined as th ecimens collected 2			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	
	ble response to			years after treatr	ment initiation; a	assessed with: num	ber of patients to exp	perience treatment su	iccess, defii	ned as the su	um of cure,	treatment
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 com	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	

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		
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
groups, ¹² it is und used in ¹³ Camer ¹⁴ unclea length d ¹⁵ the me baselin ¹⁶ 2 patie - the re ¹⁷ wide co ¹⁸ odds ra ¹⁹ see ev ²⁰ Kim et ²¹ unclea groups, ²³ 22.6% surgery ²⁴ multive ²⁵ Kwon e ²⁶ methoo lesion); ²⁷ some µ intervel group; ²⁸ those t	unclear if group clear if the 2 inte each group; 'fav on & Harrison, 1 r if method of allo of follow-up was an age in the su e characteristics gimens of antitul onfidence interva atio and 95% cor idence table in th al, 2008 r if method of allo tivariate analysis of patients had a r - in particular, the interval groups at al, 2008 d of allocation to blinding unclear batients had a con tions varied by a substitute for out hat received surg	as compara rventions v vourable ou 997 ocation was appropriate grery group grery group groups ap urgery group berculosis of als offidence int he appendi ocation to t s comparable s were con a comorbid here is insu treatment g morbidity t more than tcomes of in gery were s	ble for treatment of aried by more than tcome' is a compo- s related to potenti bo was significantly ppeared to receive- up, had comorbidit chemotherapy con rervals calculated la for full definition reatment groups u a at baseline; group parable for treatm ity that might affect that might affect the hat might affect the the presence or at selected due to a h	ompletion and a n the presence of site of outcome al confounding in older than in the d the same 'othe ties that might e tained, on avera by reviewer nrelated to pote ps appeared to nent completion t the choice or m nd the precise r d to potential con- per to have be e choice or man sence of surger high likelihood of	availability of ou or absence of su s of interest factors; blinding e group that rece er' care, althoug ffect the choice age, more drugs natial confoundir received the sau and availability nanagement of egimens of anti- phounding factor een made to bai agement of anti- ry - in particular, f treatment failu	tcome data urgery - in particular unclear, though un eived antituberculos th details provided a or management of s in the surgery grou ng factors; blinding t me 'other' care, alth of outcome data antituberculosis treat tuberculosis chemo rs (criteria for surge lance confounders i ituberculosis treatm ; there is insufficien re (criteria for perfo	r, there is insufficient likely; attempts do no sis chemotherapy alc 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 ry: MDR-TB refractoo in the multiple logistic ent (15% diabetes m t detail around the pr rming surgery: MDR-	d are limited; unclear detail around the pre- bit appear to have be- one (41 vs 27 years); groups were followe entions used varied b e is a surrogate for o ely; attempts appear d are limited; unclear f the 2 interventions v group; outcome is a ry to at least 6 month cregression relitus, 5% chronic lin ecise regimens of an TB was refractory to infounding factor wer	ecise regime en made to unclear if g d for an equ y more tha utcomes of to have bee r if follow-up varied by m s sof medica ver disease, tituberculos chemother	ens of antitul balance com roups were of lal period in the presen interest en made to b o was compa ore than the for outcomes I treatment w 3% maligna is chemothe apy after at I	perculosis of founders; u comparable ce or abset palance cor arable betw presence of s of interest with a prima ancy); it is u erapy used	chemotherapy inclear if for other nce of surgery afounders in een the or absence of any localized inclear if the 2 in each

Poor 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% CI)	Absolute	Quality	Importanc
oor re	sponse to treatm	nent (follow	-up unclear; asses		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	
	sponse to treatm	nent (follow		sed with: numbe	er of patients to	experience a poor	outcome, defined as	treatment failure, de	eath during t	reatment or	default)	
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	
he final	12 months or an	y 1 of the fir		g positive), relap	se (defined as a		ent failure, defined as patient who complet					
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	
oor re	sponse to treatr	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)
20	observational studies ⁹	serious ²¹	serious ²²	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 prospe ³ decisio tolerat indepe ⁴ unclea groups ⁵ some absen ⁵ GRAD ⁷ a bina ³ Jeon e ⁹ retrosp ¹⁰ alloca selecto	te resection and a endent associatio r if groups were of s comparable for patients had com ce of surgery; in p E rule of thumb: ry multivariable lo de al, 2009 pective cohort tion to surgery w	localised le n of potentia comparable treatment co orbidities the particular, the <300 events gistic regress as based or ilateral lesico	esion amenable to al risk factors with at baseline; unclea ompletion and ava at may affect the c are is insufficient ssion model was u a specific criteria (s	resection were in poor outcome; u ar if groups appe- ilability of outcor hoice or manage detail around the sed to evaluate surgical resection	required; blindir inclear if the len eared to receive me data ement of treatme precise regime the independer n was considere	ng unclear, though u ngth of follow-up wa d the same 'other' nent (e.g. 9% had d ens of antituberculo nt association of pot ed for patients with	ce Committee, and w inlikely; a binary mul s appropriate care; unclear if the le abetes mellitus); it is sis chemotherapy us ential risk factors wit localised cavitary les nclear, though unlike	tivariable logistic reg ength of follow-up wa unclear if the 2 inte ed in each group; 'p h poor outcome ions and anticipated	gression mod as comparab rventions va oor outcome l adequate p	del was used ole across the ried by more e' is a substit	I to evaluat groups; u than the p ute outcon	e the nclear if resence or ne ion, and for

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						No of p	oatients	Ef	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	chemotherapy		Relative (95% CI)		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 Date: 2004 15-29 ≥60 ye refere	0-14 years	Observational with multivariate analysis	very serious ^{1,2,3}	serious ⁴	no serious indirectness	no serious imprecision	234	1.0 (0.3 to 3.4)	VERY LOW
	15-29 years					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	nt				Number of	Summary of findings	
Study	Factor	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 popul	ation characteristics					

⁴Unclear 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	
Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Male	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	no serious	234	1.0 (0.7 to 1.4)	VERY LOW
reference: female	multivariate analysis Observational with			indirectness	imprecision		-	
Female	Observational with multivariate analysis	very serious ^{1,2,3}	no serious	no serious	no serious	380	0.70 (0.33 to 1.49)	LOW
reference: male			inconsistency	indirectness	imprecision		-	
	Male reference: female Female reference: male	FactorDesignMaleObservational with multivariate analysisreference: femaleObservational with multivariate analysisFemaleObservational with multivariate analysisreference: mostic factor and outcome measurement b	MaleObservational with multivariate analysisvery serious1.2.3reference: femaleObservational with multivariatevery serious1.2.3FemaleObservational with multivariatevery serious1.2.3	FactorDesignRisk of biasInconsistencyMaleObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ FemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyFemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyFemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistency	FactorDesignRisk of biasInconsistencyIndirectnessMaleObservational with multivariate analysisVery serious ^{1,2,3} serious ⁴ no serious indirectnessFemaleObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessFemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessFemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectness	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionMaleObservational with multivariate analysisVery serious ^{1,2,3} serious ⁴ no serious indirectnessno serious imprecisionFemaleObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessno serious imprecisionFemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecisionFormaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionPatientsMaleObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessno serious imprecision234FemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious indirectnessno serious indirectnessno serious imprecision234FemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision380reference: maleobservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision380mostic factor and outcome measurement blindedseriousseriousseriousseriousserious	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionNullide of patientsAdjusted OR (95% CI)MaleObservational with multivariate analysisvery serious ^{1,2,3} serious ⁴ no serious indirectnessno serious imprecisionno serious imprecision2341.0 (0.7 to 1.4)FemaleObservational with multivariate analysisvery serious ^{1,2,3} no serious indirectnessno serious indirectnessno serious imprecision2341.0 (0.7 to 1.4)Female reference: maleObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision2341.0 (0.70 (0.33 to 1.49)For the component blindedvery seriousno serious indirectnessno serious imprecision3800.70 (0.33 to 1.49)

³Analyses not reported for a number of variables recorded and reported in population characteristics

Abbreviations: CI, confidence interval; OR, odds ratio

HIV status

		Quality assessmen	ıt				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	serious⁵	380	1.93 (0.70 to 5.23)	VERY LOW
East London/ Essex Date: 2003-6	reference: HIV- negative	multivariate analysis		inconsistency	indirectness			-	
¹ Unclear if prog	nostic factor and out	come measurement b	linded						
² Multivariate an	alysis used, but uncl	ear which confounders	s were controlled for						
³ Analyses not re	eported for a number	of variables recorded	and reported in popul	ation characteristics					
⁴ Unclear if loss	to follow-up sufficien	tly unrelated to key ch	aracteristics						
⁵ Wide confiden	ce interval								

Abbreviations: CI, confidence interval; OR, odds ratio

Previous history of tuberculosis

							Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	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 assessmer	it				Number of	f 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	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	serious ⁵	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 und reported for a numbe to follow-up sufficie	Itcome measurement b clear which confounder er 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

Exposure

		Quality assessmen	it				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	Previous exposure to drug resistant tuberculosis	Observational with multivariate analysis	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							-	

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

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		Adjusted OR (95% CI)	Quality

Study Factor		it				Number of	Summary of findings	
Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
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		very serious ^{1,2,3}					-	
Date of arrival in the UK ≥2000 i.e. less than 3-6 years in the UK	Observational with multivariate analysis	very serious ^{1,2,3} no serious inconsistency		no serious indirectness	no serious imprecision	380	0.71 (0.27 to 1.87)	LOW
reference: date of arrival in the UK <2000 i.e. more than 3-6 years in the UK							-	
C viir d r c viir d E ti i. y r c L n	Country of origin with high ncidence of drug resistance reference: country of origin without high ncidence of drug resistance Date of arrival in he UK ≥2000 .e. less than 3-6 years in the UK reference: date of arrival in the JK <2000 i.e. more than 3-6	Country of origin with high ncidence of drug resistanceObservational with multivariate analysisreference: country of origin without high ncidence of drug resistanceObservational with multivariate analysisDate of arrival in he UK ≥2000 .e. less than 3-6 years in the UK veference: date of arrival in the UK <2000 i.e. more than 3-6Observational with multivariate analysis	Country of origin with high ncidence of drug resistanceObservational with multivariate analysisvery serious1.2.3reference: country of origin without high ncidence of drug resistanceObservational with analysisvery serious1.2.3Date of arrival in he UK ≥2000 .e. less than 3-6 years in the UKObservational with multivariate analysisvery serious1.2.3Observational with multivariate analysisvery serious1.2.3	Country of origin with high ncidence of drug resistanceObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyreference: country of origin without high ncidence of 	Country of origin with high ncidence of drug resistanceObservational with multivariate analysisvery serious 1.2.3no serious inconsistencyno serious indirectnessreference: country of origin without high ncidence of drug resistanceObservational with multivariate analysisvery serious 1.2.3no serious inconsistencyno serious indirectnessDate of arrival in he UK ≥2000 i.e. reference: date of arrival in the UK <2000 i.e. more than 3-6Observational with multivariate analysisvery serious 1.2.3no serious inconsistencyno serious indirectness	Country of origin with high ncidence of drug resistanceObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessreference: country of origin without high ncidence of drug resistanceObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessDate of arrival in he UK ≥2000 .e. less than 3-6 rears in the UK UK <2000 i.e. more than 3-6Observational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectness	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionpatientsCountry of origin with high necidence of drug resistanceObservational with multivariate analysisVery serious ^{1,2,3} hout bigh necidence of drug resistanceno serious inconsistencyno serious indirectnessno serious indirectnessno serious imprecisionDate of arrival in he UK ≥2000 e.e. less than 3-6Observational with multivariate analysisvery serious ^{1,2,3} very serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecisionNo serious imprecisionDate of arrival in he UK ≥2000 e.e. less than 3-6Observational with multivariate analysisvery serious ^{1,2,3} very serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecisionDate of arrival in he UK ≥2000 e.e. less than 3-6Observational with multivariate analysisvery serious ^{1,2,3} efference: date of arrival in the JK <2000 i.e. more than 3-6very serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision	FactorDesignRisk of biasInconsistencyIndirectnessImprecisionpatientsAdjusted OR (95% Cl)Country of origin with high neidence of drug resistanceObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessno serious imprecision3800.61 (0.25 to 1.47)Country of origin without high neidence of drug resistanceObservational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious imprecision3800.61 (0.25 to 1.47)Date of arrival in he UK ≥2000 u.e. less than 3-6 gears in the UK MK <2000 i.e. more than 3-6Observational with multivariate analysisvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessno serious indirectness0.61 (0.25 to 1.47)Date of arrival in he UK ≥2000 u.e. less than 3-6 gears in the UK MK <2000 i.e. more than 3-6very serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessno serious indirectness0.71 (0.27 to 1.87)JK <2000 i.e. more than 3-6Prove seriousvery serious ^{1,2,3} no serious inconsistencyno serious indirectnessno serious indirectnessassocial precision

⁴ Unclear if loss to follow-up sufficiently unrelated to key characteristics

Abbreviations: CI, confidence interval; OR, odds ratio

Ethnicity

		Quality assessmen	ıt				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	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	2004 Black African analysis			no serious imprecision		1.3 (0.8 to 2.0)			
	Black Caribbean					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	ıt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
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
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 r	nalysis used, but uncl reported for a numbe	tcome measurement b lear which confounders r of variables recorded	s were controlled for and reported in popu	lation characteristics					

⁴ Unclear if loss to follow-up sufficiently unrelated to key 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 r	nalysis used, but unc reported for a numbe	tcome measurement b lear which confounders r of variables recorded htly unrelated to key ch	were controlled for and reported in popul	ation characteristics					

Abbreviations: CI, confidence interval; OR, odds ratio

.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	serious ⁵	104	4.8 (1.6 to 14.4)	VERY LOW
Leicestershire	reference: no	multivariate						-	

	-	Quality assessmen	ıt				Number of	Summary of findings	Quality
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	
Data: 1993-8	evidence of poor adherence	analysis							
 ² Unclear if prog ³ Authors had to ⁴ Multivariate an ⁵ Wide confidentiation 	nostic factor and out rely on others' notes alysis used, but uncl	on ethnic group, gend come measurement b s (potential for recall b ear which confounders al; OR, odds ratio	linded ias)						

Previous history of tuberculosis

	Design	Risk of bias		uality assessment					
		THIST OF MUS	Inconsistency	Indirectness	Imprecision	Number of patients	Adjusted OR (95% CI)	Quality	
story of perculosis	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	
erence: no tory of perculosis	analysis						-		
c factor and outco on others' notes	ome measurement bli (potential for recall bia	inded as)							
ere tory perc we c fa on s us terv	culosis ence: no y of culosis ere matched o actor and outc others' notes sed, but uncle val	culosis multivariate analysis y of culosis ere matched on ethnic group, gende actor and outcome measurement bli others' notes (potential for recall bia sed, but unclear which confounders	culosis multivariate analysis analysis analysis y of culosis ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val	culosis multivariate analysis ence: no y of culosis analysis ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val	culosis multivariate analysis ence: no y of culosis analysis ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val	culosis multivariate analysis ence: no y of culosis analysis ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val set	culosis multivariate analysis ence: no y of culosis analysis ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val but unclear which confounders were controlled for	culosis multivariate analysis multivariate analysis multivariate analysis y of culosis analysis - - ere matched on ethnic group, gender and age group actor and outcome measurement blinded others' notes (potential for recall bias) sed, but unclear which confounders were controlled for val - -	

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						-	
¹ Cases and cor	ntrols were matched	on ethnic group, gend	ler and age group						
² Unclear if prog	pnostic factor and ou	tcome measurement b	blinded						
³ Authors had to	rely on others' note	s (potential for recall b	ias)						
⁴ Multivariate an	alysis used, but unc	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	Summary of findings	
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 ³ Authors had to ⁴ Multivariate an 	nostic factor and out rely on others' notes	on ethnic group, gend tcome measurement b s (potential for recall b ear which confounder s imprecision	linded ias)						

Abbreviations: CI, confidence interval; OR, odds ratio

Foreign travel

		Quality assessmer	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Pritchard, 2003 Leicestershire	Travel outside the UK	Matched case- control ¹ with multivariate	very serious ^{1,2,3,4,5}		no serious indirectness	serious ⁶	104	No statistic provided Authors state that the effect was not significant	VERY LOV
Data: 1993-8	1993-8 reference: no travel outside the UK						-		
² Unclear if prog	gnostic factor and ou	on ethnic group, gend tcome measurement b s (potential for recall b	blinded						
	,	lear which confounder	,						
	ta provided to assess								
Abbroviations: (CL confidence interv	al: OR odds ratio							

Abbreviations: CI, confidence interval; OR, odds ratio

Time in the UK

		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 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				
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
¹ Cases and c	controls were matche	d on ethnic group, geno	der and age group						
		utcome measurement l							
³ Authors had	to rely on others' no	es (potential for recall b	bias)						
⁴ Multivariate a	analysis used, but ur	clear which confounder	rs were controlled fo	r					
⁵ Effect estimation	ate not reported								
⁶ Insufficient d	ata provided to asse	ss imprecision							
Abbreviations	: CI, confidence inte	val; 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}	very serious ^{1,2,7,8} no serious inconsistency		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)	
quarter of 2006	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	Unmatched case- control with multivariate analysis				-		-	
Neely, 2009 London	≤24 years		control with	serious ⁴	no serious indirectness	no serious imprecision	355	1.7 (0.5 to 6.3)	VERY LOW
Data: 2004	25-44 years		multivariate			serious⁵		2.1 (0.6 to 7.7)	
	reference: ≥45 years					-		-	

		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 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	o previous tubercu	Ilosis							
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)	
2000	reference: 15-44 years					-		-	
² Multivariate an ³ Analyses not re ⁴ Unclear if loss ⁵ Wide confiden ⁶ Loss to follow- ⁷ Approach to di ⁸ Cases and cor ⁹ A number of fa	alysis used, but unc eported for all variab to follow-up sufficier ice interval up, its reasons and t rug susceptibility tes 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	
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
Patients living	in London								
Kruijshaar,	Female	Observational with	serious ¹	serious ^{5,6}	no serious	no serious	11 848	0.92 (0.79 to 1.08)	LOW
2008 London	reference: male	multivariate analysis			indirectness	imprecision		-	
Data: 1998		,							
and 2005									
Maguire, 2011	Male	Unmatched case- control with	very serious ^{1,2,7,8}	no serious	no serious indirectness	no serious	18040	1.34 (0.98 to 1.83)	LOW
London Data: 1995 to		multivariate		inconsistency	indirectness	imprecision			
the third	reference:	analysis						-	
quarter of 2006	female								
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	reference:	control with			indirectness				
Data: 2004	female	multivariate analysis							
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-	reference:	multivariate			indirectness	imprecision		-	
outbreak) Date: 2004	female	analysis							
	outside of London								
Kruijshaar,	Female	Observational with	serious ¹	serious ^{5,6}	no serious	no serious	16 633	0.81 (0.69 to 0.96)	LOW
2008		multivariate		00040	indirectness	imprecision			
England, Wales and		analysis							
Northern									
Ireland, excluding	reference: male							-	
London									
Data: 1998 and 2005									
¹ Unclear if prog	nostic factor and out	tcome measurement b	blinded						
		lear which confounder							
		r of variables recorded		lation characteristics					
		ntly unrelated to key ch the characteristics of th							
	rug susceptibility tes		nose lost not reported						
⁷ Cases and cor	ntrols unmatched	-							
		aire (i.e. may be some	reliance on recall)						
⁹ Wide confiden	ce interval CI, confidence interva	al: OR odds ratio							
Abbieviations.	si, connuence interva	ai, ON, OUUS Tallo							

Exposure

		Quality assessment	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	Close	Unmatched case-	very serious ^{1,2,3}	serious ⁴	no serious	serious⁵	355	6.2 (1.7 to 21.8)	VERY LOV	
London Data: 2004	reference: casual	control with multivariate analysis			indirectness			-		
Neely, 2009 London Data: 2004	Cases to whom contact was exposed: ≥2	Unmatched case- control with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	serious⁵	355	3.1 (1.1 to 8.4)	VERY LOW	
Dala. 2004	reference: 1	analysis						-		
Exposure to s	mear-positive drug	resistant tuberculos	is							
Neely, 2009 London Data: 2004	Exposure to cases with smear-positive drug resistant tuberculosis		very serious ^{1,2,3}	very serious ^{1,2,3} serious ⁴	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 c	rs were controlled for whom contact expos	ed, which was record	ed and reported in po	pulation characteristic	25			

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							-	
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	reference: no history of tuberculosis							-	
 ² Unclear if prog ³ Authors had to ⁴ Multivariate and ⁵ Wide confidence ⁶ Loss to follow-to ⁷ Approach to dr 	nostic factor and out rely on others' notes alysis used, but uncl ce interval	• •	linded ias) s were controlled for						

Smear status

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Maguire, 2011	Smear-positive	Unmatched case-	very serious ^{1,2,3,4}	no serious	no serious	no serious	18040	1.37 (0.98 to 1.93)	LOW
London Data: 1995 to the third quarter of 2006	reference: smear-negative	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
Patients with p	revious tuberculos	is							
Conaty, 2004	Smear-positive	Unmatched case- control with multivariate analysis		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	control with i multivariate analysis	inconsistency ind	indirectness	imprecision		-	

Number of	Summary of findings	
Study Factor Design Risk of bias Inconsistency Indirectness Imprecision patients	Adjusted OR (95% CI)	Quality
¹ Unclear if prognostic factor and outcome measurement blinded		
² Cases and controls unmatched		
³ Some data collected by questionnaire (i.e. may be some reliance on recall)		
⁴ Multivariate analysis used, but unclear which confounders were controlled for		
⁵ Wide confidence interval		
⁶ Not all factors that underwent univariate analysis were entered into the multivariate analyses; unclear how factors were selected for the multivariate analyses		
⁷ 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	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Patients living i	in London								
Maguire, 2011 _ondon	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 he third quarter of 2006	reference: pulmonary tuberculosis	multivariate analysis						-	
Kruijshaar, 2008	Pulmonary tuberculosis	Observational with multivariate	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	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	CI, confidence interva	al; OR, odds ratio							

HIV status

ndings	Summary of findings Adjusted OR (95% CI)	Number of							
-		patients	Imprecision	Indirectness	Inconsistency	Risk of bias	Design	Factor	Study
							losis	o previous tubercu	Patients with n
LOW	1.3 (0.8 to 1.9)	8762	no serious	no serious	no serious	very serious ^{1,2,3}	Unmatched case-	HIV-positive	Conaty, 2004
	-		imprecision		control with multivariate analysis	reference: HIV- negative	England and Wales Data: 1993-4 and 1998- 2000		
30) LOW	1.02 (0.80 to 1.30)	18005	no serious	no serious	no serious	very serious ^{1,4,5,6}	Unmatched case-	HIV-positive	French, 2008
	-		imprecision	indirectness	inconsistency	variate	control with multivariate analysis	reference: HIV- negative	England and Wales Data: 1999- 2005
							is	revious tuberculos	Patients with p
LOW	0.6 (0.1 to 4.6)	639	no serious	no serious	no serious	very serious ^{1,2,3}	Unmatched case-	HIV-positive	Conaty, 2004
	-		imprecision	indirectness	inconsistency		control with multivariate analysis	reference: HIV- negative	England and Wales Data: 1993-4 and 1998- 2000
		riate analyses	elected for the multiva -2000)		two periods of analy		h effect estimates only h it was unclear which	that underwent univa alysis used, althoug ntrols unmatched alysis used, althoug	2000 ¹ Unclear if prog ² Not all factors i ³ Multivariate an ⁴ Cases and cor ⁵ Multivariate an

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 assessmen	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	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	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	that underwent univa		ntered into the multiva				ate analyses		
	alysis used, althoug htrols unmatched	h effect estimates only	y adjusted for age and	two periods of analys	is (1993-4 and 1998-2	000)			

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 pre	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				serious ⁵		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	very serious ^{1,3,6} no set	no serious inconsistency	no serious 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

		Quality assessmen	it				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
and 1998- 2000	In the UK ≥10 years					no serious imprecision		0.9 (0.7 to 1.3)	LOW
	reference: born in the UK					-		-	-
Time in the UK i	in patients who ha	ve residence in Lond	lon						
Kruijshaar, 2008 London Data: 1998 and 2005	Years in the UK (linear)	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 patients who have	ve residence outside	of London						
Kruijshaar, 2008 England, Wales and Northern Ireland, excluding London Data: 1998 and 2005	Years in the UK (linear)	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	n patients who have	e residence in Londo	n						
Kruijshaar, 2008	Born outside of the 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
London Data: 1998 and 2005	reference: born in the UK	analysis						-	
Maguire, 2011	Born in the UK	Unmatched case-	very serious ^{1,2,9,10}	no serious	no serious	no serious	18040	2.40 (1.68 to 3.43)	LOW
London Data: 1995 to the third quarter of 2006	reference: born outside of the UK	control with multivariate analysis		inconsistency	indirectness	imprecision		-	
Story, 2007	Born in the UK	Observational with	very serious ^{1,2,3}	serious ⁴	no serious	serious ⁵	38	2.8 (1.1 to 7.0)	VERY LOW
London (outbreak) Date: 2004	reference: born outside of the UK	multivariate analysis			indirectness			-	
Place of birth in	n patients who have	e residence outside	of London						
Kruijshaar,	Born outside of	Observational with	serious ¹	serious ^{7,8}	no serious	no serious	16 633	1.49 (1.16 to 1.92)	LOW

		Quality assessme	ent			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	reference: born in the UK	analysis						-	
Data: 1998 and 2005									
¹ Unclear if prog	nostic factor and out	tcome measurement	blinded						
² Multivariate and	alysis used, but uncl	lear which confounde	rs were controlled for						
•	•		d and reported in popul	ation characteristics					
⁴ Unclear if loss	to follow-up sufficien	ntly unrelated to key o	characteristics						
⁵ Wide confidence	ce interval								
			ly adjusted for age and	two periods of analys	s (1993–1994 and 19	98–2000)			
			those lost not reported						
	ug susceptibility test	ting not reported							
⁹ Cases and con									
	• •	aire (i.e. may be som	e reliance on recall)						
Abbreviations: C	I, confidence interva	al; 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	11 848	2.93 (2.11 to 4.09)	LOW	
London 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	serious⁵	18040	12.52 (7.69 to 20.37)	VERY LOW
Data: 1995 to	Black (other)	multivariate analysis				serious⁵		3.29 (1.35 to 8.02)	VERY LOW
the third quarter of 2006	White	anarysis			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					serious⁵		0.68 (0.09 to 5.05)	VERY LOW
	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	serious⁵	38	1.1 (0.2 to 6.7)	VERY LOW
London	Black African	multivariate			indirectness			0.8 (0.1 to 7.2)	VERY LOW
(outbreak) Date: 2004	Black Caribbean						9.7 (2.6 to (35.4)	VERY LOW	
	Other							6.1 (1.6 to 23.3)	VERY LOW
	reference: White							-	-

		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	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-	Black African	multivariate analysis			indirectness			1.4 (0.7 to 2.6)	VERY LOW
outbreak) Date: 2004	Black Caribbean	unaryoro						1.6 (0.3 to 10.2)	VERY LOW
20101 2001	Other							2.5 (0.9 to 7.1)	VERY LOW
	reference: White							-	-
Patients with r	no previous tubercu	losis							
Conaty, 2004 England and	Indian subcontinent	Unmatched case- control with multivariate analysis very serious ^{1,2,10} no serious inconsistency indirectness no serious indirectness no serious indirectness no serious indirectness no serious imprecision no serious imprecision	8762	1.6 (1.2 to 2.1)	LOW				
Wales Data: 1993-4	Black African						1.7 (1.2 to 2.4)	LOW	
and 1998- 2000	Other					no serious imprecision		1.7 (1.2 to 2.4) 1.9 (1.3 to 2.8)	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	18005	3.11 (2.36 to 4.08)	LOW
Wales Data: 1999-	Black African	multivariate analysis				no serious imprecision		1.22 (1.00 to 1.50)	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					-		-	-

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 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

		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 col ³ Some data co ⁴ Multivariate ar ⁵ Wide confident 	ntrols unmatched llected by questionna nalysis used, but unc	tcome measurement b aire (i.e. may be some lear which confounder al: OR, odds ratio	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	Observational with multivariate	very serious ^{1,2,3}	serious ⁴	no serious indirectness	serious⁵	38	3.5 (1.6 to 7.7)	VERY LOW
(outbreak) Date: 2004	reference: no problem drug use	analysis						•	
	5	tcome measurement b							

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

Asylum seekers/refugee

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	serious⁵	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)	control with multivariate analysis						-	
² Cases and cor ³ Some data col	trols unmatched lected by questionna	come measurement b ire (i.e. may be some ear which confounder	reliance on recall)						
⁵ Wide confidence	•		s were controlled for						
Abbreviations: C	I, confidence interva	l; OR, odds ratio							

Imprisonment

		Quality assessmen	nt				Number of	Summary of findings	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Maguire, 2011	Imprisonment	Unmatched case-	very serious ^{1,2,6,7} no serious		no serious	serious⁵	18040	20.21 (6.75 to 60.56)	VERY 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			-	
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

	Study Factor	Quality assessme	ent		Number of	Summary of findings			
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
⁷ Some data	a collected by question	naire (i.e. may be som	ne reliance on recall)						
Abbreviation	ns: CI, confidence inter	val; 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 London (non-	ondon (non- utbreak) reference: not	Observational with multivariate	ultivariate	serious ⁴ no serious indirectness	no serious imprecision	129	2.0 (0.9 to 4.5)	VERY LOW	
outbreak) Date: 2004		analysis						-	
² Multivariate an ³ Analyses not re	alysis used, but uncl	come measurement b ear which confounders of variables recorded tly unrelated to key ch	s were controlled for and reported in popu	lation characteristics					

Abbreviations: CI, confidence interval; OR, odds ratio

.12.4 Rifampicin resistance

Age

		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 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-	•	tcome measurement b he characteristics of th							

Abbreviations: CI, confidence interval; OR, odds ratio

Sex

		Quality assessmen	nt				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	0.83 (0.64 to 1.08)	LOW
2008 England, Wales and Northern Ireland Data: 1998 and 2005	reference: male	multivariate analysis			indirectness	imprecision		-	
² Loss to follow- ³ Approach to d	-	ing not reported	linded nose lost not reported						

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
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	0	• •							

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	ıt				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 prog	nostic factor and out	come measurement b	linded						
² Loss to follow-u	up, its reasons and th	he characteristics of th	nose lost not reported						
³ Approach to dr	ug susceptibility test	ing not reported							
Abbreviations: C	I, confidence interva	I; 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
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	reference: born in the UK	analysis						-	
Data: 1998 and 2005									
Time in the UK									
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									
² Loss to follow- ³ Approach to dr									

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	Black African	analysis				no serious imprecision		0.98 (0.59 to 1.64)	LOW
Northern Ireland	Black other				serious ⁴		1.87 (0.69 to 5.06)	VERY LC	
Data: 1998 and 2005	: 1998 Indian,				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	t				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	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	losis							
French, 2008 England and	45-64 years		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					serious⁵		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						
	•	ear which confounder	s were controlled for						
	ntrols unmatched								
	•	univariate analyses w	vere not reported as n	nultivariate analyses					
⁵ Wide confider									
_	•	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	reference: male multivar	multivariate analysis			indirectness	imprecision		-	
Data: 1998 and 2005									

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	t				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 dr 	nostic factor and out rely on others' notes alysis used, but uncl ce interval	• ·	linded ias) s were controlled for						

Smear 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 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	Ilosis Unmatched case- control with multivariate analysis	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			inconsistency	indirectness	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	Quality	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)		
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 Data: 1998 and 2005	reference: extrapulmonary tuberculosis	analysis			indirection of the			-		
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										

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	llosis							
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	Unmatched case- control with multivariate analysis	control with multivariate	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	control with multivariate analysis		inconsistency	indirectness			-	

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 assessmen	t					Summary of findings		
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Adjusted OR (95% CI)	Quality	
⁵ Multivariate an	⁵ Multivariate analysis used, although it was unclear which confounders were accounted for									
⁶ A number of fa	actors reported in the	univariate analyses w	ere not reported as m							

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 is					-				
Patients with p	revious tuberculos	is									
Conaty, 2004 England and	London residence		n	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	reference: non- London residence							-			
		come measurement b									
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)											
	alysis used, althougi		adjusted for age and	two periods of analysi	s (1993-4 and 1998-2	000)					

Abbreviations: CI, confidence interval; OR, odds ratio

Place of birth

	Quality assessmen	t		Number of	Summary of findings			
Study Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients	Adjusted OR (95% CI)	Quality
Fime in the UK								
2008 (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

		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 years	multivariate analysis				serious ³		3.0 (1.1 to 8.5)	LOW
and 1998- 2000 In	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 r ³ Wide confiden ⁴ Loss to follow-	eported for a numbe ice interval -up, its reasons and t	tcome measurement to r of variables recorded the characteristics of the ting not reported	and reported in popu						
⁵ Approach to d ⁶ Multivariate ar	rug susceptibility tes nalysis used, althoug	ting not reported h effect estimates only	/ adjusted for age and	two periods of analys	sis (1993–1994 and 1	998–2000)			

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					serious ⁵		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	is							
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-	Other	anarysis				serious⁵		1.7 (0.4 to 6.9)	VERY LOW
2000	reference: white					-		-	-
Story, 2007 London	South Asian	Observational with very serious multivariate analysis	·····	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					serious ⁵		1.6 (0.3 to 10.2)	VERY LOW
	Other					serious ⁵		2.5 (0.9 to 7.1)	VERY LOW
	reference: White					-		-	-
Patients with r	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	analysis				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					-		-	-
² Multivariate an ³ Analyses not re ⁴ Unclear if loss ⁵ Wide confiden ⁶ Loss to follow- ⁷ Approach to di ⁸ Cases and con ⁹ Some data col ¹⁰ Multivariate a ¹¹ A number of f	alysis used, but uncl eported for a number to follow-up sufficien ce interval up, its reasons and t rug susceptibility test ntrols unmatched llected by questionna nalysis used, althoug	tly unrelated to key ch he characteristics of th ing not reported ire (i.e. may be some gh effect estimates onl e univariate analyses	s were controlled for and reported in popu- naracteristics hose lost not reported reliance on recall)	d two periods of analys	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 prog	nostic factor and out	come measurement b	linded								
² Multivariate an	alysis used, but uncl	ear which confounders	s were controlled for								
³ Analyses not re	eported for a number	nber of variables recorded and reported in population characteristics									
⁴ Unclear if loss	nclear 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 assessme	ent		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	ent						No of patients	
No of studies	Design	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisio n	Other considerations	AntiTB regimen	Quality
Response to 6RSI	4							
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 assessment 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	nt						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 mon	ths									
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 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 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 mo	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 assessment 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 S3H3	Response to S3H3Z3R3/ 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	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

3RSZH

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 mon	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 6SRZ	Н							
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

2EHRZ2/4EHR₂-

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 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 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	essment				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	s – recurrenc	e of drug-induced	hepatitis1 (number	of patients in whom	drug-induced h	epatitis1 recurred	following treatment	t 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 normalisa	ation of liver function	ns after withdrawal o	of all antitubercu	losis drugs, and a	t 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 ass	essment				Number of pati	ents		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n R→H→Z	Simultaneous reintroduction HRZ	Summary of findings	Qualit y
Adverse events	s – recurrenc	e of drug-induced	hepatitis ¹ (number	of patients in whom	drug-induced he	epatitis ¹ recurred	following treatment	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/l) 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 events	s – recurrenc	e of drug-induced	hepatitis ¹ (number	of patients in whom	drug-induced h	epatitis ¹ recurred	following treatment	t reintroduction)	
1 ²	RCT	serious ³	serious ⁴	no serious	serious⁵	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 increase	in serum total in serum AS		l; above pretreatment v with hepatitis A, B, C,	•	n anorexia, nause	a, vomiting, and	jaundice;		
5) improvement 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	
³ Unclear blindi	ng; unclear le	ength of follow-up							
	•	ip equal in each gro	oup						
⁵ GRADE rule of	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 ass	essment				Number of pati	ents		
Number of evaluations	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sequential reintroductio n	Simultaneous reintroduction	Summary of findings	Qualit y
Adverse events	s – recurrenc	e of drug-induced	hepatitis ^{1,2} (numbe	r of patients in whor	n drug-induced	hepatitis ^{1,2} recurre	ed following treatmo	ent 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	 n			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	ssment				Numb	er 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%)	
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%)	

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

	Quality asses	sment				Number of		
Evaluation	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	individuals	Summary of Findings	Quality
TB exposure episode	'descriptive case series' observational	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
TST conversion in HCWs evaluated every 6 months x 2.5 years	'descriptive case series' observational	Very Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision		Jan 1992 3.3% to June 1994 0.04%	VERY LOW
Cumulative number of exposure per month	'descriptive case series' observational	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

Abbreviations: HCW; health care workers, RCT randomized control trial; CI, confidence interval; OR, odds ratio

A.15.3 Chamie et al 2013. Household ventilation and tuberculosis transmission in Kampala, Uganda

Outcome of Interest	Quality asses	sment			Summary of findings Co-prevalent (n) vs no-co-			
	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) P = 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) p = 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 assessment						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% CI)	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

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

¹ Limitations in study design, unclear/lack of blinding, unclear exclusion of participants or lost to follow up

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	posure –non		No serious inconsistency	No serious inconsistency	Serious imprecision ²	Corridor 98±30 / 10±3 Bioch Lab (<10) /-	2	VERY LOW

Limitations in study design, unclear/lack of blinding, unclear how authors address confounders

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		due to low numb	nding, potential rec per of households p erculosis)			

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	ent						
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Summary	of Findings	Quality
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
Double blind placebo/control field trial	Serious ¹	No serious inconsistency	No serious indirectness	Serious imprecision ²			VERY LOW
					Skin or eye symptol	m	
					95/223 (43%) occur UV periods	red entirely in active	
					36/223 (16%) uncer occurred	tain when symptoms	
					· · · · · · · · · · · · · · · · · · ·	•	
	Design Double blind placebo/control field trial Double blind	DesignbiasDouble blind placebo/control field trialSerious1Double blind placebo/controlSerious1	DesignRisk of biasInconsistencyDouble blind placebo/control field trialSerious1No serious inconsistencyDouble blind placebo/controlSerious1No serious inconsistency	DesignRisk of biasInconsistencyIndirectnessDouble blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessDouble blind placebo/controlSerious1No serious inconsistencyNo serious indirectness	DesignRisk of biasInconsistencyIndirectnessImprecisionDouble blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious2Double blind placebo/controlSerious1No serious inconsistencyNo serious indirectnessSerious2Double blind placebo/controlSerious1No serious inconsistencyNo serious indirectnessSerious2	PesignRisk of biasInconsistencyIndirectnessImprecisionSummaryDouble blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious1Serious133611 staff and homeless residentsDouble blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious1Serious1Double blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious inconsistencyNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious indirectnessNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious indirectnessNo serious indirectnessSerious2Serious2Double blind placebo/control field trialSerious1No serious indirectnessSerious2Serious2Serious2Serious2Serious2Serious2Serious2Serious2Serious2Serious2Serious2Serious2Serio	Risk of bias Inconsistency Indirectness Imprecision Summary of Findings Double blind placebo/control field trial Serious ¹ No serious inconsistency No serious indirectness Serious indirectness Serious imprecision ² 33611 staff and homeless residents "inconclusive results" Double blind placebo/control field trial Serious ¹ No serious inconsistency 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> Skin or eye symptom Skin or eye symptom 95/223 (43%) occurred entirely in active UV periods 92/223 (42%) occurred entirely in placebo UV periods 92/223 (16%) uncertain when symptoms occurred 36/223 (16%) uncertain when symptoms occurred 36/223 (16%) uncertain when symptoms occurred

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	(average sizes of 31 students and class volume of 180,000 litters or 180 m ³) Ventilation rate: 60.2% of students time was spent		
						above the recommended threshold		
² Uncertainty		due to low numb	nding, lack on infor per of students part		iders and how the	ey were addressed, loss to follow up		

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
² Heterogene ³ Does not di ⁴ Small samp	utcome measurement bl eity in populations, rectly asses infectivity, a le size according to GR s: CI, confidence interva	and does not directly me ADE rule of thumb >30	00 events	tcome of interest					

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		observational serious ^{1,}	serious ^{1,} Serious ²	Serious ²		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 assessment							
Study	Study Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	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

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

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 LOW
Taiwan	Grade 3+	multivariate analysis	serious ^{1,2}		indirectness	imprecision ⁴	72	HR: 0.47 (0.33-0.66)	
	Grade 4+ Reference: Grade 1+					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

	Study Factor	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
	0	and outcome measureme out unclear which confour		d 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 Factor	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			d 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	
Bouti 2013 Morocco	Bilateral radiological lesions	Observational with multivariate analysis	very serious ^{1,2,}	no serious inconsistency	no serious indirectness	Serious ³	68	OR (95% Cl) 13.4 (1.8-55.6)	VERY LOW	
Horne 2010 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	
¹ Unclear if pro	ognostic factor a	and outcome measureme	ent 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; 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 very serious ^{1,2,3} no serious no serious Serious ³ inconsistency	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 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
² Multivariate ³ Sample size	analysis used, but and wide confide	nd outcome measureme t unclear which confour ince interval nterval; ns, no statistica	nders were controlle		, hazard ratio				

A.16.3 Risk factors for continued risk of infection – time to culture conversion

Age

		Quality assessmen	t							
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	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	t						
Study	Factor	Design	Risk of bias Inconsiste		Indirectness Imprecision		Number of patients	Summary of findings (95% Cl)	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 assess	ment						
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number of patients	Summary of findings (95% CI)	Quality
India		analysis							
	f prognostic factor and o								
² Multivaria	ite analysis used, but ur	nclear which confound	ders were controlled	d for					
³ Small sar	mple size and wide con	fidence interval							
Abbreviatio	ons: CI. confidence inte	rval: OR. odds ratio: H	R. hazard ratio						

Culture grade

		Quality assessmen	ıt					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 ⁴ Small samp	analysis used, but ent and sample het le size and wide co	0 ,	nders were controlle	d for					

Drug resistance

		Quality assessment						Summary of findings (95%	
							Number of	CI)	
Study	Factor	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	patients		Quality
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% Cl)	Quality	Importance
Radhakr	ishnan et al (as	sessed wit	h: clinical and bi	ochemical diag	nosis) follow ι	p adjusted for per	son years (follow up period 15 y	vears)		
1	studies	serious ¹	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 med	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) 	©000 VERY LOW	CRITICAL
Mori et a	I (case control)									
1	observational studies	very serious ⁴	no serious inconsistency	serious ⁵	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 e	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% CI)	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 porious			2020	N 7000 400 perticipente with		0000	CDITICAL
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, 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 ¹ Uncleai	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) 	⊙OOO VERY LOW	CRITICAL

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 asses	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.

¹ 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 Fountain			no serious inconsistency			· · · ·	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 	©©OO 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	5)								
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 	-	⊙000 VERY LOW	CRITICAL
Lee et al	(n=3788)					_				
1	observational studies	serious ¹³	no serious inconsistency	no serious indirectness	serious ¹²	none'	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	⊙000 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)					-				
1	observational studies	very serious ¹⁴	no serious inconsistency	no serious indirectness	no serious risk	none'	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

			Quality asse	ssment			No of patients	Effect		
lo of		Risk of				Other		Relative		
tudies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	Risk of Hepatotoxicity	(95% CI)	Quality	Importance
mith et	al (retrospectiv		n=9145)							
	observational studies	serious	no serious inconsistency	no serious indirectness	no serious	none	 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 51-65- 5.7 	 Age stratified adjusted odds ratio ≤ 35- (reference) 36-50- (0.5-16.0) 51-65- (1.0-33.7) 	©OOO VERY LOW	CRITICAL
analysi infecter group. appear since p docum were tr Populat patient Number	is thereby confo d people in the p The cases and to have been ta patients with high entation supplie acked for. ion does not exa	unding the s population w controls are aken to prev n random or d many of th actly match uberculosis g	study data. Also sin who receive preven taken from compa ent knowledge of p fasting blood gluc ne other diagnosis population of intern group had a docum	nce documented trive therapy. The trable population primary exposure ose recordings v such as notation est: Native Amer	TST ¹ reactors e data on risk fa is, however, co e(s) from influer vere listed as b n of alcohol abu ican people we	are more likely to b actors for developin ntrol patients were ncing case ascertai eing diabetic, howe se or admissions re re enrolled; these p	e offered chemoprophylaxis, the co g tuberculosis is more useful but st found to be more compliant to treat nment. Exposure to diabetes may f ver British guidelines require more elated to alcoholism which may not	a reactors however some non-reactors introl group is likely to overestimate the ill confounded by the presence of non- ment when compared to tuberculosis of have not been measured in a standard than just one isolated raised blood glue have been accurate. Unclear how long to three times that of the surrounding inknown infection status.	proportion TST ¹ reacto ases. No n and reliable cose level. participant	of latently ors in the ca neasures a fashion Chart 's histories
Patients treatme unclear Patients	s did not receive ent. Treatment c who provided fu s did not receive	ompletion w Inding for th the same le	vas poor across the is study evel of care as rule	e board with only es regarding mor	v 43.13 % of pa itoring adheren	tients completing 3 ice; some of the pa	months of therapy. rticipants were enrolled in a methad	ad of 6 months. Follow up did not inclu done maintenance therapy programme	where isor	iazid was
comple Treatme made. patient unclea	etion was fairly lo ent completion v 84% of patients s would be sympt r source of fundi	ow with 76.9 vas fairly lov on the mult otomatic, su ng	9% of patients com v with 64% of patie idrug therapy arm bclinical cases wo	pleting. ents completing t completed thera uld have been n	6 months of the py. Dose and le iissed.	rapy. Attempts to fine final strength of treatment with the second strength of treatment with the second strength of the second strengt o	nd the systematic differences betwe vas unclear and may vary. Method	not appear to continue beyond treatm een those who did or did not complete of diagnosis was based on the assump	treatment w otion that al	vere not I hepatotoxi
Popula	tion does not ex	actly match	population of inte	rest. Participants	included 36 wi	no were PPD ¹ nega	tive and therefore potentially not la	tently infected. These patients recieved	a shorter	duration of

			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
rifampi	icin and pyrazina	mide initially	y followed guidelin	es established fo	or HIV infected	patients and those	with active tuberculosis but dose of	f pyrazinamide was subsequently limite	ed based or	n 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 e	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)	©OOO 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)								
	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)		

Patients oid 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

⁴ 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	ssessed with: o	completion	of 6 months isor	iazid therapy) ((n=335)					
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.	-	©OOO VERY LOW	CRITICAL
Lobue e	t al (at risk for le	ower comp	letion rates of an	ti-tuberculosis	regimen) (3788	3)				
1	observational studies	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	Odds ratio Risk of lower completion rates Self-reported excess alcohol use • N- reference • Y- 0.1 Homelessness • N- reference • Y- 0.2	Odds ratio Risk of lower completion rates Self-reported excess alcohol use • N- reference • Y- (0.0-0.6) Homelessness • N- 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
							 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) 		
		lower com	pletion rates of a			,246)				
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 diagnosis 1.0-3.9 	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 coho	rt) (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) • ≥ 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 white- 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% Cl) 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)	©OOO 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% CI) Absolute	Quality	Importanc
	al (retrospectiv									
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 work or residence in a correctional facility in past year 	 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) 	©000 VERY LOW	CRITICAL
to incl. popular source Patient monito comple Multiva why al valid a Unclea isonia: clear t Partici hospit There v outcor consid	Irr recording bias tion was low at 3 of funding was us s did not receive ored with monthly etion was poor w riate analysis wa II significant facto nd reliable meth r if the type of pr zid participants w out unlikely to be on of risk factors out also reliant up ipants did not receive was no attempt to me was clear but lered to have con	befinition 35 patients inclear the same ley transamine with only 64% as used how ors could noi od of measu eventive the vas 52%, co valid or relia was clear b pon retrospe- seive the sai o adjust for i also reliant mpleted treat	of treatment comp evel of care as rule ase levels as well a 6 of patients comp rever the significan t have been includ urement was not u erapy used was inc mpletion rate in the able since all risk for but unlikely to be re- factive data. Due to me level of care ap sts at every visit wh the differing types upon retrospective atment if they took	letion was uncle as regarding mor as those at highe leting 6 months t factor of smoki ed. Definition of sed as patients cluded in multival ose treated with actors were self- eliable since this differences in the oart from interver hich may have ir of dosing schedu e data. Different 6-9 months of is	ar as patients w itoring were alt of therapy. The ng was not inclu- risk factors was vere assumed riate analysis. S rifampicin was reported at bas was a retrospe e methods of e inton studied as nproved adhere illes in the isoni methods of eva oniazid daily or	vere assumed to be ered during the stu- toxicity; later this v paper does not pro- uded in the multiva s unlikely to be vali to be compliant if the come patients were 61% (p=0.3). At lease the study and data valuating adherence different participal ence as patients kr azid group, or for t uluating adherence twice weekly withi	nts completing. This was a retrospe- e compliant if they kept monthly app ody due to changes in American The vas changed to only those at higher ovide the exact doses and lengths of riate analysis model as the alcohol d or reliable since alcohol use and s hey kept monthly appointments at th e taking 4 months of rifampicin, som ast six months of isoniazid was com- ta was retrieved from administrative ce on the different hospital sites trea- nts were taking different drugs in va- new they would be tested he patients taking rifabutin or rifamp was used depending on the age an n a 9-12 month period; or > 4 month	pracic Society Guidelines. Initially all pa risk. Follow up did not exceed treatme	tients over nt period. T del instead. er importar ompletion ou ndpoint ins ons. Patier f treatment ged >18 ye ths. Patier	35 were reatment It is unclean t factors.A ate of ctors was tead. tts on one completion pars were ts younger

therapy within 9 months. Outcome measure was not reliable as there was no guarantee that patients were taking their medication despite regular attendance at clinic to pick up their monthly supply of medications. ⁹ Definition of risk factors was clear but unlikely to be reliable since number of buses required to commute was discovered by asking the transportation agency rather than the patients themselves who may have another means of transport. Data was gathered by questionnaire. 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.

Appendix E: GRADE profiles

			Quality asse	ssment			No of patients	Effect		
No of		Risk of				Other		Relative	1	
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	patients	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months isoniazid	3 months placebo	Relative (95% CI)	Absolute	Quality	Importance
Incidend	e of active tube	rculosis (fo	llow-up median	5 years ¹ ; asses	sed with: Clini	cal diagnosis and	biomedical testing	3)				
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 asses	ssment			No of p	oatients	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months isoniazid	6 months placebo	Relative (95% CI)	Absolute	Quality	Importance
ncidenc	e of active tube	rculosis (fo	llow-up median	5 years ¹ ; asses	sed with: clini	cal and biomedica	I diagnosis)					
	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
unclear		omparable f	v up was complete or 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	atients	Eff	ect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months Isoniazid	12 months placebo	Relative (95% Cl)	Absolute	Quality	Importance
Incidenc	e of active TB (follow-up m	nedian 5 years ¹ ; a	assessed with:	Clinical and bi	omedical diagnos	is)					
	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

² Unclear is groups were comparable for availability of outcome data 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	Eff	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months isoniazid	No treatment	Relative (95% CI)	Absolute	Quality	Importance
Incidenc	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

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 asse	ssment			No of p	oatients	Eff	ect		
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month isoniazid and rifampicin	No treatment	Relative (95% Cl)	Absolute	Quality	Importance
e of active tube	erculosis (fo	ollow-up 8 years;	assessed with:	clinical and b	iochemical diagno	osis)					
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
;	e of active tube randomised	Designbiase of active tuberculosis (for randomisedvery	DesignRisk of biasInconsistencye of active tuberculosis (follow-up 8 years; randomisedveryno serious	DesignbiasInconsistencyIndirectnesse of active tuberculosis (follow-up 8 years; assessed with randomisedveryno seriousno serious	Risk of bias Inconsistency Indirectness Imprecision e of active tuberculosis (follow-up 8 years; assessed with: clinical and b randomised very no serious no serious no serious serious ¹	Risk of bias Inconsistency Indirectness Imprecision Other considerations e of active tuberculosis (follow-up 8 years; assessed with: clinical and biochemical diagnor randomised very no serious no serious serious ¹ none ²	Risk of bias Inconsistency Indirectness Imprecision Other considerations 1 month isoniazid and rifampicin e of active tuberculosis (follow-up 8 years; assessed with: clinical and biochemical diagnosis) randomised no serious serious ¹ none ² 9/83	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerations1 month isoniazid and rifampicinNo treatmente of active tuberculosis (follow-up 8 years; assessed with: randomised trialsvery seriousno serious inconsistencyno serious indirectnessserious ¹ none ² 9/83 (10.8%)17/85 (20%)	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerations1 month isoniazid and rifampicinNo treatmentRelative (95% CI)e of active tuberculosis (follow-up 8 years; assessed with: randomised trialsno serious inconsistencyno serious indirectnessserious ¹ none ² 9/83 (10.8%)17/85 (20%)-	Risk of biasInconsistencyIndirectnessImprecisionOther considerations1 month isoniazid and rfampicinNo treatmentRelative (95% Cl)Absolutee of active tuberculosis (follow-up 8 years; assessed with: randomised trialsvery seriousno serious inconsistencyno serious 	Risk of bias Inconsistency Indirectness Imprecision Other considerations 1 month isoniazid and rifampicin No treatment Relative (95% Cl) Absolute Quality e of active tuberculosis (follow-up 8 years; assessed with: randomised trials very serious no serious inconsistency no serious indirectness serious ¹ none ² 9/83 (10.8%) 17/85 (20%) - 200 fewer per 1000 (from 200 fewer to 200 0\OOOV VERY LOW

Author(s):

Date: 2014-03-04

Question: Should 3 months isoniazid and rifampicin vs no treatment be used for latent tuberculosis?

Settings:

Bibliography:

			Quality asse	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
Incidend	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)	⊙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 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 asses	ssment			No of p	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
Incidend	ce of active tube	rculosis (fo	llow-up 8 years;	assessed with:	clinical and b	iochemical diagno	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

opriate 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 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 asses	ssment			No of p	oatients	Ef	iect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	36 months isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
Incidend	e of active tube	rculosis (fo	ollow-up 3 years ¹	; assessed with	: clinical and	biochemical diagr	osis)					
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	y (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
¹ No follo ² event r	ow up beyond 3 y ates less than 30	vear treatme 0	nt period							,		

Date: 2014-03-04 Question: Should 4 months rifampicin vs 6 months isoniazid be used for latent tuberculosis? Settings: Bibliography:

			Quality asse	ssment			No of p	patients	Eff	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 discontinua	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 treat	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	patients	Eft	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
Incidence	e of active tube	rculosis (fo	llow-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	Eff	iect		
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
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-ι	ıp 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
Inciden	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	er 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

			· · · · · · · · · · · · · · · · · · ·								
	Risk of bias	Inconsistency	Indirectness	Imprecision		3 months rifampicin and isoniazid	6 months isoniazid	Relative (95% CI)	Absolute	Quality	Importance
ity (follow-up	3-6 years;	assessed with:	Grade 3 or 4 ra	ised aminotra	nsferases)						
	- 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
ity do Is	ign y (follow-up omised	ign bias y (follow-up 3-6 years; pomised very serious ¹	ignbiasInconsistencyy (follow-up 3-6 years; assessed with: pmisedon serious serious1no serious inconsistency	ignbiasInconsistencyIndirectnessy (follow-up 3-6 years; assessed with:Grade 3 or 4 raomisedveryno seriousno seriousserious ¹ inconsistencyindirectness	ignbiasInconsistencyIndirectnessImprecisiony (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotranomisedveryno seriousno seriousserious²inconsistencyindirectnessserious²	ignbiasInconsistencyIndirectnessImprecisionconsiderationsy (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotransferases)omisedvery serious1no serious inconsistencyno serious indirectnessserious2None	ignbiasInconsistencyIndirectnessImprecisionconsiderationsisoniazidy (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotransferases;omisedvery serious1no serious inconsistencyno serious indirectnessserious2None8/329 (2.4%)3	ignbiasInconsistencyIndirectnessImprecisionconsiderationsisoniazidisoniazidy (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotransferases)pmisedvery serious1no serious inconsistencyno serious indirectnessserious2None8/329 (2.4%)318/327 (5.5%)30%	ignbiasInconsistencyIndirectnessImprecisionconsiderationsisoniazidisoniazid(95% Cl)y (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotransferases)pmisedvery serious1no serious inconsistencyno serious indirectnessserious2None8/329 (2.4%)318/327 (5.5%)3-0%0%18/327 (5.5%)30%	ignbiasInconsistencyIndirectnessImprecisionconsiderationsisoniazidisoniazid(95% Cl)Absolutey (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotransferases)pmisedvery serious1no serious inconsistencyno serious indirectnessserious2None8/329 (2.4%)318/327 (5.5%)3-55 fewer per 1000 	ignbiasInconsistencyIndirectnessImprecisionconsiderationsisoniazidisoniazid(95% CI)AbsoluteQualityy (follow-up 3-6 years; assessed with:Grade 3 or 4 raised aminotraised am

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 of	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
Incidend	ce of active tube	erculosis (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	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	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	ip 3-6 years	; assessed with:	grade 3 or 4 ra	ised aminotra	nsferases)				, i		
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 J	oatients	Eff	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	nt completion (f	follow-up m	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)	0000 VERY LOW	CRITICAL

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 asse	ssment			No of p	oatients	Eff	fect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months rifabutin 600 mg and isoniazid	6 months isoniazid	Relative (95% Cl)	Absolute	Quality	Importance
Freatme	nt completion (follow-up m	nean 17-19 month	s; assessed wi	th: adherence	to drug regimen >	•80%)					
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	None	13/14 (92.9%)	10/14 (71.4%)	-	714 fewer per 1000 (from 714	⊙OOO VERY LOW	CRITICAL

were blinded to treatment group. Unclear if groups were comparable for treatment completion. No precise definition of outcome. 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)	©©OO LOW	CRITICAL
Hepatot	oxicity (follow-u		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
Cutaneo	ous toxicity (follo	ow-up 5 yea	ars; assessed wi	th: Rash, prurit	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:

			Quality asse	essment			No of	oatients	Ef	ifect		
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
			ollow-up 33 months									
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	ion of therapy (follow-up 3	3 months; assesse	ed with: patients	who completed	I therapy)						
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 moi	nths; 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%		-		
Hepatoto	oxicity (follow-u	p 33 month	is months; assess	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 asse	essment			No of J	patients	Ef	ifect		
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	ed 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 asses	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	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%		-		

¹ results were taken from 3 months into the trial; no data from beyond this point. Unclear if groups were comparable for treatment completion or availability of outcome data. 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	Ē	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months isoniazid	No treatment	Relative (95% Cl)	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	800	S. Bilable in evidence ta	bla								

number adjusted for person-years available in evidence table

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 pati	ents	Ef	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	an 36-37 mo	nths; assessed with	th: Number of de	eaths)							
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	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:

No of studies Des		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	12 months isoniazid	12 months placebo	Relative (95% Cl)	Absolute	Quality	Importance
ncidence of	f active tuberc	ulosis (asse	essed with: broad r	eview of history a	and chest xray)							
ran tria		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%		-		

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	patients	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
Incidenc	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 in rate ratio (1.48 (0.55 Adjusted in rate ratio (per protoc 1.57 (0.50 36 months n=132 Adjusted in	ncidence 95% Cl ²) , 3.96) ncidence 95% Cl ²), ol analysis , 4.9) s isoniazid,	0000 LOW	CRITICAL

			Quality asse	essment			No of p	patients	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) (95% Cl ²)		

² event number less than 300

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		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-9 months of isoniazid therapy	No treatment	Relative (95% Cl)	Absolute	Quality	Importance
Incidence	e of active tuber	culosis (foll	ow-up 10 years; as	sessed with: clin	ical or bacterio	logical diagnosis)						
1	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%		-		
Mortality	(follow-up 10 ye	ears; assess	ed with: number of	f deaths)								
1	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%		-		
random	isation by date of	birth was us	ed, unclear if adequa	ate concealment. I	Patients in the tre	eatment grouo were y	ounger. Uncle	ar if compariso	on groups re	ecieved the sam	ne care apa	art 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% CI, 0.3-26.8; p=0.66 i.e. non significant	©OOO VERY LOW	CRITICAL

Quality assessment						No of patients			Effect		1 1	
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% CI)	Quality	Importance
Mortality	(follow-up at le	east 2 years	; assessed with: n	umber 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%)	-	16 fewer per 1000 (from 16 fewer to 16 fewer)	⊙OOO VERY LOW	CRITICAL
								0%	-	-		
Hepaxici	ity (follow-up at	least 2 year	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%)	-	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