1 Appendix D: Evidence Tables – Diagnosis of active TB RQ C, D, E, G & H

1.1 RQ C Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in adults with suspected respiratory TB?

1.1.1 SYSTEMATIC REVIEWS

1.1.1.1 Dinnes et al, 2007

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? no – allows for some case-control; where possible, the reviewer has removed these data Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? review criteria included both adults and children, and data relating to final inclusions was not provided Is there concern that the index test, its conduct, or interpretation differ from the review question? no Is there concern that the target condition as defined by the reference standard does not match the review question? no Study quality – phage-based tests

Study	Reference standard	Index blinded	Design	Reference standard blinded	Representative sample

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**					
	Albert, 2002	culture + X-ray + clinical + Tx response	yes	?	yes	yes
	Albay, 2003	culture alone	?	?	?	yes
	Alcaide, 2003	culture alone	?	?	?	no
	Cavusoglu, 2002	culture + X-ray + clinical + Tx response	?	retrospective	?	?
	Muzaffar, 2002	culture alone	?	?	?	yes
	Study quality – commercial antituberculosis antibody tests					
	Study	Reference standard	Index blinded	Design	Reference standard blinded	Representative sample
	Al-Zahrani, 2000	culture + clinical + Tx response	yes	prospective	yes	yes
	Chander, 1996	clinical	?	?	?	yes
	Charpin, 1990	culture alone	?	prospective	?	yes
	Luh, 1996	culture + histology + X-ray + clinical + Tx response	?	?	?	yes
	Somi, 1999	culture + clinical + Tx response	?	?	yes	yes
Number of patients	Phage-based tests					

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)
	5 studies
	Antituberculosis antibody tests 5 studies, 8 evaluations 1571 participants
Patient characteristics	Adults or children Studies of adults or children with any form of active TB were eligible for inclusion Patients with any co-morbidity (including HIV infection) were included Studies exclusively conducted in patients with non-tuberculous mycobacterial infection were excluded on the basis that these infections are rare and inclusion of them was outwith the resource constraints of the review
	Phage-based tests Disease prevalence in sample (mean (range)) = 0.32 (0.14 to 0.52) Sample types: sputum (4), respiratory (1)
	Antituberculosis antibody tests Disease prevalence in sample (mean (range)) = 0.21 (0.09 to 0.45) Sample types: respiratory (2), serum (14), urine (1)
Index test	For most tests, studies with more than one specimen per patient were included only where accuracy data could be extracted on a per patient as opposed to a per specimen basis or where the difference in the number of specimens compared with the number of patients was less than 10% Studies of specimens ‘spiked’ with mycobacteria were excluded as they did not use clinical samples Any study that compared a rapid test for detection of active TB with a reference standard was included; ‘rapid’ tests were defined as those tests for which a result could be obtained in less than the time taken for standard culture (on solid or liquid media) Studies evaluating tests used for strain typing of TB were excluded, as these are more of an epidemiological tool than tests for use in routine clinical practice Studies evaluating drug susceptibility tests were also excluded, as they were beyond the scope of this project
	Phage-based tests FASTPlaqueTB = 4 evaluations PhageTek MB = 1 evaluation

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**		
	Study	Test	Cut-off used to define test positivity
	Albert, 2002	FASTPlaqueTB	20
	Albay, 2003	FASTPlaqueTB	20
	Alcaide, 2003	PhageTek MB	20
	Cavusoglu, 2002	FASTPlaqueTB	20
	Muzaffar, 2002	FASTPlaqueTB	manufacturer's imstructions
	Commercial antituberculosis antibody tests		
	Study	Test	Cut-off used to define test positivity
	Al-Zahrani, 2000	Detect TB	1 1.6
	Chander, 1996	EIA Pathozyme TB Complex	-
	Charpin, 1990	Anda TB IgG	0.5
		Anda TB IgM	0.43
	Luh, 1996	Anda TB IgG	200
		Anda TB IgM	-
	Somi, 1999	Mycodot	-
Reference standard	Reference standards for tests for detecting active tuberculosis can be defined as follows:		

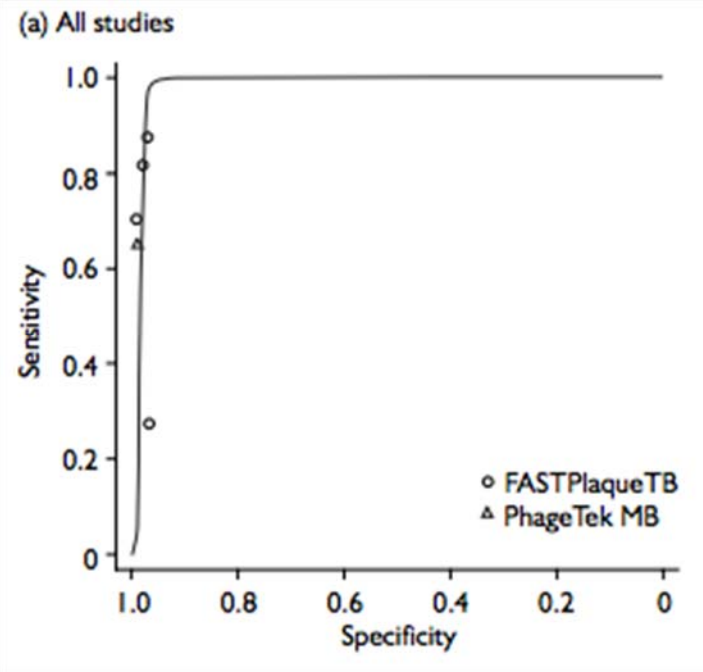
Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**
	A: culture and/or microscopy smear test B: very high clinical suspicion of TB, with or without a response to treatment C: clinical suspicion of TB, but it is not certain one way or the other Studies may use one or more of these reference tests either alone or in combination with each other as a reference strategy Strategy A alone, although previously considered good practice is now recognised as an inadequate reference standard, especially in smear-negative patients; although culture specificity is high, sensitivity is much poorer Clinical diagnosis, although improving sensitivity, has a relatively low specificity for tuberculosis diagnosis
	Phage-based tests Culture alone was used as the reference strategy in 60% (n = 3) of the studies (two FastPlaque and one PhageTek); the remaining two studies combined culture with clinical TB diagnosis, treatment response and X-ray
	Antituberculosis antibody tests Culture alone was used as the reference strategy in five of the 21 evaluations (24%); culture was combined with clinical diagnosis with or without additional tests in eight studies (38%) and clinical diagnosis alone used in three studies
Outcomes measures and effect size	Diagnostic test accuracy – phage-based tests

Study	Test	n	TP	FN	TN	FP	Sensitivity	Specificity
Albert, 2002	FASTPlaqueTB	781	78	33	663	16	70.27	97.64
smear positive	FASTPlaqueTB	87	57	11	17	2	83.82	89.47
smear negative	FASTPlaqueTB	694	21	22	646	5	48.84	99.23
Albay, 2003	FASTPlaqueTB	192	56	8	124	4	87.5	96.88
Alcaide, 2003	PhageTek MB	1483	87	47	1332	17	64.93	98.74
Cavusoglu, 2002	FASTPlaqueTB	63	9	24	29	1	27.27	96.67
Muzaffar, 2002	FASTPlaqueTB	514	200	45	263	6	81.63	97.77
smear positive	FASTPlaqueTB	192	153	22	15	2	87.43	88.24

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)

smear negative	FASTPlaqueTB	322	47	23	248	4	67.14	98.41

ROC plot:



Pooled sensitivity = 68.7%
Pooled specificity = 98.0%
Diagnostic odds ratio (95% CI) = 926.88 (5.34 to 160998.45)

Diagnostic test accuracy – commercial antituberculosis antibody tests

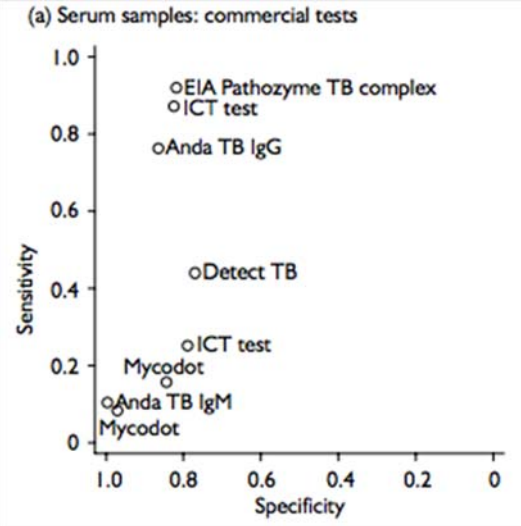
Study	Test	n	TP	FN	TN	FP	Sensitivity	Specificity
Al-Zahrani, 2000	Detect TB (serum) (cut-off: 1)	421	21	27	287	96	43.75	74.93

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)								
	Al-Zahrani, 2000	Detect TB (serum) (cut-off: 1.6)	421	16	32	325	47	33.33	87.37
	Chander, 1996	EIA Pathozyme TB complex (serum)	130	34	3	76	17	91.89	81.72
	Charpin, 1990	Anda TB IgG (respiratory)	83	12	13	41	17	48	70.69
	Charpin, 1990	Anda TB IgM (serum)	83	19	6	57	1	76	98.28
	Luh, 1996	Anda TB IgG (serum)	593	112	35	385	61	76.19	86.32
	Luh, 1996	Anda TB IgM (serum)	593	15	132	444	2	10.20	99.55
	McConkey, 2002	ICT test (serum)	73	4	12	45	12	25	78.95
	McConkey, 2002	ICT test (serum)	159	74	11	61	13	87.06	82.43
	Somi, 1999	Mycodot (serum) (onsite testing)	185	13	70	86	16	15.66	84.31
	smear positive	Mycodot (serum) (onsite testing)	146	10	29	0	0	25.64	-
	smear negative	Mycodot (serum) (onsite testing)	39	3	41	86	16	6.82	84.31

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)

HIV-positive	Mycodot (serum) (onsite testing)	94	4	52	37	1	7.14	97.37
HIV-negative	Mycodot (serum) (onsite testing)	91	9	18	49	15	33.33	76.56
Somi, 1999	Mycodot (serum) (repeat testing by manufacturer)	185	7	76	99	3	8.43	97.06

ROC plots:



Pooled sensitivity = 87.9%
Pooled specificity = 50.0%
Diagnostic odds ratio (95% CI) = 7.30 (1.95 to 27.24)

Source of funding	NIHR Health Technology Assessment Programme
Comments	Meta-analysis for commercial NAATs not extracted as superceded by more recent systematic review (Ling et al, 2008) –

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**
	references included in this review but not included in Ling et al (2008) were identified and extracted
Abbreviations: FN, false negative; FP, false positive; NAAT, nucleic acid amplification test; TN, true negative; TP, true positive; TST, tuberculin skin test	

1.1.1.2 Ling et al, 2008

Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? 1 of the 125 included evaluations was conducted using a case-control design; reviewer excluded case-control data Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Study quality Characteristic — Number of evaluations (%) Number of evaluations — 125 (100) Study direction: — 108 (86) • prospective — 9 (7) • retrospective — 8 (6) • both Study design: — 124 (99) • case-control

Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536	
	Recruitment:	43 (34)
	• consecutive	2 (2)
	• random	24 (19)
	• convenient	5 (4)
	• consecutive and convenient	51 (41)
	• not reported	
	Verification of whole sample by reference standard?	123 (98)
	• yes	
	Blinding:	8 (6)
	• double-blind	7 (6)
	• NAAT blinded to reference standard	5 (4)
	• reference standard blinded to NAAT	2 (2)
	• none	123 (98)
	• not reported	
	Reference standard:	105 (84)
	• culture	3 (2)
	• clinical data	17 (14)
	• culture and clinical data	

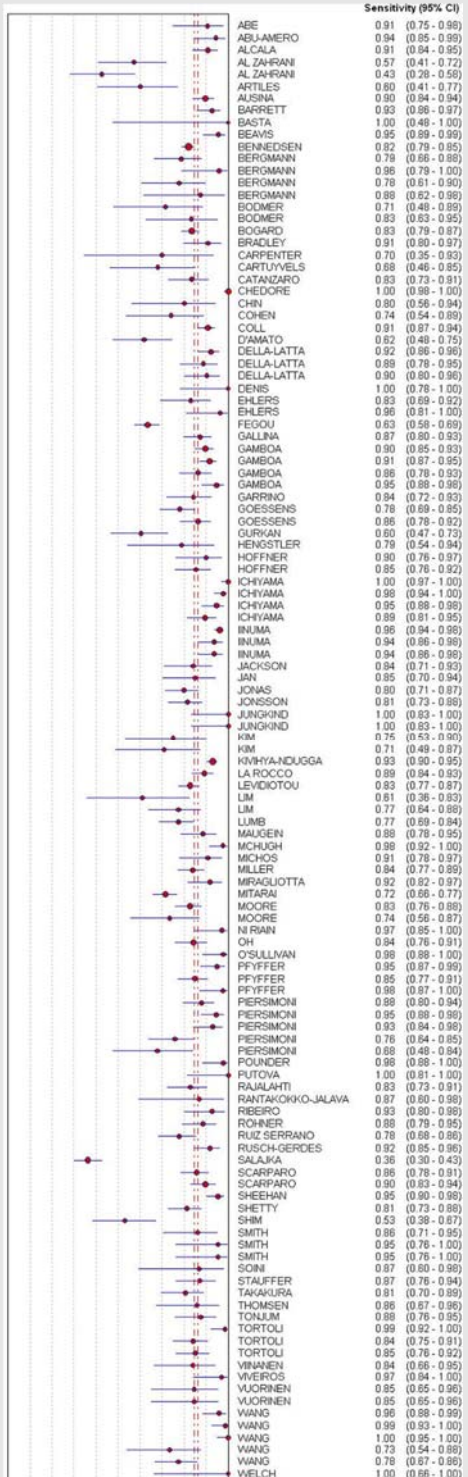
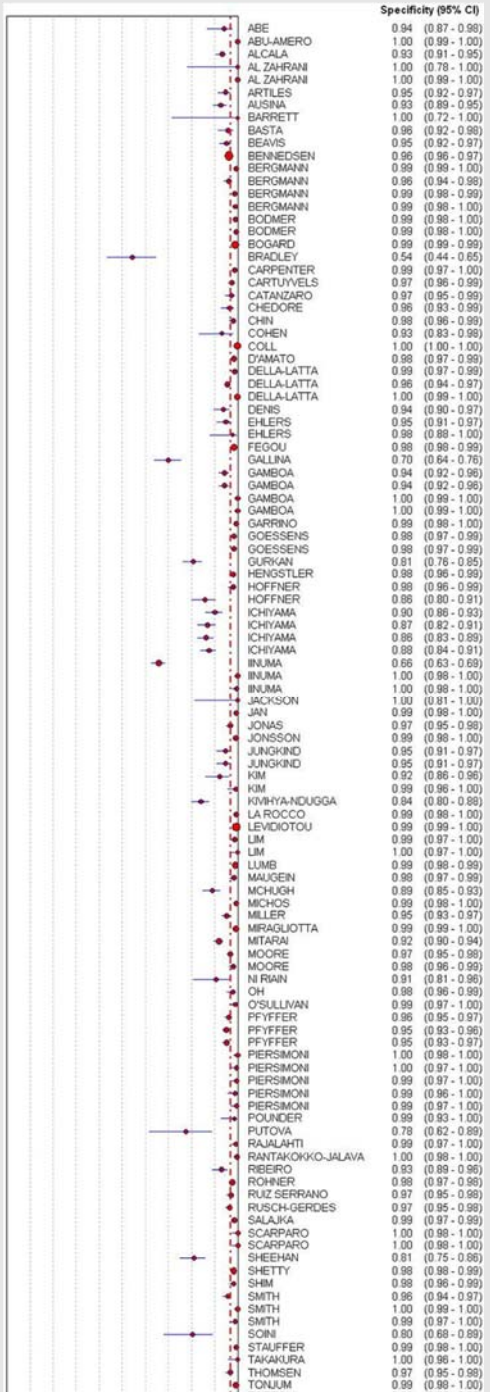
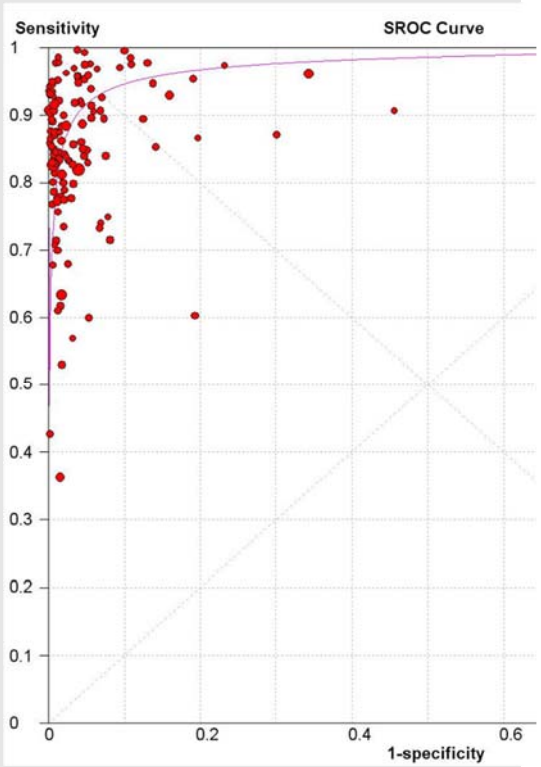
Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536
	Domain 1: Patient selection Could the selection of patients have introduced bias? risk of bias low • Was a consecutive or random sample of patients enrolled? reporting was poor (41% of evaluations did not report), but amongst those that reported approximately 68% used a consecutive or random sampling method • Was a case-control design avoided? 1 of 125 evaluations was conducted using a case-control design • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? risk of bias low • Were the index test results interpreted without knowledge of the results of the reference standard? 67% of evaluations blinded the interpretation of index test results to the results of the reference standard • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? risk of bias low • Is the reference standard likely to correctly classify the target condition? yes, although 3 of the 125 evaluations used clinical data alone • Were the reference standard results interpreted without knowledge of the results of the index test? 56% of evaluations blinded the interpretation of index test results to the results of the reference standard Is there concern that the target condition as defined by the reference standard does not match the review

Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536
	question? no Domain 4: Flow and timing Could the patient flow have introduced bias? risk of bias moderate to low • Was there an appropriate interval between index test(s) and reference standard? unclear • Did all patients receive a reference standard? 98% of evaluations used the reference standard for verification in all patients • Did patients receive the same reference standard? the reference standard varied from study to study, although it is unclear from the information provided if the reference standard used was consistent within trials • Were all patients included in the analysis? unclear
Number of patients	125 evaluations, 105 papers Mean sample size (range) = 715 (57 to 7539)
Patient characteristics	Inclusion Respiratory specimens for diagnosing pulmonary TB Minimum sample size of 50 to avoid selection bias Among included evaluations Ninety-five (76%) evaluations tested respiratory specimens, while 30 (24%) evaluations only used sputum specimens
Index test	Inclusion Commercially available NAATs Among included evaluations

NAAT	Method	Number of evaluations (%)
Amplified M. Tuberculosis Direct Test	Transcription-mediated amplification of rRNA	31 (25)
Enhanced M. Tuberculosis Direct Test	Transcription-mediated amplification of rRNA	9 (7)
Amplicor MTB	PCR amplification of 16s rRNA	34 (27)
Cobas Amplicor	PCR amplification of 16s rRNA	18 (14)
LCx (discontinued)	Ligase chain reaction amplification of 38kDa protein	18 (14)
BD-ProbeTec Direct	Strand displacement amplification of IS6110 and 16s rRNA	6 (5)

Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536
	BD-ProbeTec Direct-ET — Strand displacement amplification of IS6110 and 16s rRNA — 9 (7) Loop-mediated Isothermal Amplification — Isothermal amplification + visual readout with UV fluorescence — 0 (0)
Reference standard	Inclusion Culture Among included evaluations Reference standard — Number of evaluations (%) Culture — 105 (84) Clinical data — 3 (2) Culture and clinical data — 17 (14)

Bibliographic reference	Ling DI, Flores LL, Riley LW and Pai M (2008) Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression. PLOS One 3(2): e1536

Outcomes measures and effect size	Diagnostic test accuracy Pooled sensitivity of commercial NAATs (95% CI)a = 85% (84.7% to 86%) P value for heterogeneity < 0.001  Specificity of commercial NAATs (95% CI)a = 96.8% (96.7% to 96.9%) P value for heterogeneity < 0.001  ROC plot:  Positive likelihood ratio (95% CI) = 32.74 (26.01 to 41.22) Negative likelihood ratio (95% CI) = 0.14 (0.12 to 0.16) Diagnostic odds ratio (95% CI) = 268.88 (212.07 to 340.90) Amplicor Positive likelihood ratio (95% CI) = 26.04 (17.04 to 39.80) Negative likelihood ratio (95% CI) = 0.15 (0.11 to 0.22) Diagnostic odds ratio (95% CI) = 174.92 (120.77 to 253.35) Cobas Amplicor Positive likelihood ratio (95% CI) = 58.59 (37.77 to 90.86) Negative likelihood ratio (95% CI) = 0.17 (0.13 to 0.22)

Source of funding	The authors have no support or funding to report
Comments	
a 0.5 added to all cells of studies with 0 values Abbreviations: CI, confidence interval; NAAT, nucleic acid amplification test	

1.1.1.3 Pinto et al, 2013

Bibliographic reference	**Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? no, a number of case-control studies were included (2 out of 13); reviewer excluded this data Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? review criteria included those over 15 years of age, and data relating to final inclusions was not provided so it is unclear how many under-18s were ultimately included Is there concern that the index test, its conduct, or interpretation differ from the review question? no Is there concern that the target condition as defined by the reference standard does not match the review question? no

Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94									
	Study	Case-control design avoided?	Representative sample?	Acceptable reference standard?	Acceptable delay between the index and reference tests	Partial verification avoided?	Reference standard results blinded?	Index test results blinded?	Relevant clinical information available?	Uninterpretable results reported?	Withdrawals explained?
	Bock, 1996	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
	El-Solh, 1997	yes	yes	yes	yes	no	yes	yes	yes	no	yes
	El-Solh, 1999	yes	yes	yes	yes	no	yes	yes	yes	yes	yes
	Moran, 2009	yes	no	yes	yes	no	yes	unclear	yes	yes	no
	Mylotte, 1997	yes	yes	yes	yes	no	yes	yes	yes	yes	no
	Solari, 2008	yes	no	yes	yes	no	yes	unclear	yes	yes	no
	Smear-negative only										
	Lagrange-Xelot, 2010	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
	Soto, 2008	yes	no	yes	yes	no	yes	unclear	yes	yes	yes
	Soto, 2011	yes	yes	yes	yes	no	yes	yes	yes	unclear	yes
	Wisnivesky, 2000	no	no	yes	yes	no	yes	unclear	yes	yes	yes

Bibliographic reference	**Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94**

							r			
	Wisnivesky, 2005	yes	no	yes	yes	no	yes	yes	yes	yes	yes
	HIV-negative only									
	Rakoczy, 2008	no	no	yes	yes	no	yes	yes	yes	yes	yes

Number of patients

12 included studies

Study	Total included	Number of patients with possible tuberculosis (%)
Bock, 1996	378	295 (78)
El-Solh, 1997	286	286 (100)
El-Solh, 1999	119	119 (100)
Moran, 2009	2786	2535 (91)
Mylotte, 1997	220	220 (100)
Solari, 2008	486	345 (71)
Smear-negative only		
Lagrange-Xelot, 2010	134	134 (100)
Soto, 2008	262	262 (100)
Soto, 2011	684	663 (97)
Wisnivesky, 2005	516	516 (100)

Bibliographic reference	**Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94**
Patient characteristics	Inclusion Patients with possible tuberculosis 15 years or older Minimum of 10 patients with tuberculosis Sites of interest: pulmonary parenchyma, pleura and intrathoracic lymph nodes Miliary tuberculosis included if the disease involved either pulmonary parenchyma or multiple sites, one of which was the lung Exclusion Patients with pneumoconiosis, malignancies (both haematological and solid organ), immune-mediated inflammatory disease and patients on haemodialysis Asymptomatic contacts of tuberculosis patients Among included evaluations

Study	Inclusion criteria
Bock, 1996	Active tuberculosis in the differential diagnosis with smears and cultures ordered, or HIV-positive with abnormal chest X-ray
El-Solh, 1997	All isolated patients, based on symptoms, prior exposure to tuberculosis, HIV status, medical and social risk factors, and radiographic findings
El-Solh, 1999	All patients in whom smear and culture were requested
Moran, 2009	Admission diagnosis of pneumonia or suspected tuberculosis
Mylotte, 1997	All patients in whom smear and culture were requested
Solari, 2008	Productive cough for >1 week, or cough of any duration plus fever for >3 weeks, weight loss

Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94	
		of >3 Kg in the previous month, night sweats, haemoptyisis or differential diagnosis of pulmonary tuberculosis
	Smear-negative only	
	Lagrange-Xelot, 2010	Suspected tuberculosis
	Soto, 2008	Cough >1 week and 1 or more of the following: fever, weight loss of >4 kg in 1 month, breathlessness, or constitutional symptoms (such as malaise, or hypoxia for >2 months)
	Soto, 2011	Cough >2 weeks and 1 or more of the following: fever, weight loss or breathlessness
	Wisnivesky, 2005	Patients admitted and isolated because of suspicion of pulmonary tuberculosis
Index test	Inclusion Radiographic scoring system, defined as a system that assigned numerical weights to specific features of chest radiographs consistent with pulmonary tuberculosis (such as cavitary lesions), with or without the presence of clinical findings Among included evaluations No study used a scoring system based exclusively on radiographic criteria All included studies involved scoring systems that combined clinical and radiographic criteria Among included evaluations	
	Study	Details of chest radiograph scoring system
	Bock, 1996	chest X-ray with upper lobe infiltrate chest X-ray with cavity contact with someone with active tuberculosis self-report of positive tuberculin skin test in the past

Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94	
	El-Solh, 1997	self-report of isoniazid preventive therapy in the past Test-positive: any of 1 to 3 or 4 (in the absence of 5) Test-negative: • upper zone disease and fever absent • 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 apical infiltrate cavitation
	Moran, 2009	immigrant weight loss positive tuberculosis history homeless incarcerated
	Mylotte, 1997	Test-positive: any of 1 to 7 AFB-positive smear – scores 3 localised chest X-ray change – scores 2

Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94	
		incarcerated – scores 2
		history of weight loss – scores 1
		Test-positive: score of 3 or above
		age <35 years – scores 0
		age 35-60 years – scores -1
		age 60 or over – scores -2
		weight loss – scores 5
	Solari, 2008	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
	Smear-negative only	
		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
	Lagrange-Xelot, 2010	temperature <38.5°C – scores 0
		temperature 38.5-39°C – scores 3
		temperature >39°C – scores 6

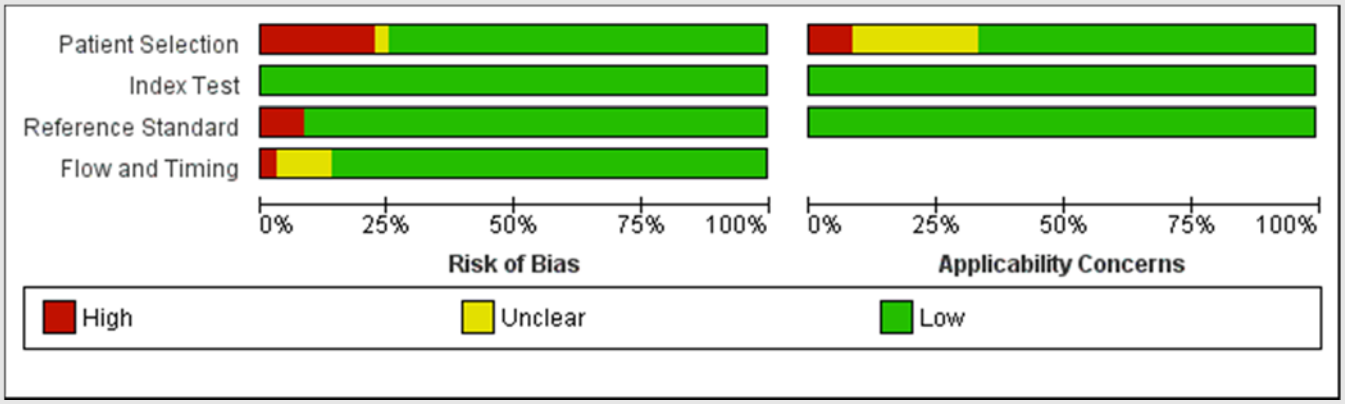
Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94	
	Soto, 2008	crackles on physical examination – scores -3 upper lobe disease on chest x-ray – scores 6 Test-positive: score of 1 or above haemoptysis – scores 2 weight loss – scores 1 age >45 years – scores -1 expectoration – scores -1 apical infiltrate – scores 3 miliary infiltrate – scores 4 score <0 = low probability score >4 = high probability
	Soto, 2011	haemoptysis – scores 2 weight loss – scores 1 age >45 years – scores -1 expectoration – scores -1 apical infiltrate – scores 3 miliary infiltrate – scores 4 score ≥5 = high probability
	Wisnivesky, 2005	tuberculosis risk factors or chronic symptoms – scores 4

Bibliographic reference	**Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94**		
	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		
Reference standard	Liquid or solid culture		
Outcomes measures and effect size	Diagnostic test accuracy		
	Study	Sensitivity (95% CI)	Specificity (95% CI)
	Bock, 1996	81 (66 to 91)	62 (56 to 68)
	El-Solh, 1997	100 (78 to 100)	50 (44 to 57)
	El-Solh, 1999	100 (91 to 100)	72 (65 to 77)
	Moran, 2009	96 (91 to 99)	49 (47 to 51)
	Mylotte, 1997	88 (47 to 100)	63.2 (56 to 70)
	Solari, 2008	93 (86 to 97)	42 (36 to 49)
	Smear-negative only		
	Lagrange-Xelot, 2010	96.2 (80 to 100)	21.3 (14 to 30)

Bibliographic reference	Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D and Steingart KR (2013) Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. European Respiratory Journal 42: 480-94		
	Soto, 2008	93	at cut-off <0: 50 at cut-off >4: 92
	Soto, 2011	at cut-off <0: 97.8 (94.5 to 99.4) at cut-off >5: 23.9 (17.9 to 30.7)	at cut-off <0: 14 (11 to 17.4) at cut-off >5: 93.1 (90.5 to 95.2)
	Wisnivesky, 2005	95 (74 to 100)	35 (31 to 40)
Source of funding	No details given		
Abbreviations: CI, confidence interval			

1.1.1.4 Steingart et al, 2014

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Summary

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593
	 Al-Ateah, 2012

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Balcells, 2012

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Barnard, 2012

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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Bibliographic reference	**Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593**

Boehme, 2010a

Scott LE, McCarthy K, Gous N, Nduna M, Van Rie A, et al. (2011) Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study. PLoS Med 8(7): e1001061

Boehme, 2010b

Methodological quality

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			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Boehme, 2010c

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Boehme, 2010d

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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DOMAIN 1: Patient Selection			
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Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
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			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Boehme, 2010e

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Boehme, 2011a

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Boehme, 2011b

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Boehme, 2011c

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Boehme, 2011d

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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Boehme, 2011e

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DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Boehme, 2011f

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		

Bowles, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
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Were all patients included in the analysis?	Unclear		

Carriquiry, 2012

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Ciftci, 2011

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Were all patients included in the analysis?	Unclear		

Friedrich, 2011

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Hanif, 2011

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Hanrahan, 2013

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Helb, 2010

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

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Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		

Ioannidis, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Unclear
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Kurbatova, 2013

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Unclear
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Lawn, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Malbruny, 2011

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Marlowe, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Unclear
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Miller, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Moure, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Rachow, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Unclear
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		

Safianowska, 2012

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Scott, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Teo, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Unclear
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	No		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	No		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Theron, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
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Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Van Rie, 2013

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

Williamson, 2012

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Zeka, 2011

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
			Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
			Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	No		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	No		
			Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Additional criteria

Is there concern that the included patients do not match the review question? many included papers lack data relating to the age of the included patients

Is there concern that the index test, its conduct, or interpretation differ from the review question? no

Is there concern that the target condition as defined by the reference standard does not match the review question? no

Number of patients	27 studies, 36 evaluations

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Study	n
	Al-Ateah, 2012	172
	Balcells, 2012	160
	Barnard, 2012	68
	Boehme, 2010a	216
	Boehme, 2010b	310
	Boehme, 2010c	332
	Boehme, 2010d	261
	Boehme, 2010e	222
	Boehme, 2011a	536
	Boehme, 2011b	1005
	Boehme, 2011c	904
	Boehme, 2011d	289
	Boehme, 2011e	788
	Boehme, 2011f	387
	Bowles, 2011	89
	Carriquay, 2012	131
	Ciftci, 2011	85
	Friedrich, 2011	126
	Hanif, 2011	206
	Hanrahan, 2013	551
	Helb, 2010	107
	Ioannidis, 2011	66
	Kurbatova, 2013	228
	Lawn, 2011	778 samples from 394 patients
	Malbruny, 2011	58
	Marlowe, 2011	216
	Miller, 2011	89 pulmonary specimens (in addition, study included 23 extrapulmonary specimens)

Bibliographic reference	**Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593**
	Moure, 2011 107 Rachow, 2011 172 Safianowska, 2012 145 Scott, 2011 177 Teo, 2011 106 Theron, 2011 480 Van Rie, 2013 199 Williamson, 2012 89 Zeka, 2011 103 Total 11201
Patient characteristics	Inclusion Adult or predominantly adult patients, aged 15 years or oldera Presumed to have pulmonary TB, with or without HIV infection Assessment of the diagnostic accuracy of Xpert MTB/RIF using sputum and other respiratory specimens (such as fluid obtained from bronchial alveolar lavage and tracheal aspiration) consistent with the intended use of the manufacturer All types of health facilities and all laboratory levels (peripheral, intermediate, and central) from all countries Exclusion Studies that specifically evaluated the use of Xpert MTB/RIF in children Specimens obtained by gastric aspirationb Amongst included studies Study — Patient characteristics Al-Ateah, 2012 — Presenting signs and symptoms: not stated Age: not stated Sex, female: 46.2% HIV infection: 0.6% History of TB: not stated Country: Saudi Arabia World Bank Income Classification: high-income TB incidence rate: 17 per 100,000 Proportion of TB cases in the study: 25.6%

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Balcells, 2012	Presenting signs and symptoms: patients who fulfilled at least one of the following criteria: cough (> 10 days), bloody sputum, pneumonia unresponsive to previous antibiotics, fever (> 10 days), abnormal chest X-ray or weight loss Age: mean 37.4 years (range 19 to 65) Sex, female: 20.6% HIV infection: 100% History of TB: 11.8% Country: Chile World Bank Income Classification: middle-income TB incidence rate: 18 per 100,000 Proportion of TB cases in the study: 7.5%
	Barnard, 2012	Presenting signs and symptoms: not stated Age: predominantly adult, median age 41 Sex, female: 43.6% HIV infection: not stated History of TB: 100% Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 76.5%
	Boehme, 2010a	Presenting signs and symptoms: persistent productive cough for ≥ two weeks Age: median 37 years; range 20 to 69 years Sex, female: 0% HIV infection: 4.7% History of TB: 54.6% Country: Azerbaijan World Bank Income Classification: middle-income TB incidence rate: 113 per 100,000 Proportion of TB cases in study centre: 68.1%
	Boehme, 2010b	Presenting signs and symptoms: persistent productive cough for ≥ two weeks Age: median 31 years; range 18 to 79 years Sex, female: 43.3%

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		HIV infection: 1.7% History of TB: 23.7% Country: Peru World Bank Income Classification: middle-income TB incidence rate: 101 per 100,000 Proportion of TB cases in study centre: 67.4%
	Boehme, 2010c	Presenting signs and symptoms: persistent productive cough for ≥ two weeks Age: median 36 years; range 18 to 80 years Sex, female: 34.1% HIV infection: 76.1% History of TB: 43.0% Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: per 993 per 100,000 Proportion of TB cases in study centre: 44.0%
	Boehme, 2010d	Presenting signs and symptoms: persistent productive cough for ≥ two weeks Age: median 32 years; range 18 to 68 years Sex, female: 59.4% HIV infection: 71.4% History of TB: 45.1% Country: South Africa, Durban World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in study centre: 16.5%
	Boehme, 2010e	Presenting signs and symptoms: persistent productive cough for ≥ two weeks Age: median 30 years; range 17 to 88 years Sex, female: 39.1% HIV infection: 4.4% History of TB: 75.2% High MDR-TB setting Country: India World Bank Income Classification: middle-income

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		TB incidence rate: 181 per 100,000 Proportion of TB cases in study centre: 84.2%
	Boehme, 2011a	Presenting signs and symptoms: cough lasting at least two weeks Age: median 36 years; interquartile range 30 to 44 years Sex, female: < 1% HIV infection: < 1% History of TB: not stated Country: Azerbaijan World Bank Income Classification: middle-income TB incidence rate: 113 per 100,000 Proportion of TB cases in study centre: 42.7%
	Boehme, 2011b	Presenting signs and symptoms: cough lasting at least two weeks Age: median 37 years; interquartile range 26 to 53 years Sex, female: 49% HIV infection: < 1% History of TB: not stated Country: Peru World Bank Income Classification: middle-income TB incidence rate: 101 per 100,000 Proportion of TB cases in study centre: 17.6%
	Boehme, 2011c	Presenting signs and symptoms: cough lasting at least two weeks Age: median 36 years; interquartile range 29 to 46 years Sex, female: 49% HIV infection: 38% History of TB: not stated Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in study centre: 25.8%
	Boehme, 2011d	Presenting signs and symptoms: cough lasting at least two weeks Age: median 32 years; interquartile range 26 to 38 years Sex, female: < 46%

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		HIV infection: < 68% History of TB: not stated Country: Uganda World Bank Income Classification: low-income TB incidence rate: 193 per 100,000 Proportion of TB cases in the study centre: 50.2%
	Boehme, 2011e	Presenting signs and symptoms: cough lasting at least two weeks Age: median 45 years; interquartile range 32 to 58 years Sex, female: 30% HIV infection: 4% History of TB: not stated Country: India World Bank Income Classification: middle-income TB incidence rate: 181 per 100,000 Proportion of TB cases in the study centre: 12.8%
	Boehme, 2011f	Presenting signs and symptoms: cough lasting at least two weeks Age: median 47 years; interquartile range 34 to 58 years Sex, female: 36% HIV infection: < 1% History of TB: not stated Country: Philippines World Bank Income Classification: middle-income TB incidence rate: 270 per 100,000 Proportion of TB cases in the study centre: 38.2%
	Bowles, 2011	Presenting signs and symptoms: not reported Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated Country: Netherlands World Bank Income Classification: high-income TB incidence rate: 6.8 per 100,000 Proportion of TB cases in the study: 71.9%

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Carriquay, 2012	Presenting signs and symptoms: cough for greater than 10 days with abnormal chest X-ray and at least one of the following symptoms: fever, fatigue, night sweats, haemoptysis, chest pain, or weight loss Age: median 35 years, interquartile range 29 to 42 Sex, female: 27.5% HIV infection: 100% History of TB: 57.3% Country: Peru World Bank Income Classification: middle-income TB incidence rate: 101 per 100,000 Proportion of TB cases in the study: 34.4%
	Ciftci, 2011	Presenting signs and symptoms: symptoms suggestive of TB Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated Country: Turkey World Bank Income Classification: middle-income TB incidence rate: 24 per 100,000 Proportion of TB cases in the study: 29.4%
	Friedrich, 2011	Presenting signs and symptoms: patients recently diagnosed with smear-positive first time TB, untreated Age: eligible aged 18 to 65 years Sex, female: not stated HIV infection: not stated History of TB: not stated Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 100.0%
	Hanif, 2011	Presenting signs and symptoms: presumed TB based on presence of cough and radiographic findings

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		Age: range 20 to 57 years old Sex, female: not stated HIV infection: not stated History of TB: not stated Country: Kuwait World Bank Income Classification: high-income TB incidence rate: 36 per 100,000 Proportion of TB cases in the study: 29.1%
	Hanrahan, 2013	Presenting signs and symptoms: prolonged (> two weeks) cough and/or other TB symptoms Age: 18 and older Sex, female: not stated HIV infection: not stated History of TB: not stated Country: South Africa, Johannesburg World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 11.6%
	Helb, 2010	Presenting signs and symptoms: cough lasting at least two weeks Age: median 34 years; range 18 to 76 years Sex, female: 30.8% HIV infection: 0.9% History of TB: 1.9% TB incidence rate: 199 per 100,000 Proportion of TB cases in the study: 76.6%
	Ioannidis, 2011	Presenting signs and symptoms: high suspicion of TB in patients found to be predominantly smear negative by microscopy examination Age: not stated Sex, female: not stated

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		HIV infection: not stated History of TB: not stated Country: Greece World Bank Income Classification: high-income TB incidence rate: 3.8 per 100,000 Proportion of TB cases in the study: 48.0%
	Kurbatova, 2013	Presenting signs and symptoms: presumptive or recently diagnosed TB Age: not stated Sex, female: not stated HIV infection: estimated < 5 % History of TB: not stated Country: Russia World Bank Income Classification: middle-income TB incidence rate: 97 per 100,000 Proportion of TB cases in the study: 46.9%
	Lawn, 2011	Presenting signs and symptoms: HIV-infected patients with advanced immunodeficiency; the majority of patients had one or more of the following TB symptoms: current cough, fever, night sweats, or weight loss Age: median 34 years; interquartile range 28 to 41 years Sex, female: 65.4% HIV infection: 100% History of TB: 26.5% Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 18.3%
	Malbruny, 2011	Presenting signs and symptoms: clinical symptoms suggestive of TB Age: median 52 years Sex, female: 40.2% HIV infection: not stated History of TB: not stated Country: France

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		World Bank Income Classification: high-income TB incidence rate: 4.3 per 100,000 Proportion of TB cases in the study: 20.7%
	Marlowe, 2011	Presenting signs and symptoms: not reported Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated Country: USA World Bank Income Classification: high income TB incidence rate: 3.9 per 100,000 Proportion of TB cases in the study: 60.2%
	Miller, 2011	Presenting signs and symptoms: not reported Age: data provided for patients with pulmonary and extrapulmonary combined; 95% of patients were 15 years and older Sex, female: not stated HIV infection: not stated History of TB: not stated Country: USA World Bank Income Classification: high income TB incidence rate: 3.9 per 100,000 Proportion of TB cases in the study: 32.6%
	Moure, 2011	Presenting signs and symptoms: patients found to be smear negative by microscopy examination Age: all patients were 15 years of age or older Sex, female: not stated HIV infection: not stated History of TB: not stated Country: Spain World Bank Income Classification: high income TB incidence rate: 15 per 100,000 Proportion of TB cases in the study: 72.9%

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Rachow, 2011	Presenting signs and symptoms: presumed pulmonary TB based on clinical and radiographic findings Age: mean 39 years (standard deviation 13.8) Sex, female: 51.7% HIV infection: 58.9% History of TB: not stated Country: United Republic of Tanzania World Bank Income Classification: low-income TB incidence rate: 169 per 100,000 Proportion of TB cases in the study: 40.1%
	Safianowska, 2012	Presenting signs and symptoms: patients presumed to have TB Age: mean 61 years; range 20 to 97 years Sex, female: 36.6% HIV infection: 0% History of TB: not stated Country: Poland World Bank Income Classification: high-income TB incidence rate: 23 per 100,000 Proportion of TB cases in the study: 11.8%
	Scott, 2011	Presenting signs and symptoms: patients presumed to have TB, presenting with cough, fever, night sweats, and/or weight loss Age: mean 32 years; range 19 to 75 years Sex, female: 41.1% HIV infection: 69.0% History of TB: not stated Country: South Africa, Johannesburg World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 37.9%
	Teo, 2011	Presenting signs and symptoms: patients thought to have TB based on symptoms and radiographic findings Age: not stated

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		Sex, female: not stated HIV infection: not stated History of TB: not stated Country: Singapore World Bank Income Classification: high-income TB incidence rate: 37 per 100,000 Proportion of TB cases in the study: 58.5%
	Theron, 2011	Presenting signs and symptoms: patients presumed to have TB based on compatible signs and symptoms Age: median 36 years; range 18 to 83 years Sex, female: 32.3% HIV infection: 31.3% History of TB: 34.3% Country: South Africa, Cape Town World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 29.4%
	Van Rie, 2013	Presenting signs and symptoms: prolonged (> two weeks) cough or other TB symptoms, or both, and had two prior-negative smear by fluorescence microscopy Age: median 36 years (IQR 30 to 34) Sex, female: 56.8% HIV infection: 72.4% History of TB: 17.6% Country: South Africa, Johannesburg World Bank Income Classification: middle-income TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 9.3%
	Williamson, 2012	Presenting signs and symptoms: clinical symptoms not reported: smear-positive specimens Age: > 15 years Sex, female: not stated

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		HIV infection: estimated < 1% History of TB: not stated Country: New Zealand World Bank Income Classification: high-income TB incidence rate: 7.6 per 100,000 Proportion of TB cases in the study: 75.3%
	Zeka, 2011	Presenting signs and symptoms: clinical findings of possible TB Age: median 48 years; range 25 to 70 years Sex, female: 42.4% HIV infection: not stated History of TB: not stated Country: Turkey World Bank Income Classification: middle-income TB incidence rate: 24 per 100,000 Proportion of TB cases in the study: 34.0%
Index test	Inclusion Xpert MTB/RIF Amongst included studies	
	Study	Details of test
	Al-Ateah, 2012	Specimen condition: fresh Specimen preparation: processed Clinical setting: laboratory-based evaluation of respiratory specimens Laboratory level: intermediate
	Balcells, 2012	Specimen condition: fresh Specimen preparation: processed Clinical setting: five hospitals and their respective HIV clinics Laboratory level: intermediate
	Barnard, 2012	Specimen condition: fresh Specimen preparation: processed Clinical setting: laboratory-based evaluation of clinical specimens from previously treated patients

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		Laboratory level: intermediate
	Boehme, 2010a	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: special treatment facility for prisoners, high MDR-TB setting Laboratory level: central
	Boehme, 2010b	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: primary health care DOTS (directly observed treatment, short-course) centres in shanty towns Laboratory level: intermediate
	Boehme, 2010c	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: clinic Laboratory level: intermediate
	Boehme, 2010d	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: TB clinics Laboratory level: central
	Boehme, 2010e	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: tertiary hospital Laboratory level: intermediate
	Boehme, 2011a	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: MDR-TB screening facility Laboratory level: intermediate
	Boehme, 2011b	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: two health centres and one district hospital Laboratory level: intermediate
	Boehme, 2011c	Specimen condition: fresh Specimen preparation: unprocessed

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		Clinical setting: one health centre and one provincial hospital Laboratory level: intermediate
	Boehme, 2011d	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: emergency unit of referral hospital Laboratory level: intermediate
	Boehme, 2011e	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: health centre Laboratory level: intermediate
	Boehme, 2011f	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: MDR-TB screening facility Laboratory level: intermediate
	Bowles, 2011	Specimen condition: 26 fresh and 63 frozen (previously stored) samples Specimen preparation: unprocessed Clinical setting: laboratory-based evaluation of respiratory specimens (predominantly sputum specimens) from a TB reference clinic Laboratory level: central
	Carriquay, 2012	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: two tertiary hospitals Laboratory level: intermediate
	Ciftci, 2011	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: laboratory-based evaluation of respiratory specimens (predominantly sputum) at a university hospital Laboratory level: intermediate
	Friedrich, 2011	Specimen condition: fresh Specimen preparation: processed Clinical setting: two medical centres Laboratory level: intermediate

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Hanif, 2011	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: laboratory-based evaluation of respiratory specimens (predominantly sputum) at a university hospital Laboratory level: central
	Hanrahan, 2013	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: primary care clinic Laboratory level: peripheral
	Helb, 2010	Specimen condition: frozen Specimen preparation: unprocessed Clinical setting: TB hospital Laboratory level: intermediate
	Ioannidis, 2011	Specimen condition: fresh Specimen preparation: processed Clinical setting: laboratory-based evaluation in routine hospital setting Laboratory level: central
	Kurbatova, 2013	Specimen condition: fresh Specimen preparation: unprocessed Clinical setting: laboratory-based evaluation Laboratory level: central and intermediate
	Lawn, 2011	Specimen condition: fresh Specimen preparation: processed Clinical setting: HIV anti-retroviral clinic; all patients were screened for TB Laboratory level: intermediate
	Malbruny, 2011	Specimen condition: fresh and frozen Specimen preparation: processed Clinical setting: laboratory-based evaluation of respiratory specimens (predominantly bronchial aspirates) at a university hospital Laboratory level: intermediate
	Marlowe, 2011	Specimen condition: fresh and frozen Specimen preparation: processed

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
		Clinical setting: laboratory-based evaluation of respiratory samples
		Laboratory level: central (one laboratory) and intermediate (two laboratories)
	Miller, 2011	Specimen condition: frozen
		Specimen preparation: processed
		Clinical setting: laboratory-based evaluation of clinical specimens at a university hospital
		Laboratory level: intermediate
	Moure, 2011	Specimen condition: frozen
		Specimen preparation: processed
		Clinical setting: laboratory-based evaluation of clinical specimens at a university hospital
		Laboratory level: intermediate
	Rachow, 2011	Specimen condition: frozen
		Specimen preparation: unprocessed
		Clinical setting: referral hospital
		Laboratory level: central
	Safianowska, 2012	Specimen condition: fresh
		Specimen preparation: processed
		Clinical setting: laboratory-based evaluation
		Laboratory level: intermediate
	Scott, 2011	Specimen condition: frozen
		Specimen preparation: processed
		Clinical setting: primary care clinic
		Laboratory level: intermediate
	Teo, 2011	Specimen condition: fresh
		Specimen preparation: processed
		Clinical setting: university hospital
		Laboratory level: central
	Theron, 2011	Specimen condition: frozen
		Specimen preparation: unprocessed
		Clinical setting: two primary care clinics in a high HIV prevalence area
		Laboratory level: intermediate

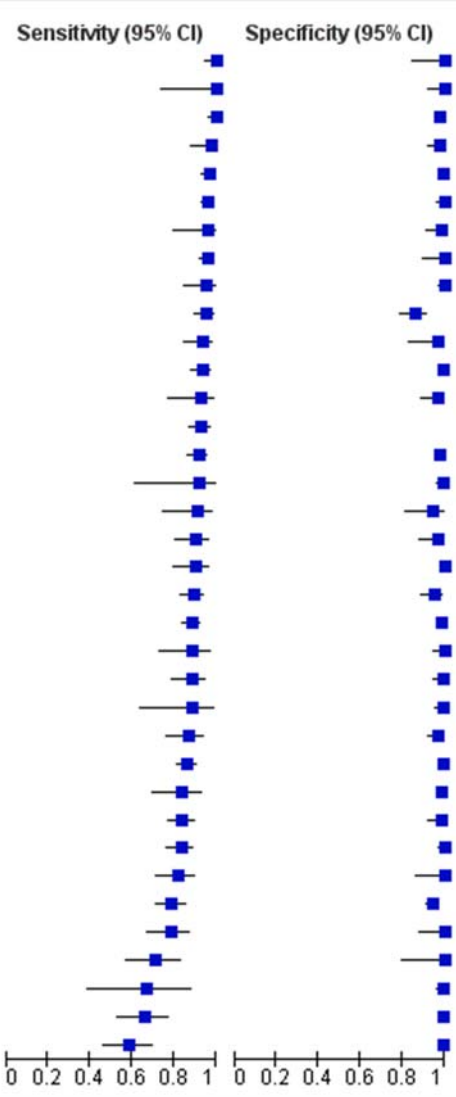
Bibliographic reference	**Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593**
	Van Rie, 2013: Specimen condition: fresh; Specimen preparation: processed; Clinical setting: primary care clinic; Laboratory level: peripheral Williamson, 2012: Specimen condition: fresh; Specimen preparation: processed; Clinical setting: laboratory-based evaluation; Laboratory level: intermediate Zeka, 2011: Specimen condition: frozen; Specimen preparation: processed; Clinical setting: laboratory-based evaluation of routine sputum specimens at a university hospital; Laboratory level: intermediate
Reference standard	Inclusion Acceptable reference standards used solid media (Löwenstein-Jensen, Middlebrook 7H10 or 7H11, or Ogawa media) or a commercial liquid culture system, (such as BACTEC™ 460TB System or BACTEC™ MGIT™ 960 Mycobacterial Detection System, BacT/ALERT® System, or VersaTREK® Mycobacteria Detection & Susceptibility) Amongst included studies Study: Details of test Al-Ateah, 2012: Löwenstein-Jensen culture and MGIT 960 Balcells, 2012: Löwenstein-Jensen culture and MGIT 960 Barnard, 2012: MGIT 960 Boehme, 2010a: Löwenstein-Jensen culture and MGIT 960 Boehme, 2010b: Löwenstein-Jensen culture and MGIT 960 Boehme, 2010c: Löwenstein-Jensen culture and MGIT 960 Boehme, 2010d: Middlebrook 7H11 culture and MGIT 960 Boehme, 2010e: Löwenstein-Jensen culture and MGIT 960 Boehme, 2011a: MGIT 960 Boehme, 2011b: MGIT 960 Boehme, 2011c: MGIT 960

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593	
	Boehme, 2011d	Löwenstein-Jensen culture and MGIT 960
	Boehme, 2011e	Löwenstein-Jensen culture
	Boehme, 2011f	Ogawa culture and MGIT 960
	Bowles, 2011	MGIT 960
	Carriquay, 2012	Löwenstein-Jensen culture and MGIT 960
	Ciftci, 2011	BACTEC 460
	Friedrich, 2011	MGIT 960
	Hanif, 2011	Löwenstein-Jensen culture and MGIT 960
	Hanrahan, 2013	MGIT 960
	Helb, 2010	Löwenstein-Jensen culture and MGIT 960
	Ioannidis, 2011	Löwenstein-Jensen culture and MGIT 960
	Kurbatova, 2013	MGIT 960
	Lawn, 2011	MGIT 960
	Malbruny, 2011	MGIT 960
	Marlowe, 2011	Löwenstein-Jensen culture, Middlebrook 7H11 culture, and MGIT 960
	Miller, 2011	Löwenstein-Jensen culture and MGIT 960
	Moure, 2011	Löwenstein-Jensen culture and MGIT 960
	Rachow, 2011	Löwenstein-Jensen culture and MGIT 960
	Safianowska, 2012	Löwenstein-Jensen culture
	Scott, 2011	MGIT 960
	Teo, 2011	Löwenstein-Jensen culture and MGIT 960
	Theron, 2011	MGIT 960
	Van Rie, 2013	MGIT 960
	Williamson, 2012	MGIT 960
	Zeka, 2011	Löwenstein-Jensen culture and MB/MBacT liquid medium
Outcomes measures and effect size	Diagnostic test accuracy Xpert MTB/RIF used as ‘an initial test replacing smear microscopy’ Pooled sensitivity (95% CrI) (n = 8998)c,d = 89% (85% to 92%)	

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

Pooled specificity (95% CrI) (n = 8998)c,d = 99% (98% to 99%)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	Not estimable
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]



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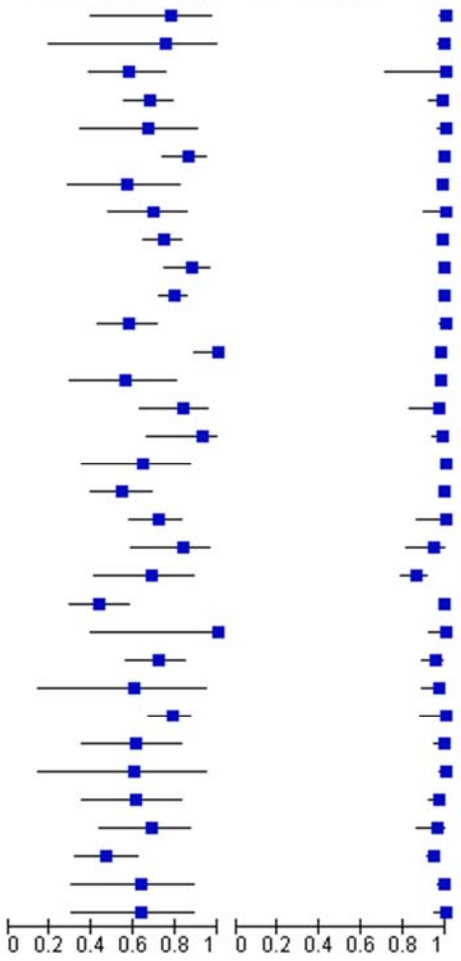
Smear-negative

Pooled sensitivity (95% CrI) (n = 6950)e = 67% (60% to 74%)
Pooled specificity (95% CrI) (n = 6950)e = 99% (98% to 99%)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	7	0	2	127	0.78 [0.40, 0.97]	1.00 [0.97, 1.00]
Balcells 2012	3	1	1	145	0.75 [0.19, 0.99]	0.99 [0.96, 1.00]
Barnard 2012	18	0	13	11	0.58 [0.39, 0.75]	1.00 [0.72, 1.00]
Boehme 2010a	46	1	22	68	0.68 [0.55, 0.78]	0.99 [0.92, 1.00]
Boehme 2010b	8	0	4	101	0.67 [0.35, 0.90]	1.00 [0.96, 1.00]
Boehme 2010c	44	1	7	185	0.86 [0.74, 0.94]	0.99 [0.97, 1.00]
Boehme 2010d	8	3	6	215	0.57 [0.29, 0.82]	0.99 [0.96, 1.00]
Boehme 2010e	18	0	8	35	0.69 [0.48, 0.86]	1.00 [0.90, 1.00]
Boehme 2011a	68	4	23	303	0.75 [0.65, 0.83]	0.99 [0.97, 1.00]
Boehme 2011b	37	3	5	825	0.88 [0.74, 0.96]	1.00 [0.99, 1.00]
Boehme 2011c	121	2	32	669	0.79 [0.72, 0.85]	1.00 [0.99, 1.00]
Boehme 2011d	30	0	22	144	0.58 [0.43, 0.71]	1.00 [0.97, 1.00]
Boehme 2011e	31	16	0	671	1.00 [0.89, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	9	5	7	234	0.56 [0.30, 0.80]	0.98 [0.95, 0.99]
Bowles 2011	20	1	4	29	0.83 [0.63, 0.95]	0.97 [0.83, 1.00]
Carriquiry 2012	13	1	1	82	0.93 [0.66, 1.00]	0.99 [0.93, 1.00]
Hanif 2011	9	0	5	146	0.64 [0.35, 0.87]	1.00 [0.98, 1.00]
Hanrahan 2013	26	2	22	478	0.54 [0.39, 0.69]	1.00 [0.99, 1.00]
Helb 2010	38	0	15	25	0.72 [0.58, 0.83]	1.00 [0.86, 1.00]
Ioannidis 2011	15	2	3	33	0.83 [0.59, 0.96]	0.94 [0.81, 0.99]
Kurbatova 2013	11	17	5	104	0.69 [0.41, 0.89]	0.86 [0.78, 0.92]
Lawn 2011	23	2	30	320	0.43 [0.30, 0.58]	0.99 [0.98, 1.00]
Malbruny 2011	4	0	0	45	1.00 [0.40, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	31	4	12	82	0.72 [0.56, 0.85]	0.95 [0.89, 0.99]
Miller 2011	3	2	2	58	0.60 [0.15, 0.95]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	11	1	7	102	0.61 [0.36, 0.83]	0.99 [0.95, 1.00]
Safianowska 2012	3	0	2	120	0.60 [0.15, 0.95]	1.00 [0.97, 1.00]
Scott 2011	11	3	7	107	0.61 [0.36, 0.83]	0.97 [0.92, 0.99]
Teo 2011	13	2	6	49	0.68 [0.43, 0.87]	0.96 [0.87, 1.00]
Theron 2011	22	19	25	320	0.47 [0.32, 0.62]	0.94 [0.91, 0.97]
Van Rie 2013	7	1	4	142	0.64 [0.31, 0.89]	0.99 [0.96, 1.00]
Zeka 2011	7	0	4	68	0.64 [0.31, 0.89]	1.00 [0.95, 1.00]



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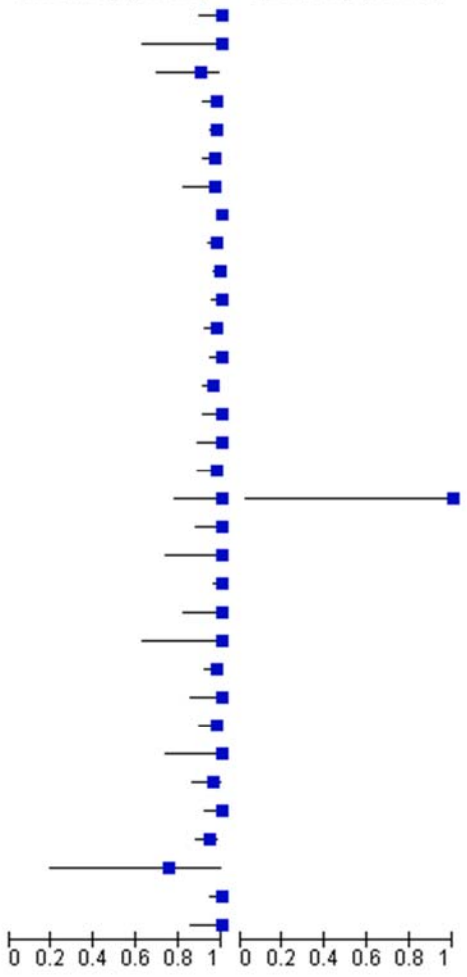
Smear-positive, culture-positivef

Pooled sensitivity (95% CrI) (n = 1936)g = 98% (97% to 99%)

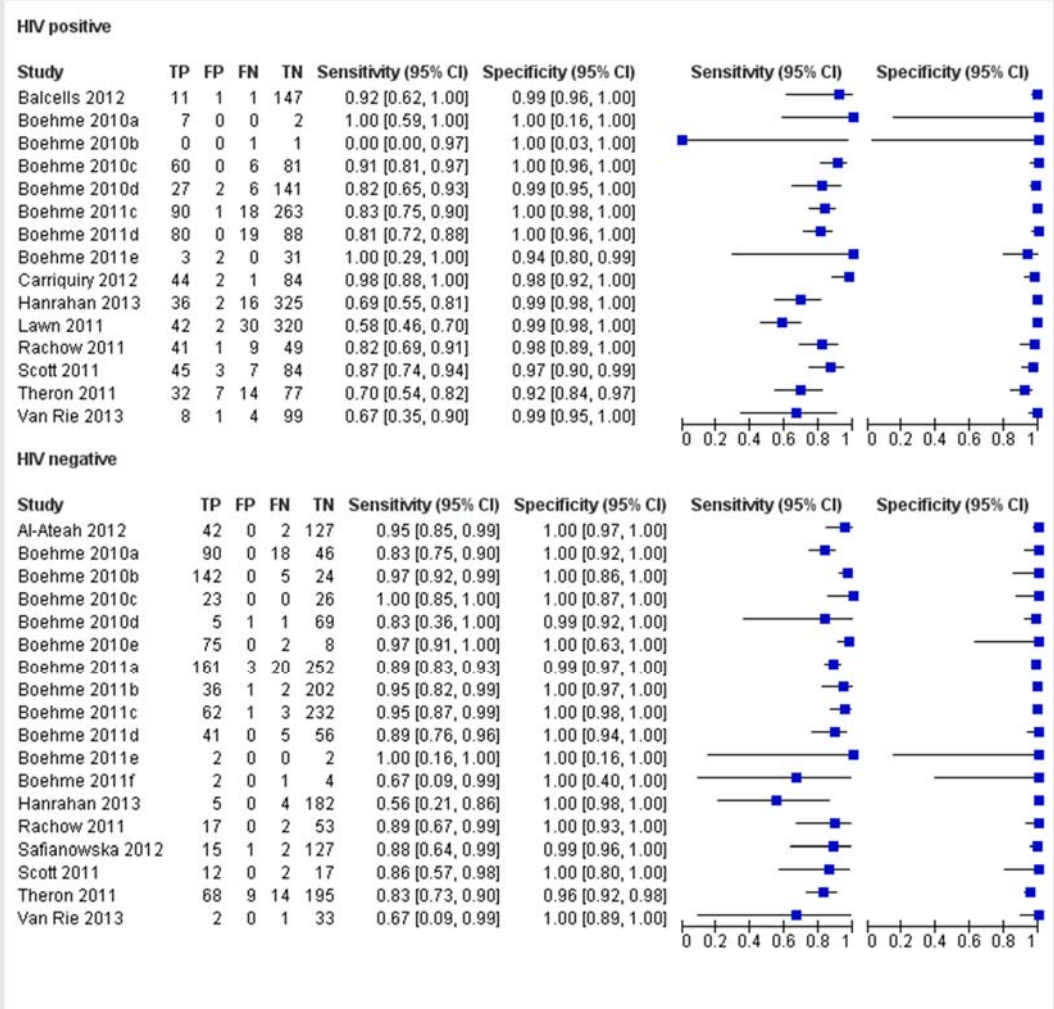
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	35	0	0	0	1.00 [0.90, 1.00]	Not estimable
Balcells 2012	8	0	0	0	1.00 [0.63, 1.00]	Not estimable
Barnard 2012	19	0	2	0	0.90 [0.70, 0.99]	Not estimable
Boehme 2010a	77	0	2	0	0.97 [0.91, 1.00]	Not estimable
Boehme 2010b	193	0	4	0	0.98 [0.95, 0.99]	Not estimable
Boehme 2010c	92	0	3	0	0.97 [0.91, 0.99]	Not estimable
Boehme 2010d	28	0	1	0	0.97 [0.82, 1.00]	Not estimable
Boehme 2010e	161	0	0	0	1.00 [0.98, 1.00]	Not estimable
Boehme 2011a	135	0	3	0	0.98 [0.94, 1.00]	Not estimable
Boehme 2011b	134	0	1	0	0.99 [0.96, 1.00]	Not estimable
Boehme 2011c	80	0	0	0	1.00 [0.95, 1.00]	Not estimable
Boehme 2011d	91	0	2	0	0.98 [0.92, 1.00]	Not estimable
Boehme 2011e	70	0	0	0	1.00 [0.95, 1.00]	Not estimable
Boehme 2011f	127	0	5	0	0.96 [0.91, 0.99]	Not estimable
Bowles 2011	40	0	0	0	1.00 [0.91, 1.00]	Not estimable
Carriquiry 2012	31	0	0	0	1.00 [0.89, 1.00]	Not estimable
Hanif 2011	45	0	1	0	0.98 [0.88, 1.00]	Not estimable
Hanrahan 2013	15	0	0	1	1.00 [0.78, 1.00]	1.00 [0.03, 1.00]
Helb 2010	29	0	0	0	1.00 [0.88, 1.00]	Not estimable
Ioannidis 2011	12	0	0	0	1.00 [0.74, 1.00]	Not estimable
Kurbatova 2013	91	0	0	0	1.00 [0.96, 1.00]	Not estimable
Lawn 2011	19	0	0	0	1.00 [0.82, 1.00]	Not estimable
Malbruny 2011	8	0	0	0	1.00 [0.63, 1.00]	Not estimable
Marlowe 2011	85	0	2	0	0.98 [0.92, 1.00]	Not estimable
Miller 2011	24	0	0	0	1.00 [0.86, 1.00]	Not estimable
Rachow 2011	50	0	1	0	0.98 [0.90, 1.00]	Not estimable
Safianowska 2012	12	0	0	0	1.00 [0.74, 1.00]	Not estimable
Scott 2011	47	0	2	0	0.96 [0.86, 1.00]	Not estimable
Teo 2011	43	0	0	0	1.00 [0.92, 1.00]	Not estimable
Theron 2011	89	0	5	0	0.95 [0.88, 0.98]	Not estimable
Van Rie 2013	3	0	1	0	0.75 [0.19, 0.99]	Not estimable
Williamson 2012	67	0	0	0	1.00 [0.95, 1.00]	Not estimable
Zeka 2011	24	0	0	0	1.00 [0.86, 1.00]	Not estimable



HIV-negative

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593
	Pooled sensitivity (95% CrI) (n = 1470)h = 86% (76% to 92%) Pooled specificity (95% CrI) (n = 1470)h = 99% (98% to 100%) HIV-positive Pooled sensitivity (95% CrI) (n = 1789)h = 79% (70% to 86%) Pooled specificity (95% CrI) (n = 1789)h = 98% (96% to 99%)

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593



HIV-positive, smear-negative, culture-positive

Pooled sensitivity (95% CrI) (n = not provided)i = 61% (40% to 81%)

Pooled sensitivity (95% CrI) (n = not provided)i = 99% (97% to 100%)

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593
	HIV-positive, smear-positive, culture-positive Pooled sensitivity (95% CrI) (n = not provided)i = 97% (90% to 99%)
	Time to diagnosis/treatment initiation

Study	Time to diagnosis	Time to treatment initiation
Al-Ateah, 2012	-	-
Balcells, 2012	Median (range): • Xpert MTB/RIF: 0 days • liquid culture 10 days (5 to 22 days) • 8 days for smear-positive cases • 15 days for smear-negative cases	-
Barnard, 2012	-	-
Boehme, 2010	-	-
Boehme, 2011	Median (interquartile range) • Xpert MTB/RIF: 0 days (0, 1) • smear: 1 day (0, 1) • solid culture: 30 days (23, 43) • liquid culture: 16 days (13, 21)	Median (interquartile range) for smear-negative, culture-positive cases • before Xpert MTB/RIF introduced: 56 days (39, 81) • after Xpert MTB/RIF introduced: 5 days (2, 8)
Bowles, 2011	-	-
Carriquay, 2012	-	-
Ciftci, 2011	-	-
Friedrich, 2011	-	-
Hanif, 2011	-	-
Hanrahan, 2013	-	-
Helb, 2010	• Xpert MTB/RIF (1 sample): 1 hour 55 minutes • Xpert MTB/RIF (8 samples processed together): 2 hours	-
Ioannidis, 2011	-	-
Kurbatova, 2013	-	-
Lawn, 2011	Median (interquartile range) • Xpert MTB/RIF: 4 days (3, 6)	-

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593		
		• smear: 3 days (2, 5) • liquid culture (smear-positive): 12 days (10, 14) • liquid culture (smear-negative): 20 days (17, 27)	
	Malbruny, 2011	-	-
	Marlowe, 2011	Xpert MTB/RIF: hands-on time was 5 minutes; run time was less than 2 hours	-
	Miller, 2011	Xpert MTB/RIF: hands-on time was 15 minutes: run time was 113 minutes	-
	Moure, 2011	Xpert MTB/RIF: total time of 2 hours	-
	Rachow, 2011	Xpert MTB/RIF: within two hours	-
	Safianowska, 2012	-	-
	Scott, 2011	-	-
	Teo, 2011	-	-
	Theron, 2011	-	-
	Van Rie, 2013	Xpert MTB/RIF: results available the same day	Median (interquartile range) Xpert MTB/RIF positive patients: 0 days (0, 0) Patients diagnosed by other methods: 13 days (10, 20)
	Williamson, 2012	-	-
	Zeka, 2011	Xpert MTB/RIF (routine practice): 3 to 24 hours Liquid culture: 19 days mean (range 3 to 42 days)	-
Source of funding	Cochrane Collaboration		
Comments			

a Assumed that studies that did not report age data involved all or mostly adults for the following reasons: the vast majority of specimens evaluated with Xpert MTB/RIF were sputum specimens and children have difficulty producing sputum;

b This specimen collection method is used mostly for investigating TB in children

c The individual studies are ordered by decreasing sensitivity

d Included 22 of the total 27 studies; excluded five studies that enrolled primarily only smear-positive or smear-negative patients

Bibliographic reference	Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M and Dendukuri N (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Library 1, article no. CD009593

e Included 21 of the total 27 studies
f Pooled specificity in the studies in the smear-positive subgroup was not estimated because almost all participants were considered to be true positives
g Included 21 of the total 27 studies
h Included 7 of the total 27 studies
i Included 4 of the total 27 studies
Abbreviations: CrI, credibility interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.1.2 PRIMARY STUDIES

1.1.2.1 Abe, 1993

Bibliographic reference	Abe C, Hirano K, Wada M, Kazumi Y, Takahashi M, Fukasawa Y, Yoshimura T, Miyagi C and Goto S (1993) Detection of Mycobacterium tuberculosis in clinical specimens by polymerase chain reaction and Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 31: 3270-4
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear; limited details provided Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no

Bibliographic reference	**Abe C, Hirano K, Wada M, Kazumi Y, Takahashi M, Fukasawa Y, Yoshimura T, Miyagi C and Goto S (1993) Detection of Mycobacterium tuberculosis in clinical specimens by polymerase chain reaction and Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 31: 3270-4**
	Domain 4: Flow and timing Could the patient flow have introduced bias? unclear risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	135 participants; no microscopy data for 18 nontuberculous mycobacteria
Patient characteristics	Inclusion Sample characteristics Sputum
Index test	Ziehl-Neelson microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	MB-Check and Ogawa culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Fukujuji Hospital, Tokyo, Japan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 22, FP 3 Index test – Negative: FN 10, TN 82

Bibliographic reference	**Abe C, Hirano K, Wada M, Kazumi Y, Takahashi M, Fukasawa Y, Yoshimura T, Miyagi C and Goto S (1993) Detection of Mycobacterium tuberculosis in clinical specimens by polymerase chain reaction and Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 31: 3270-4**
	Sensitivity of index test (95% CI)a = 68.8% (52.7% to 84.8%) Specificity of index test (95% CI)a = 96.5% (92.6% to 100%)
Source of funding	Supported by grants from the Ministry of Health and Welfare of Japan, the Tuberculosis Panel, US-Japan Co-opeative Medical Science Program and the International Atomic Energy Agency
Comments	Data for the Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.2 Alcalá, 2001

Bibliographic reference	**Alcalá L, Ruiz-Serrano MJ, Hernangómez S, Marín M, García de Viedma D, San Juan R and Bouza E (2001) Evaluation of the upgraded amplified Mycobacterium tuberculosis direct test (gen-probe) for direct detection of Mycobacterium tuberculosis in respiratory and non-respiratory specimens. Diagnostic Microbiology and Infectious Disease 41(1-2): 51-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? age of the participants unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	**Alcalá L, Ruiz-Serrano MJ, Hernangómez S, Marín M, García de Viedma D, San Juan R and Bouza E (2001) Evaluation of the upgraded amplified Mycobacterium tuberculosis direct test (gen-probe) for direct detection of Mycobacterium tuberculosis in respiratory and non-respiratory specimens. Diagnostic Microbiology and Infectious Disease 41(1-2): 51-6**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	663 specimens
Patient characteristics	Inclusion Suspected tuberculosis Exclusion Patients known to have been on therapy for more than 7 days during the previous 6 months Sample characteristics 606 sputa, 38 bronchial aspirates, 15 gastric fluids, and 4 bronchial brushings
Index test	Ziehl-Neelsen microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide

Bibliographic reference	**Alcalá L, Ruiz-Serrano MJ, Hernangómez S, Marín M, García de Viedma D, San Juan R and Bouza E (2001) Evaluation of the upgraded amplified Mycobacterium tuberculosis direct test (gen-probe) for direct detection of Mycobacterium tuberculosis in respiratory and non-respiratory specimens. Diagnostic Microbiology and Infectious Disease 41(1-2): 51-6**
Reference standard	Löwenstein-Jensen and MGIT 960 culture plus clinical data Culture: • decontamination with N-acetyl-L-cysteine and sodium hydroxide • incubation for 8 and 5 weeks, respectively
Location	Madrid, Spain
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 79, FP 3 Index test – Negative: FN 40, TN 541 Sensitivity of index test (95% CI)a = 66.4% (57.9% to 74.9%) Specificity of index test (95% CI)a = 99.5% (98.8% to 100%)
Source of funding	Supported by grant from bioMerieux
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.3 Al-Ateah, 2012

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**
Study type	Cross-sectional

Bibliographic reference	Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Methods: all clinically suspected TB samples received in the TB Section of the Division of Microbiology, Central Military Laboratory and Blood Bank, Prince Sultan Military Medical City (PSMMC), Riyadh during the study period • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? details provided were limited, and data relating to the age of participants was lacking Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**
	Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	172
Patient characteristics	Presenting signs and symptoms: not stated Age: not stated Sex, female: 46.2% HIV infection: 0.6% History of TB: not stated TB incidence rate: 17 per 100,000 Proportion of TB cases in the study: 25.6%
Index test	Fluorescence microscopy Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method; smears were prepared, fixed, and stained with auramine-rhodamine stain Suspected slides were confirmed by Ziehl-Neelson stain
Reference standard	Löwenstein-Jensen culture and MGIT 960 Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method
Location	Country: Saudi Arabia World Bank Income Classification: high-income
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative

Bibliographic reference	Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 35	FP 1
	Negative	FN 9	TN 127

Sensitivity of index test (95% CI)a = 79.6% (67.6% to 91.5%)
Specificity of index test (95% CI)a = 99.2% (97.7% to 100%)
Sputum-only (n = 56)

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 31	FP 0
	Negative	FN 7	TN 18

Sensitivity of index test (95% CI)a = 81.6% (69.3% to 93.9%)
Specificity of index test (95% CI)a = 100% (100% to 100%)
Bronchoalveolar lavage (n = 116)

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 4	FP 1

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**
	Negative: FN 2, TN 109 Sensitivity of index test (95% CI)a = 66.7% (30.0% to 100%) Specificity of index test (95% CI)a = 99.1% (97.3% to 100%)
Source of funding	This study was not funded by any pharmaceutical company or research organization
Comments	Data for Xpert MTB/RIF included in Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.4 Ausina, 1997

Bibliographic reference	**Ausina V, Gamboa F, Gazapo E, Manterola JM, Lonca J, Matas L, Manzano JR, Rodrigo C, Cardona PJ and Padilla E (1997) Evaluation of the semiautomated Abbott LCx Mycobacterium tuberculosis assay for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 35(8): 1996-2002**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	**Ausina V, Gamboa F, Gazapo E, Manterola JM, Lonca J, Matas L, Manzano JR, Rodrigo C, Cardona PJ and Padilla E (1997) Evaluation of the semiautomated Abbott LCx Mycobacterium tuberculosis assay for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 35(8): 1996-2002**
	• If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	520 specimens collected from 326 participants
Patient characteristics	Inclusion Patients suspected of having pulmonary tuberculosis Specimens from patients with pulmonary tuberculosis who were being monitored for treatment with antituberculosis drugs Sample characteristics Respiratory specimens – 449 expectorated sputum specimens, 60 bronchial or tracheal aspirates, 8 bronchoalveolar lavage specimens and 3 gastric juice aspirates
Index test	Fluorescence microscopy Auramine-rhodamine staining

Bibliographic reference	**Ausina V, Gamboa F, Gazapo E, Manterola JM, Lonca J, Matas L, Manzano JR, Rodrigo C, Cardona PJ and Padilla E (1997) Evaluation of the semiautomated Abbott LCx Mycobacterium tuberculosis assay for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 35(8): 1996-2002**
	Ziehl-Neelson confirmation
Reference standard	Löwenstein-Jensen, Colestos and BACTEC 12B culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Barcelona, Spain
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 141, FP 46 Index test Negative: FN 31, TN 302 Sensitivity of index test (95% CI)a = 82.0% (76.2% to 87.7%) Specificity of index test (95% CI)a = 86.8% (83.2% to 90.3%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.5 Beavis, 1995

Bibliographic reference	**Beavis KG, Lichty MB, Jungkind DL and Giger O (1995) Evaluation of Amplicor PCR for direct detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 33(10): 2582-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias

Bibliographic reference	Beavis KG, Lichty MB, Jungkind DL and Giger O (1995) Evaluation of Amplicor PCR for direct detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 33(10): 2582-6
	• methods: both prospective and retrospective • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no, though information provided is limited; it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? • Were the index test results interpreted without knowledge of the results of the reference standard? • If a threshold was used, was it pre-specified? Is there concern that the index test, its conduct, or interpretation differ from the review question? Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? • Is the reference standard likely to correctly classify the target condition? • Were the reference standard results interpreted without knowledge of the results of the index test? Is there concern that the target condition as defined by the reference standard does not match the review question? Domain 4: Flow and timing Could the patient flow have introduced bias? • Was there an appropriate interval between index test(s) and reference standard?

Bibliographic reference	**Beavis KG, Lichty MB, Jungkind DL and Giger O (1995) Evaluation of Amplicor PCR for direct detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 33(10): 2582-6**
	• Did all patients receive a reference standard? • Did patients receive the same reference standard? • Were all patients included in the analysis?
Number of patients	532 sputum specimens from 270 patients
Patient characteristics	Inclusion Sputum specimens submitted for acid-fast bacilli culture at Thomas Jefferson University Hospital and Episcopal Hospital, Philadelphia Sample characteristics Specimens divided into 2 groups: • prospective – 248 specimens from 129 patients stored at -75°C for less than 7 days • retrospective – 284 specimens from 144 patients stored at -75°C for more than 1 month
Index test	Fluorescence microscopy Decontamination and concentration conducted according to CDC guidelines Auramine-rhodamine staining
Reference standard	Löwenstein-Jensen and BACTEC culture Decontamination and concentration conducted according to CDC guidelines
Location	Thomas Jefferson University Hospital and Episcopal Hospital, Philadelphia, US
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative Index test – Positive: TP 81, FP 21 Index test – Negative: FN 6, TN 424 Sensitivity of index test (95% CI)a = 93.1% (87.8% to 98.4%)

Bibliographic reference	Beavis KG, Lichty MB, Jungkind DL and Giger O (1995) Evaluation of Amplicor PCR for direct detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 33(10): 2582-6
	Specificity of index test (95% CI)a = 95.3% (93.3% to 97.3%)
Source of funding	Supported by a grant from Roche Molecular Systems
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.6 Bell and Brown, 1962

Bibliographic reference	Bell WJ and Brown PP (1962) Fluorescence microscopy in the laboratory diagnosis and assessment of pulmonary tuberculois. The Central African Journal of Medicine 8(1): 4-9
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

Bibliographic reference	**Bell WJ and Brown PP (1962) Fluorescence microscopy in the laboratory diagnosis and assessment of pulmonary tuberculois. The Central African Journal of Medicine 8(1): 4-9**
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? unclear risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	1600 specimens
Patient characteristics	Inclusion Patients with suspected pulmonary tuberculosis who are already receiving tuberculosis treatmentGhana Sample characteristics Sputum
Index test	Fluorescence microscopy Auramine-phenol staining
	Ziehl-Neelson microscopy
Reference standard	Löwenstein-Jensen culture Incubation for 12 weeks
Location	Ghana
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative

Bibliographic reference	**Bell WJ and Brown PP (1962) Fluorescence microscopy in the laboratory diagnosis and assessment of pulmonary tuberculois. The Central African Journal of Medicine 8(1): 4-9**
	Index test / Positive: TP 322, FP 573 Index test / Negative: FN 57, TN 648 Sensitivity of index test (95% CI)a = 85.0% (81.4% to 88.6%) Specificity of index test (95% CI)a = 53.1% (50.3% to 55.9%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard: Positive / Negative Index test / Positive: TP 319, FP 474 Index test / Negative: FN 60, TN 747 Sensitivity of index test (95% CI)a = 84.2% (80.5% to 87.8%) Specificity of index test (95% CI)a = 61.2% (58.5% to 63.9%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.7 Bergmann and Woods, 1996

Bibliographic reference	**Bergmann JS and Woods GL (1996) Clinical evaluation of the Roche AMPLICOR PCR Mycobacterium tuberculosis test for detection of M. tuberculosis in respiratory specimens. Journal of Clinical Microbiology 34(5): 1083-5**

Bibliographic reference	Bergmann JS and Woods GL (1996) Clinical evaluation of the Roche AMPLICOR PCR Mycobacterium tuberculosis test for detection of M. tuberculosis in respiratory specimens. Journal of Clinical Microbiology 34(5): 1083-5
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? age of participants unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	Bergmann JS and Woods GL (1996) Clinical evaluation of the Roche AMPLICOR PCR Mycobacterium tuberculosis test for detection of M. tuberculosis in respiratory specimens. Journal of Clinical Microbiology 34(5): 1083-5
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	956 specimens from 502 participants
Patient characteristics	Respiratory specimens: 808 sputum specimens, 90 bronchoalveolar lavage fluid specimens, 55 tracheal aspirate specimens, 1 throat specimen, 1 protected specimen brush, and 1 lung biopsy specimen
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine O staining
Reference standard	Löwenstein-Jensen, BACTEC 460 (using 12B) and Middlebrook 7H10/11 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	Texas, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 41, FP 11 Index test – Negative: FN 20, TN 884 Sensitivity of index test (95% CI)a = 67.2% (55.4% to 79.0%) Specificity of index test (95% CI)a = 98.8% (98.1% to 99.5%)
Source of funding	Supported in part by Roche Molecular Systems

Bibliographic reference	Bergmann JS and Woods GL (1996) Clinical evaluation of the Roche AMPLICOR PCR Mycobacterium tuberculosis test for detection of M. tuberculosis in respiratory specimens. Journal of Clinical Microbiology 34(5): 1083-5
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.8 Bergmann, 1999

Bibliographic reference	Bergmann JS, Yuoh G, Fish G and Woods GL (1999) Clinical evaluation of the enhanced Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test for rapid diagnosis of tuberculosis in prison inmates. Journal of Clinical Microbiology 37(5): 1419-25
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? age of participants unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes

Bibliographic reference	**Bergmann JS, Yuoh G, Fish G and Woods GL (1999) Clinical evaluation of the enhanced Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test for rapid diagnosis of tuberculosis in prison inmates. Journal of Clinical Microbiology 37(5): 1419-25**
	• Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	1005 specimens from 489 particpants
Patient characteristics	Inclusion Specimens submitted to the clinical microbiology laboratory for detection of mycobacteria Prison inmates for whom mycobacterial culture had been requested Sample characteristics Respiratory specimens: expectorated and induced sputum, bronchial washings, bronchoalveolar lavage fluid, and tracheal aspirates
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine O staining
Reference standard	BACTEC 460 (using 12B) and Middlebrook 7H11 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	Texas, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard

Bibliographic reference	**Bergmann JS, Yuoh G, Fish G and Woods GL (1999) Clinical evaluation of the enhanced Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test for rapid diagnosis of tuberculosis in prison inmates. Journal of Clinical Microbiology 37(5): 1419-25**
	Index test: Positive — TP 13, FP 9; Negative — FN 23, TN 959 Sensitivity of index test (95% CI)a = 36.1% (20.4% to 51.8%) Specificity of index test (95% CI)a = 99.1% (98.5% to 99.7%)
Source of funding	Supported in part by a Tuberculosis Academic Award from the National Heart, Lung, and Blood Institute
Comments	Data for enhanced Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.9 Blair, 1976

Bibliographic reference	**Blair EB, Brown GL and Tull AH (1976) Computer files and analyses of laboratory data from tuberculosis patients. II. Analyses of 6 years' data on sputum specimens. American Review of Respiratory Disease 113: 427-32**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? age of the included participants

Bibliographic reference	Blair EB, Brown GL and Tull AH (1976) Computer files and analyses of laboratory data from tuberculosis patients. II. Analyses of 6 years' data on sputum specimens. American Review of Respiratory Disease 113: 427-32
	unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	1620 specimens
Patient characteristics	Inclusion Patients admitted to the Tuberculosis Service Sample characteristics

Bibliographic reference	**Blair EB, Brown GL and Tull AH (1976) Computer files and analyses of laboratory data from tuberculosis patients. II. Analyses of 6 years' data on sputum specimens. American Review of Respiratory Disease 113: 427-32**
	Early morning sputum samples
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Stained with auramine O
Reference standard	Middlebrook 7H10 and 7H11 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 to 10 weeks
Location	US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive / Negative Index test – Positive: TP 693, FP 17 Index test – Negative: FN 455, TN 455 Sensitivity of index test (95% CI)a = 60.4% (57.5% to 63.2%) Specificity of index test (95% CI)a = 96.4% (94.7% to 98.1%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.10 Bodmer, 1994

Bibliographic reference	Bodmer T, Gurtner A, Schopfer K and Matter L (1994) Screening of respiratory tract specimens for the presence of Mycobacterium tuberculosis by using the Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 32(6): 1483-7
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Methods: prospective • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? details provided were limited, and data relating to the age of participants was lacking Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear, therefore moderate to high risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? moderate risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review

Bibliographic reference	**Bodmer T, Gurtner A, Schopfer K and Matter L (1994) Screening of respiratory tract specimens for the presence of Mycobacterium tuberculosis by using the Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 32(6): 1483-7**
	question? no Domain 4: Flow and timing Could the patient flow have introduced bias? no • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no, 4 were excluded due to contaminated cultures
Number of patients	617 specimens from 304 patients
Patient characteristics	Inclusion All respiratory tract specimens – including sputa (510 samples), tracheobronchial washings (55 samples) and bronchoalveolar washings (52) – that were received by the mycobacteriology laboratory in a 2-month period
Index test	Fluorescence microscopy Specimens were homogenised, decontaminated with sodium dodecyl sulphate-sodium hydroxide, neutralised and resuspended in phosphate-buffered saline
Reference standard	Löwenstein-Jensen and BACTEC 460 culture
Location	Switzerland(?)
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive TP 14 FP 10

Bibliographic reference	**Bodmer T, Gurtner A, Schopfer K and Matter L (1994) Screening of respiratory tract specimens for the presence of Mycobacterium tuberculosis by using the Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 32(6): 1483-7**
	Negative: FN = 7; TN = 586 Sensitivity of index test (95% CI)a = 66.7% (46.5% to 86.8%) Specificity of index test (95% CI)a = 98.3% (97.3% to 99.4%)
Source of funding	No details provided
Comments	Data for Amplified M. Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.11 Bonnet, 2011

Bibliographic reference	**Bonnet M, Gagnidze L, Githui W, Guérin PJ, Bonte L, et al (2011) Performance of LED-Based Fluorescence Microscopy to Diagnose Tuberculosis in a Peripheral Health Centre in Nairobi. PLoS ONE 6(2): e17214**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? yes risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	Bonnet M, Gagnidze L, Githui W, Guérin PJ, Bonte L, et al (2011) Performance of LED-Based Fluorescence Microscopy to Diagnose Tuberculosis in a Peripheral Health Centre in Nairobi. PLoS ONE 6(2): e17214
	• If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	497 could produce at least 1 specimen, resulting in 1394 collected specimens; only 389 provided culture samples
Patient characteristics	Inclusion Patients over 14 years of age with a cough for more than 2 weeks Sample characteristics **Mean age** mean (SD) 34.3 (11.6) **Gender ratio** (M:F) 1.6 (311:198) **Past TB history** n (%) 105 (20.6) –Duration since the last TB event in years median (IQR) 4.4 (2.4–7.7)

Bibliographic reference	**Bonnet M, Gagnidze L, Githui W, Guérin PJ, Bonte L, et al (2011) Performance of LED-Based Fluorescence Microscopy to Diagnose Tuberculosis in a Peripheral Health Centre in Nairobi. PLoS ONE 6(2): e17214**
Index test	Ziehl-Neelsen microscopy The 1st specimen was collected on the spot at initial consultation; the 2nd in the early morning at home and the 3rd on the spot when patient delivered the morning specimen to the clinic Two smears were prepared per specimen Decontamination using N-acetyl-L-cysteine/sodium hydroxide
	Fluorescence microscopy The 1st specimen was collected on the spot at initial consultation; the 2nd in the early morning at home and the 3rd on the spot when patient delivered the morning specimen to the clinic Two smears were prepared per specimen Decontamination using N-acetyl-L-cysteine/sodium hydroxide Auramne-O staining
Reference standard	Löwenstein-Jensen culture Decontamination using N-acetyl-L-cysteine/sodium hydroxide All positive cultures were confirmed for presence of acid fast bacilli by Ziehl-Neelsen microscopy
Location	Nairobi, Kenya
Outcomes measures and effect size	Diagnostic test accuracy – Ziel-Neelsen, 2 smears Reference standard Positive Negative Index test – Positive: TP 65, FP 10 Index test – Negative: FN 28, TN 286 Sensitivity of index test (95% CI)a = 69.9% (60.6% to 79.2%) Specificity of index test (95% CI)a = 96.6% (94.6% to 98.7%) Diagnostic test accuracy – Ziel-Neelsen, 3 smears Reference standard Positive Negative

Bibliographic reference	**Bonnet M, Gagnidze L, Githui W, Guérin PJ, Bonte L, et al (2011) Performance of LED-Based Fluorescence Microscopy to Diagnose Tuberculosis in a Peripheral Health Centre in Nairobi. PLoS ONE 6(2): e17214**

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 67	FP 12
	Negative	FN 26	TN 284

Sensitivity of index test (95% CI)a = 72.0% (62.9% to 81.2%)
Specificity of index test (95% CI)a = 96.0% (93.7% to 98.2%)
Diagnostic test accuracy – fluorescence, 2 smears

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 67	FP 8
	Negative	FN 26	TN 288

Sensitivity of index test (95% CI)a = 72.0% (62.9% to 81.2%)
Specificity of index test (95% CI)a = 97.3% (95.5% to 99.1%)
Diagnostic test accuracy – fluorescence, 3 smears

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 68	FP 9

Bibliographic reference	**Bonnet M, Gagnidze L, Githui W, Guérin PJ, Bonte L, et al (2011) Performance of LED-Based Fluorescence Microscopy to Diagnose Tuberculosis in a Peripheral Health Centre in Nairobi. PLoS ONE 6(2): e17214**
	Negative: FN 25, TN 287 Sensitivity of index test (95% CI)a = 73.1% (64.1% to 82.1%) Specificity of index test (95% CI)a = 97.0% (95.0% to 98.9%)
Source of funding	These authors have no support or funding to report
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.12 Bowles, 2011

Bibliographic reference	**Bowles EC, Freyée B, van Ingen J, Mulder B, Boeree M J and van Soolingen D (2011) Xpert MTB/RIF®, a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis. International Journal of Tuberculosis and Lung Disease 15(7): 988-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? no • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? details provided were limited, and data relating to the age of participants was lacking Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes

Bibliographic reference	**Bowles EC, Freyée B, van Ingen J, Mulder B, Boeree M J and van Soolingen D (2011) Xpert MTB/RIF®, a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis. International Journal of Tuberculosis and Lung Disease 15(7): 988-9**
	• If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	89 samples, though it is unclear how many patients these were obtained from
Patient characteristics	Presenting signs and symptoms: not reported Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated TB incidence rate: 6.8 per 100,000 Proportion of TB cases in the study: 71.9% Sample characteristics

Bibliographic reference	**Bowles EC, Freyée B, van Ingen J, Mulder B, Boeree M J and van Soolingen D (2011) Xpert MTB/RIF®, a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis. International Journal of Tuberculosis and Lung Disease 15(7): 988-9**
	86 sputum samples, 1 pleural fluid, 1 gastric fluid and 1 bronchial washing
Index test	Ziehl-Neelson microscopy
Reference standard	BACTEC MGIT 960
Location	Country: Netherlands World Bank Income Classification: high-income
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 40, FP 1 Index test – Negative: FN 24, TN 24 Sensitivity of index test (95% CI)a = 62.5% (50.6% to 74.3%) Specificity of index test (95% CI)a = 96.0% (88.3% to 100%)
Source of funding	No details provided
Comments	Data for Xpert MTB/RIF included in the Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.13 Breuninger, 2014

Bibliographic reference	**Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection

Bibliographic reference	**Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381**
	Could the selection of patients have introduced bias? low risk of bias • Methods: consecutive sample • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? some risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? no – a range of thresholds used Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear • Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes

Bibliographic reference	**Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381**
	• Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	861
Patient characteristics	*Inclusion* Individuals presenting with clinical signs and symptoms suggestive of pulmonary tuberculosis All adult patients were eligible if they initially presented with persistent cough of 2 weeks or more and at least one of the following tuberculosis associated findings: haemoptysis, chest pain, fever, night sweats, constant fatigue, recent unexplained weight loss, loss of appetite, malaise or contact with a known tuberculosis case *Exclusion* Patients who received antituberculosis treatment during the last year, were severely sick or did not reside within the study area were not included *Baseline characteristics*

Bibliographic reference	**Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381**
	Characteristic / No data / All n (%) 0 861 (100) Mean age (SD[1]) 0 42 (15) Female sex n (%) 0 433 (50) HIV positive n (%) 4 379 (44) History of TB n (%) 0 144 (17) **Symptoms at first visit** Cough ≥ 2 weeks n (%) 0 820 (95) Night sweats n (%) 1 426 (50) Haemoptysis n (%) 10 91 (11) Fever n (%) 0 470 (55) Weight loss n (%) 6 447 (52)
Index test	CAD4TB on chest radiograph Computer-aided detection system in which various subsystems for the detection of textural and shape abnormalities, for symmetry and correlation analyses operate at pixel and image level The analysis is broken down to several computable steps: • radiographs are pre-processed to normalise image features like resolution and grey scale • during segmentation, the next step, the software seeks the anatomical orientation of the image by demarcating structures like the lungs, clavicles and ribs • the defined lung fields are then analysed for their shape, global symmetry and local texture; in addition, a global correlation with a typical normal CXR is determined • scores generated by these subsystems are combined to an overall score for each image which summarises the result of the automated analysis as an abnormality score for the presence of active disease between 0–100
	Reading of chest radiograph by an ‘expert reader’

Bibliographic reference	**Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381**
	Categories: 1. normal 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. abnormal, findings highly suggestive for active TB
	Reading of chest radiograph by a clinical officer with practical experience but who was not considered 'expert' Categories: 1. normal 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. abnormal, findings highly suggestive for active TB
Reference standard	Löwenstein-Jensen and MGIT culture on 2 sputum specimens, one 'spot' and one early morning Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method
Location	Tanzania
Outcomes measures and effect size	Diagnostic test accuracy

Bibliographic reference	Breuninger M, van Ginneken B, Philipsen RH, Mhimbira F, Hella JJ, Lwilla F, van den Hombergh J, Ross A, Jugheli L, Wagner D and Reither K (2014) Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS One* 9(9): e106381

	Threshold for test positivity	Sens.[1] [%] (95%CI)	Spec.[2] [%] (95%CI)
CAD4TB	≥23	95 (91–98)	33 (27–39)
	≥37	91 (86–94)	52 (46–59)
	≥56	85 (79–90)	69 (62–75)
	≥74	77 (71–83)	79 (74–84)
	≥89	62 (55–69)	85 (80–89)
	≥95	47 (40–54)	94 (91–97)
Expert reader	4	59 (52–66)	98 (95–99)
	3,4	78 (71–83)	85 (80–89)
	2,3,4	84 (78–89)	72 (65–77)
Clinical officer	4	7 (4–12)	97 (94–99)
	3,4	76 (69–82)	65 (58–71)
	2,3,4	97 (94–99)	18 (13–24)

Source of funding	No details provided
Comments	

1.1.2.14 Burdash, 1975

Bibliographic reference	Burdash NM, West ME, Bannister ER, Dyar C and Duncan RC (1975) Evaluation of a dual-staining method for acid-fast bacilli. Journal of Clinical Microbiology 2(2): 149-50
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes

Bibliographic reference	Burdash NM, West ME, Bannister ER, Dyar C and Duncan RC (1975) Evaluation of a dual-staining method for acid-fast bacilli. Journal of Clinical Microbiology 2(2): 149-50
	• Did the study avoid inappropriate exclusions? yes, although limited information provided Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	250 samples, though it is unclear how many patients these were obtained from

Bibliographic reference	**Burdash NM, West ME, Bannister ER, Dyar C and Duncan RC (1975) Evaluation of a dual-staining method for acid-fast bacilli. Journal of Clinical Microbiology 2(2): 149-50**
Patient characteristics	Inclusion Sputum sample
Index tests	Ziehl-Neelson microscopy All specimens were digested and concentrated by the acetyl-cysteine-alkali procedure All slides were heat-fixed on an electric slide warmer before being stained Stain: Ziehl-Neelson
	Fluorescence microscopy All specimens were digested and concentrated by the acetyl-cysteine-alkali procedure All slides were heat-fixed on an electric slide warmer before being stained Stain: auramine-rhodamine
Reference standard	Löwenstein-Jensen culture All specimens were digested and concentrated by the acetyl-cysteine-alkali procedure Growth observed over an 8-week period
Location	US
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test – Positive: TP 29, FP 0 Index test – Negative: FN 2, TN 219 Sensitivity of index test (95% CI)a = 93.6% (84.9% to 100%) Specificity of index test (95% CI)a = 100% (100% to 100%) Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative

Bibliographic reference	**Burdash NM, West ME, Bannister ER, Dyar C and Duncan RC (1975) Evaluation of a dual-staining method for acid-fast bacilli. Journal of Clinical Microbiology 2(2): 149-50**
	Index test: Positive — TP 30, FP 2; Negative — FN 1, TN 217 Sensitivity of index test (95% CI)a = 96.8% (90.6% to 100%) Specificity of index test (95% CI)a = 99.1% (97.8% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.15 Carriquiry, 2012

Bibliographic reference	**Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, et al (2012) A diagnostic accuracy study of Xpert®MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One 7(9): e44626**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s)

Bibliographic reference	Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, et al (2012) A diagnostic accuracy study of Xpert®MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One 7(9): e44626
	Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	133 patients
Patient characteristics	Inclusion Patients 18 years of age or older Diagnosis of HIV confirmed by Western Blot High clinical suspicion of TB, defined as cough for ten or more days with concurrent abnormal chest x-ray (cavity, focal opacity, pleural effusion, nodule or lymphadenopathy) and at least one of the following symptoms: fever, fatigue, night

Bibliographic reference	**Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, et al (2012) A diagnostic accuracy study of Xpert®MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One 7(9): e44626**
	sweats, hemoptysis, chest pain or weight loss Exclusion Patients who had received more than two doses of TB treatment Patients who did not provide a second sputum sample with the required volume Patient characteristics Presenting signs and symptoms: cough for greater than 10 days with abnormal chest X-ray and at least one of the following symptoms: fever, fatigue, night sweats, haemoptysis, chest pain, or weight loss Age: median 35 years, interquartile range 29 to 42 Sex, female: 27.5% HIV infection: 100% History of TB: 57.3% TB incidence rate: 101 per 100,000 Proportion of TB cases in the study: 34.4%
Index test	Ziehl-Neelsen microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen culture or MGIT 960 Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Country: Peru World Bank Income Classification: middle-income
Outcomes measures and effect size	Diagnostic test accuracy

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 31	FP 3
Index test: Negative		FN 14	TN 85

Bibliographic reference	Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, et al (2012) A diagnostic accuracy study of Xpert®MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One 7(9): e44626
	Sensitivity of index test (95% CI)a = 68.9% (55.4% to 82.4%) Specificity of index test (95% CI)a = 96.6% (92.8% to 100%)
Source of funding	This study was supported by Fogarty International Center at the U.S. National Institutes of Health (NIH) through Peru International Clinical, Operational, and Health Services Research and Training Award (Peru ICOHRTA network for AIDS/TB research) institutional collaboration with the Institute of Tropical Medicine in Antwerp, Belgium The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Comments	Data for Xpert MTB/RIF included in the Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.16 Cartuyvels, 1996

Bibliographic reference	Cartuyvels R, De Ridder C, Jonckheere S, Verbist L and Van Eldere J (1996) Prospective clinical evaluation of Amplicor Mycobacterium tuberculosis PCR test as a screening method in a low-prevalence population. Journal of Clinical Microbiology 34(8): 2001-3
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Methods: in the designated period (May to August 1994) all respiratory samples that contained sufficient material (>1.5 ml) were examined • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear if all participants are 18 years or older Domain 2: Index test(s)

Bibliographic reference	Cartuyvels R, De Ridder C, Jonckheere S, Verbist L and Van Eldere J (1996) Prospective clinical evaluation of Amplicor Mycobacterium tuberculosis PCR test as a screening method in a low-prevalence population. Journal of Clinical Microbiology 34(8): 2001-3
	Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? 4 excluded as they were found to have nontuberculous mycobacteria
Number of patients	656 samples, from 102 outpatients and 434 hospitalised patients; data provided for 652 (4 excluded as they were found to have nontuberculous mycobacteria)
Patient characteristics	Inclusion Respiratory samples containing sufficient material for examination (>1.5 ml) Sample characteristics 372 sputum samples, 212 bronchial and tracheal aspirates, and 72 bronchoalveolar lavages

Bibliographic reference	**Cartuyvels R, De Ridder C, Jonckheere S, Verbist L and Van Eldere J (1996) Prospective clinical evaluation of Amplicor Mycobacterium tuberculosis PCR test as a screening method in a low-prevalence population. Journal of Clinical Microbiology 34(8): 2001-3**
	13.3 cases of tuberculosis per 100,000 population – i.e. low prevalence population
Index test	Fluorescence microscopy Decontamination with sodium citrate N-acetyl-cysteine
Reference standard	Löwenstein-Jensen culture Decontamination with sodium citrate N-acetyl-cysteine
Location	Belgium
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 12, FP 0 Index test Negative: FN 13, TN 627 Sensitivity of index test (95% CI)a = 48.0% (28.4% to 67.6%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	No details provided
Comments	Data for Amplicor included in the Ling et al (2008) meta-analysis
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.17 Chaidir, 2013

Bibliographic reference	**Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, et al (2013) Implementation of LED Fluorescence Microscopy for Diagnosis of Pulmonary and HIV-Associated Tuberculosis in a Hospital Setting in Indonesia. PLoS ONE 8(4): e61727**
Study type	Cross-sectional

Bibliographic reference	Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, et al (2013) Implementation of LED Fluorescence Microscopy for Diagnosis of Pulmonary and HIV-Associated Tuberculosis in a Hospital Setting in Indonesia. PLoS ONE 8(4): e61727
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no data on age of included population Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? unclear risk of bias

Bibliographic reference	Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, et al (2013) Implementation of LED Fluorescence Microscopy for Diagnosis of Pulmonary and HIV-Associated Tuberculosis in a Hospital Setting in Indonesia. PLoS ONE 8(4): e61727
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? A total of 527 suspects were recruited into group 1; of these, cultures were contaminated in 19 patients and the results from either ZN or LED-FM results were lacking in 2 patients, leaving 506 patients for further analysis. A total of 263 suspects were included; of these, cultures were contaminated in 3 patients, and the smear results were unavailable in 4 patients, leaving 256 patients for analysis.
Number of patients	527 outpatients not (yet) taking TB treatment and with a very low risk of being HIV-infected (group 1) and 263 HIV-infected patients either from the outpatient clinic or the HIV clinic in the hospital (group 2) were included
Patient characteristics	Inclusion Patients with suspected pulmonary TB, defined by the presence of cough ≥2 week duration with or without chest X-ray (CXR) abnormalities Sample characteristics Low risk of HIV group (group 1): one sputum sample used per patient HIV-positive group (group 2): one to three consecutive sputum samples were collected per patient
Index tests	Ziehl-Neelson microscopy 102 specimens from group 1 were prepared from sputum sediment after decontamination (direct smear); all other specimens (425 from group 1, and all 263 from group 2) Slides examined with bright-field microscopy
	LED-fluorescence microscopy 102 specimens from group 1 were prepared from sputum sediment after decontamination (direct smear); all other specimens (425 from group 1, and all 263 from group 2) Stained using auramin O and examined with an LED-fluorescence microscope
Reference standard	Ogawa culture Decontaminated by a standard N-acetyl-L-cystein-NaOH method and concentrated by centrifugation Cultures were considered positive when mycobacterial growth ≥1 colony forming unit was observed within 8 weeks of incubation

Bibliographic reference	Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, et al (2013) Implementation of LED Fluorescence Microscopy for Diagnosis of Pulmonary and HIV-Associated Tuberculosis in a Hospital Setting in Indonesia. PLoS ONE 8(4): e61727
Location	West Java Province, Indonesia
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy – low risk of HIV Sensitivity of index test (95% CI) (n = 404) = 52.8% (47.9% to 57.7%) Specificity of index test (95% CI) (n = 404) = 96.6% (94.8% to 98.4%) Diagnostic test accuracy – Ziehl-Neelson microscopy – HIV-positive Sensitivity of index test (95% CI) (n = 256) = 58.0% (52.0% to 64.0%) Specificity of index test (95% CI) (n = 256) = 96.3% (94.0% to 98.6%)
	Diagnostic test accuracy – LED-fluorescence microscopy – low risk of HIV Sensitivity of index test (95% CI) (n = 404) = 75.5% (71.3% to 79.7%) Specificity of index test (95% CI) (n = 404) = 90.0% (87.1% to 93.0%) Diagnostic test accuracy – LED-fluorescence microscopy – HIV-positive Sensitivity of index test (95% CI) (n = 256) = 65.2% (59.4% to 71.0%) Specificity of index test (95% CI) (n = 256) = 90.4% (86.8% to 94.0%)
Source of funding	Financially supported by IMPACT, a 5-year HIV program supported by the European Commission The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.18 Coll, 2003

Bibliographic reference	Coll P, Garrigó M, Moreno C and Martí N (2003) Routine use of Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) test for detection of Mycobacterium tuberculosis with smear-positive and smear-negative specimens. International Journal of Tuberculosis and Lung Disease 7(9): 886-91
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes

Bibliographic reference	Coll P, Garrigó M, Moreno C and Martí N (2003) Routine use of Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) test for detection of Mycobacterium tuberculosis with smear-positive and smear-negative specimens. International Journal of Tuberculosis and Lung Disease 7(9): 886-91
	• Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	3308 specimens collected from 2352 patients

Bibliographic reference	**Coll P, Garrigó M, Moreno C and Martí N (2003) Routine use of Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) test for detection of Mycobacterium tuberculosis with smear-positive and smear-negative specimens. International Journal of Tuberculosis and Lung Disease 7(9): 886-91**
Patient characteristics	Exclusion Grossly bloody specimens Patients already diagnosed with tuberculosis and receiving antituberculosis drugs Specimens with insufficient volume to perform smear, culture and the Amplified Mycobacterium Tuberculosis Direct Test according to the laboratory's procedures
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine-rhodamine staining
Reference standard	Löwenstein-Jensen and BACTEC culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Barcelona, Spain
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive / Negative Index test – Positive: TP 185, FP 48 Index test – Negative: FN 75, TN 2996 Sensitivity of index test (95% CI)a = 71.2% (65.7% to 76.7%) Specificity of index test (95% CI)a = 98.4% (98.0% to 98.9%)
Source of funding	No details provided
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review

a Calculated by reviewer

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.1.2.19 Cuevas, 2011

Bibliographic reference	Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? moderate risk of bias

Bibliographic reference	Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? A total of 2,445 patients – 37% of 6,628 patients enrolled for the larger trial in which this study is nested – were enrolled; data only available for 2355
Number of patients	2355
Patient characteristics	Inclusion 18 years or older Cough of 2 weeks duration or more Patient characteristics

Bibliographic reference	Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057

Characteristic	Sub-Category	Ethiopia (*n* = 468)	Nepal (*n* = 526)	Nigeria (*n* = 685)	Yemen (*n* = 766)	All (*n* = 2,445)
Age, mean (SD)		34.9 (14.3)	43.6 (17.7)	34.3 (11.1)	41 (17.9)	38.6 (16.1)
Sex	Male	243 (52.5)	344 (65)	319 (46.6)	388 (59.6)	1,294 (52.9)
	Female	220 (47.5)	182 (35)	353 (51.5)	378 (49.3)	1,133 (46.3)
	Unknown	5	0	13	0	17 (0.7)
Marital status	Single	87 (18.5)	85 (16.2)	237 (34.5)	133 (17.4)	542 (22.2)
	Married	317 (67.7)	439 (83.5)	371 (54.1)	552 (72)	1,679 (68.7)
	Separated/widowed	5 (1)	2 (0.4)	64 (9.3)	81 (10.5)	152 (6.2)
	Unknown	59 (11.6)	0	13 (1.9)	0	72 (2.9)
Residence	Rural	273 (58.3)	39 (7.4)	90 (13.1)	388 (50.7)	790 (32.3)
	Study town	116 (24.8)	238 (45.2)	549 (81.1)	352 (46)	1,255 (51.3)
	Other town	49 (10.5)	249 (47.3)	33 (4.8)	26 (3.4)	357 (14.6)
	Unknown	30 (6.4)	0	13 (1.9)	0	43 (1.8)
Education	Illiterate	281 (60.0)	164 (31.2)	58 (8.5)	517 (67.5)	1,020 (41.7)
	Literate	127 (27.1)	362 (68.8)	614 (89.6)	249 (32.5)	1,352 (55.3)
	Unknown	60 (12.8)	0	13 (1.9)	0	73 (3)
Signs/symptoms	Cough duration	7.8 (9.2)	12.8 (13.6)	8.9 (16.7)	7.8 (11.9)	9.3 (13.5)
	Chest pain	321 (68.5)	424 (80.3)	443 (64.7)	680 (88.8)	1,868 (76.4)
	Weight loss	274 (58.5)	331 (62.9)	437 (63.8)	608 (79.4)	1,650 (67.5)
	Fever	259 (55.3)	243 (46.2)	461 (66.3)	625 (81.6)	1,588 (64.9)
	Night sweats	319 (68.1)	261 (49.6)	291 (42.5)	599 (78.2)	1,470 (60.1)
	Loss of appetite	313 (66.8)	361 (68.6)	301 (43.9)	527 (68.8)	1,502 (61.4)
	Haemoptysis	40 (9)	90 (17.1)	50 (7.3)	208 (27.2)	388 (15.9)
HIV	Positive	4 (0.9)	2 (0.4)	236 (34.4)	0	242 (9.9)
	Negative	33 (7.1)	8 (1.5)	109 (15.9)	9 (1.2)	159 (6.5)
	Unknown	431 (92)	516 (98)	340 (49.6)	757 (98.8)	2,044 (83.6)
Culture	Positive	159 (34)	58 (11)	120 (17.5)	192 (25.1)	529 (21.6)
	Negative	270 (57.7)	444 (84.4)	551 (81)	561 (72.2)	1,826 (74.6)
	Contaminated	10 (2.1)	23 (4.4)	14 (2)	10 (1.3)	57 (2.3)
	Not available	29 (6.2)	1 (0.2)	0 (0)	3 (0.4)	33 (1.3)

Age in years, cough duration in weeks. $p<0.01$ for all variables. SD, standard deviation.

Index test	Ziehl-Neelson microscopy

Bibliographic reference	**Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057**
	Evaluation of the second and third smears Smears were classified as positive when ≥1 AFB was detected per 100 fields, and patients were considered smear-positive if they had ≥1 positive smear
	Fluorescence microscopy Evaluation of the second and third smears Stained with auramine O and counterstained with potassium permanganate Smears were classified as positive when ≥1 AFB was detected per 100 fields, and patients were considered smear-positive if they had ≥1 positive smear
Reference standard	Solid culture The morning specimen, or, if not available, a spot specimen, was concentrated (Petroff's method) and cultured on solid medium
Location	Patients (468; 19%) enrolled in Ethiopia were attending Bushullo Major and Awassa Health Centres, the main health service providers for Awassa District in the Southern Region; smear microscopy was conducted in the health centres' laboratories, and sputum specimens were cultured at the Armauer Hansen Institute, Addis Ababa. Patients in Abuja, Nigeria (685; 28%), were enrolled in Wuse District Hospital, and sputum specimens were processed in the Zankli Medical Centre laboratory, a private laboratory acting as a diagnostic centre for the National Tuberculosis Programme In Nepal, patients (526; 22%) were enrolled from the TB DOTS centre of Tribhuvan University Teaching Hospital and the Dirgh Jeevan Health Care and Research Centre, both in Kathmandu; sputum specimens collected in both centres were processed in Tribhuvan University Health Research Laboratory In Yemen, patients (766; 31%) were enrolled at the Tuberculosis Institute, which is the reference centre and headquarters of the National Tuberculosis Programme and which provides diagnostic services to the surrounding population and referred patients
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy – 2 smears Reference standard Positive Negative Index test Positive TP FP 348 36

Bibliographic reference	Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057

	Negative	FN 181	TN 1790

Sensitivity of index test (95% CI)a = 65.8% (61.7% to 69.8%)
Specificity of index test (95% CI)a = 98.0% (97.4% to 98.7%)

Diagnostic test accuracy – Ziehl-Neelson microscopy – 3 smears

		Reference standard	
		Positive	Negative
Index test	Positive	TP 373	FP 63
	Negative	FN 156	TN 1763

Sensitivity of index test (95% CI)a = 70.5% (66.6% to 74.4%)
Specificity of index test (95% CI)a = 96.6% (95.7% to 97.4%)

Diagnostic test accuracy – fluorescence microscopy – 2 smears

		Reference standard	
		Positive	Negative
Index test	Positive	TP 385	FP 166
	Negative	FN 144	TN 1660

Bibliographic reference	**Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, et al (2011) LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation. PLoS Medicine 8(7): e1001057**
	Sensitivity of index test (95% CI)a = 72.8% (69.0% to 76.6%) Specificity of index test (95% CI)a = 90.9% (89.6% to 92.2%)
	Diagnostic test accuracy – fluorescence microscopy – 3 smears Reference standard Positive Negative Index test Positive: TP 408, FP 217 Negative: FN 121, TN 1609 Sensitivity of index test (95% CI)a = 77.1% (73.6% to 80.7%) Specificity of index test (95% CI)a = 88.1% (86.6% to 89.6%)
Source of funding	Funded by the Bill & Melinda Gates Foundation and the United States Agency for International Development through grants awarded to the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; these funders did not play any role in study design, data collection, decision to publish, the analysis or interpretation of the data for the study or preparation of the manuscript The LUMIN and the QBC Paralens Fluorescence Microscopy Systems were provided free of charge by LW Scientific, which also paid the costs of shipping the systems to study sites; no other financial support was provided by LW Scientific or by QBC Diagnostics; information supplied on the fluorescence microscopy systems by LW Scientific or QBC Diagnostics consisted only of technical support materials that are made available to all purchasers of the units, or that could be obtained via the LW Scientifics or QBC Diagnostics technical help desk, and neither LW Scientific nor QBC Diagnostics were involved in the design, conduct or analysis of the study, or in the preparation of the manuscript or decision to publish the study
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.20 Dalovisio, 1996

Bibliographic reference	Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchinson L, Lindley MF, Nunez BM, Praba A, Eisenach KD and Cooper ES (1996) Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. Clinical Infectious Diseases 23: 1099-106
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? moderate to high risk of bias • Methods: all respiratory specimens submitted to the Oschner Foundation Hospital laboratory for mycobacterial culture (n = 299); all acid-fast bacilli smear-positive specimens from the Medical Center of Lousiana (n = 83); and all acid-fast bacilli smear-negative specimens from the Medical Center of Lousiana that were ultimately culture-positive (n = 46) – fairly selective • Was a consecutive or random sample of patients enrolled? yes, but only within the aforementioned groups • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? more selective than intended; it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? • Were the index test results interpreted without knowledge of the results of the reference standard? • If a threshold was used, was it pre-specified? Is there concern that the index test, its conduct, or interpretation differ from the review question? Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? • Is the reference standard likely to correctly classify the target condition?

Bibliographic reference	**Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchinson L, Lindley MF, Nunez BM, Praba A, Eisenach KD and Cooper ES (1996) Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. Clinical Infectious Diseases 23: 1099-106**
	• Were the reference standard results interpreted without knowledge of the results of the index test? Is there concern that the target condition as defined by the reference standard does not match the review question? Protocol states that we are interested in culture-only, but this reference standard also includes the possibility for clinical diagnosis (culture and/or radiography with a history and laboratory findings consistent with tuberculosis infection, historical risk factors for tuberculosis infection, a positive tuberculin skin test and the absence of other diagnoses to explain the clinical abnormalities); however, only 7 of a total of 428 specimens (98 of which were considered to be TB) are clinically positive but culture negative Domain 4: Flow and timing Could the patient flow have introduced bias? • Was there an appropriate interval between index test(s) and reference standard? • Did all patients receive a reference standard? • Did patients receive the same reference standard? • Were all patients included in the analysis?
Number of patients	428
Patient characteristics	Inclusion All respiratory specimens submitted to the Oschner Foundation Hospital laboratory for mycobacterial culture (n = 299) All acid-fast bacilli smear-positive specimens from the Medical Center of Lousiana (n = 83) All acid-fast bacilli smear-negative specimens from the Medical Center of Lousiana that were ultimately culture-positive (n = 46) Sample characteristics Sputum and bronchoalveolar lavage
Index tests	Fluorescence microscopy (Oschner Foundation Hospital laboratory) Decontaminated by a standard N-acetyl-L-cystein-NaOH method Stained with auramine fluorochrome OR Ziehl-Neelson microscopy

Bibliographic reference	**Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchinson L, Lindley MF, Nunez BM, Praba A, Eisenach KD and Cooper ES (1996) Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. Clinical Infectious Diseases 23: 1099-106**
	Amplicor Mycobacterium tuberculosis Test Decontaminated by a standard N-acetyl-L-cystein-NaOH method
	Amplified Mycobacterium tuberculosis Direct Test Decontaminated by a standard N-acetyl-L-cystein-NaOH method
Reference standard	Culture and/or clinical findings Culture (Oschner Foundation Hospital): • decontaminated by a standard N-acetyl-L-cystein-NaOH method • inoculated into BACTEC 12B bottles, Middlebrook 7H11 and Löwenstein-Jensen • 8-week incubation • mycobacteria identification primarily by DNA hybridisation (Accuprobe), but also biochemical tests when necessary Culture (Medical Center of Lousiana): • decontaminated by a standard N-acetyl-L-cystein-NaOH method • inoculated into BACTEC 12B bottles • 6-week incubation • mycobacteria identification by DNA hybridisation (Accuprobe) Clinical findings: • radiography • a history and laboratory findings consistent with tuberculosis infection • historical risk factors for tuberculosis infection • a positive tuberculin skin test • absence of other diagnoses to explain the clinical abnormalities
Location	Oschner Foundation Hospital and the Medical Center of Lousiana, New Orleans, US
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test Positive TP 49 FP 36

Bibliographic reference	**Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchinson L, Lindley MF, Nunez BM, Praba A, Eisenach KD and Cooper ES (1996) Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. Clinical Infectious Diseases 23: 1099-106**

	Negative	FN 49	TN 294

Sensitivity of index test (95% CI)a = 50.0% (40.1% to 59.9%)
Specificity of index test (95% CI)a = 89.1% (85.7% to 92.5%)

Diagnostic test accuracy – Amplicor

		Reference standard	
		Positive	Negative
Index test	Positive	TP 78	FP 13
	Negative	FN 20	TN 317

Sensitivity of index test (95% CI)a = 79.6% (71.6% to 87.6%)
Specificity of index test (95% CI)a = 96.1% (94.0% to 98.2%)

Diagnostic test accuracy – Amplified M.TB Direct Test

		Reference standard	
		Positive	Negative
Index test	Positive	TP 82	FP 7

Bibliographic reference	**Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchinson L, Lindley MF, Nunez BM, Praba A, Eisenach KD and Cooper ES (1996) Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. Clinical Infectious Diseases 23: 1099-106**
	Negative FN 16 TN 323 Sensitivity of index test (95% CI)a = 83.7% (76.4% to 91.0%) Specificity of index test (95% CI)a = 97.9% (96.3% to 99.4%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.21 D'Amato, 1995

Bibliographic reference	**D'Amato RF, Wallman AA, Hochstein LH, Colaninno PM, Scardamaglia M, Ardila E, Ghouri M, Kim K, Patel RC and Miller A (1995) Rapid diagnosis of pulmonary tuberculosis by using Roche AMPLICOR Mycobacterium tuberculosis PCR test. Journal of Clinical Microbiology 33(7): 1832-4**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	D'Amato RF, Wallman AA, Hochstein LH, Colaninno PM, Scardamaglia M, Ardila E, Ghouri M, Kim K, Patel RC and Miller A (1995) Rapid diagnosis of pulmonary tuberculosis by using Roche AMPLICOR Mycobacterium tuberculosis PCR test. Journal of Clinical Microbiology 33(7): 1832-4
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	985 specimens from 372 participants
Patient characteristics	Sample characteristics Specimens were limited to expectorated and induced sputa, bronchoalveolar lavages, and bronchial washings
Index test	Kinyoun microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	MB-Chek AFB culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide

Bibliographic reference	**D'Amato RF, Wallman AA, Hochstein LH, Colaninno PM, Scardamaglia M, Ardila E, Ghouri M, Kim K, Patel RC and Miller A (1995) Rapid diagnosis of pulmonary tuberculosis by using Roche AMPLICOR Mycobacterium tuberculosis PCR test. Journal of Clinical Microbiology 33(7): 1832-4**
	Incubated for 8 weeks
Location	New York, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 14, FP 22 Negative: FN 41, TN 908 Sensitivity of index test (95% CI)a = 25.5% (13.9% to 37.0%) Specificity of index test (95% CI)a = 97.6% (96.7% to 98.6%)
Source of funding	No details provided
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.22 Damle and Kaundinya, 1986

Bibliographic reference	**Damle AS and Kaundinya DV (1986) Demonstration of acid-fact bacilli in sputum smears. Journal of the Indian Medical Association 84(2): 33-5**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear

Bibliographic reference	Damle AS and Kaundinya DV (1986) Demonstration of acid-fact bacilli in sputum smears. Journal of the Indian Medical Association 84(2): 33-5
	• Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear

Bibliographic reference	Damle AS and Kaundinya DV (1986) Demonstration of acid-fact bacilli in sputum smears. Journal of the Indian Medical Association 84(2): 33-5
Number of patients	208 participants
Patient characteristics	Inclusion Patients from the tuberculosis ward
Index tests	Fluorescence microscopy Auramine-phenol staining
	Ziehl-Neelson microscopy
Reference standard	Löwenstein-Jensen culture Incubation for 8 weeks
Location	Ambajogai, India
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative Index test – Positive: TP 186, FP 0 Index test – Negative: FN 14, TN 8 Sensitivity of index test (95% CI)a = 93.0% (89.5% to 96.5%) Specificity of index test (95% CI)a = 100% (100% to 100%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test – Positive: TP 186, FP 4

Bibliographic reference	Damle AS and Kaundinya DV (1986) Demonstration of acid-fact bacilli in sputum smears. Journal of the Indian Medical Association 84(2): 33-5
	Negative: FN 14, TN 4 Sensitivity of index test (95% CI)a = 93.0% (89.5% to 96.5%) Specificity of index test (95% CI)a = 66.7% (40.0% to 93.3%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.23 Denis, 1998

Bibliographic reference	Denis O, Devaster JM, Vandenberg O, Vanachter H, Lafontaine T, Lin C and Butzler JP (1998) Evaluation of ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Zentralblatt fur Bakteriologie 288(1): 59-65
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	**Denis O, Devaster JM, Vandenberg O, Vanachter H, Lafontaine T, Lin C and Butzler JP (1998) Evaluation of ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Zentralblatt fur Bakteriologie 288(1): 59-65**
	• If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	226 specimens from 208 participants
Patient characteristics	Inclusion Patients suspected of pulmonary tuberculosis on clinical basis, including the patient's history, signs, symptoms, chest X ray, and anti-tuberculous treatment Sample characteristics Respiratory
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine O staining

Bibliographic reference	**Denis O, Devaster JM, Vandenberg O, Vanachter H, Lafontaine T, Lin C and Butzler JP (1998) Evaluation of ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Zentralblatt fur Bakteriologie 288(1): 59-65**
Reference standard	Löwenstein-Jensen and Colestos culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Saint-Pierre University Hospital, Brussels, Belgium
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 12, FP 8 Index test Negative: FN 3, TN 203 Sensitivity of index test (95% CI)a = 80.0% (59.8% to 100%) Specificity of index test (95% CI)a = 96.2% (93.6% to 98.8%)
Source of funding	Supported by the Fondation Vesale of Saint-Pierre University Hospital, Brussels Abbott Laboratories provided the kits and reagents for the LCx MTB
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.24 Devallois, 1996

Bibliographic reference	**Devallois A, Legrand E and Rastogi N (1996) Evaluation of Amplicor MTB test as adjunct to smears and culture for direct detection of Mycobacterium tuberculosis in the French Caribbean. Journal of Clinical Microbiology 34(5): 1065-8**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias

Bibliographic reference	Devallois A, Legrand E and Rastogi N (1996) Evaluation of Amplicor MTB test as adjunct to smears and culture for direct detection of Mycobacterium tuberculosis in the French Caribbean. Journal of Clinical Microbiology 34(5): 1065-8
	• Methods: unclear • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no, though details provided were limited; it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? Amplicor no longer available in the UK Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias?

Bibliographic reference	**Devallois A, Legrand E and Rastogi N (1996) Evaluation of Amplicor MTB test as adjunct to smears and culture for direct detection of Mycobacterium tuberculosis in the French Caribbean. Journal of Clinical Microbiology 34(5): 1065-8**
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	784 specimens collected from 370 individuals
Patient characteristics	Inclusion Individuals suspected of or known to have tuberculosis Sample characteristics Included sputum specimens, bronchial aspirates and gastric washings
Index test	Amplicor Mycobacterium tuberculosis test Decontamination with sodium lauryl sulfate
Reference standard	Löwenstein-Jensen culture Decontamination with sodium lauryl sulfate
Location	Guadaloupe
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 33, FP 17 Index test – Negative: FN 18, TN 716 Sensitivity of index test (95% CI)a = 64.7% (51.6% to 77.8%)

Bibliographic reference	Devallois A, Legrand E and Rastogi N (1996) Evaluation of Amplicor MTB test as adjunct to smears and culture for direct detection of Mycobacterium tuberculosis in the French Caribbean. Journal of Clinical Microbiology 34(5): 1065-8
	Specificity of index test (95% CI)a = 97.7% (96.6% to 98.8%)
Source of funding	Financial support provided through Projet CORDET of the Ministry of Overseas Departments and Territories, and the Ministry of Education and Research, of the French Republic Material and reagents for PCR evaluation provided by Roche Diagnostic Systems, and Labsystems provided the Multiwash-AR apparatus and Multiskan MS microplate reader
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.25 Fegou, 2005

Bibliographic reference	Fegou E, Jelastopulu E, Sevdali M, Anastassiou ED, Dimitracopoulos G and Spiliopoulou I (2005) Sensitivity of the Cobas Amplicor system for detection of Mycobacterium tuberculosis in respiratory and extrapulmonary specimens. Clinical Microbiology and Infection 11(7): 593-6
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	**Fegou E, Jelastopulu E, Sevdali M, Anastassiou ED, Dimitracopoulos G and Spiliopoulou I (2005) Sensitivity of the Cobas Amplicor system for detection of Mycobacterium tuberculosis in respiratory and extrapulmonary specimens. Clinical Microbiology and Infection 11(7): 593-6**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	3078 specimens
Patient characteristics	Inclusion Patients (1–3 specimens/patient) with suspected tuberculosis Sample characteristics Respiratory
Index test	Ziehl-Neelson microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen, Bactec Myco/F-Sputa and Bactec Myco/F Lytic culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks

Bibliographic reference	**Fegou E, Jelastopulu E, Sevdali M, Anastassiou ED, Dimitracopoulos G and Spiliopoulou I (2005) Sensitivity of the Cobas Amplicor system for detection of Mycobacterium tuberculosis in respiratory and extrapulmonary specimens. Clinical Microbiology and Infection 11(7): 593-6**
Location	Patras, Greece
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive / Negative Index test – Positive: TP 135, FP 41 Index test – Negative: FN 164, TN 2738 Sensitivity of index test (95% CI)a = 41.2% (39.5% to 50.8%) Specificity of index test (95% CI)a = 98.5% (98.1% to 99.0%)
Source of funding	No details provided
Comments	Data for Cobas Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.26 Gamboa, 1997

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes

Bibliographic reference	Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55
	• Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
	• Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	226 respiratory specimens
Patient characteristics	Inclusion Suspicion of pulmonary tuberculosis or patients who had received antituberculosis chemotherapy Sample characteristics 184 spontaneous specimens, 28 bronchial and tracheal aspirates, and 14 bronchalveolar lavage
Index test	Ziehl-Neelson microscopy Decontamination with sodium lauryl sulfate
	Amplified Mycobacterium Tuberculosis Direct Test Decontamination with sodium lauryl sulfate
Reference standard	Löwenstein-Jensen (solid), Colestos (solid) and BACTEC 12B (liquid) culture Decontamination with sodium lauryl sulphate 8-week incubation Solid media were read weekly, and liquid culture read twice weekly for the first 2 weeks and weekly thereafter
Location	Hospital Universitario German Trias i Pujol, Barcelona, Spain
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy

		Reference standard	
		Positive	Negative
Index test	Positive	TP 28	FP 20
	Negative	FN 12	TN 166

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
	Sensitivity of index test (95% CI)a = 70.0% (55.8% to 84.2%) Specificity of index test (95% CI)a = 89.3% (84.8% to 93.7%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.27 Githui, 1993

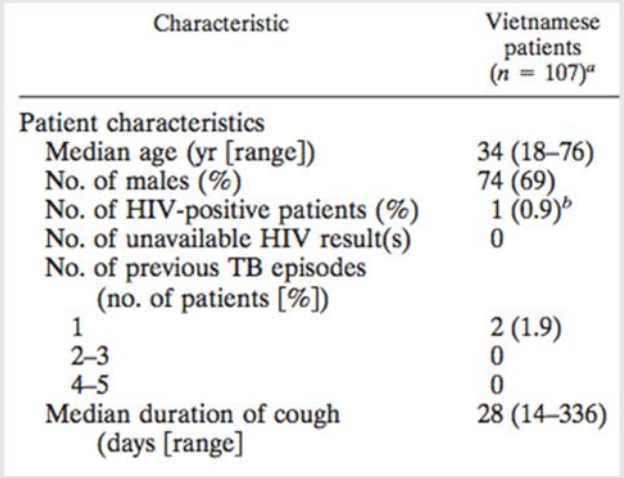
Bibliographic reference	**Githui W, Kitui F, Juma ES, Obwana DO, Mwai J and Kwamanga D (1993) A comparative study on the reliability of the fluorescence microscopy and Ziehl-Neelsen method in the diagnosis of pulmonary tuberculosis. East African Medical Journal 70(5): 263-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, were under 18 years of age Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	**Githui W, Kitui F, Juma ES, Obwana DO, Mwai J and Kwamanga D (1993) A comparative study on the reliability of the fluorescence microscopy and Ziehl-Neelsen method in the diagnosis of pulmonary tuberculosis. East African Medical Journal 70(5): 263-6**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	1480 specimens
Patient characteristics	Sample characteristics Sputum samples sent to the laboratory for examination for acid-fast bacilli
Index test	Fluorescence microscopy Auramine staining
	Ziehl-Neelson microscopy
Reference standard	Löwenstein-Jensen culture Incubation for 8 weeks
Location	Nairobi, Kenya
Outcomes measures and	Diagnostic test accuracy – fluorescence microscopy

Bibliographic reference	**Githui W, Kitui F, Juma ES, Obwana DO, Mwai J and Kwamanga D (1993) A comparative study on the reliability of the fluorescence microscopy and Ziehl-Neelsen method in the diagnosis of pulmonary tuberculosis. East African Medical Journal 70(5): 263-6**
effect size	Reference standard Positive Negative Index test Positive: TP 760, FP 22 Index test Negative: FN 192, TN 506 Sensitivity of index test (95% CI)a = 79.8% (77.3% to 82.4%) Specificity of index test (95% CI)a = 95.8% (94.1% to 97.5%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test Positive: TP 618, FP 16 Index test Negative: FN 334, TN 512 Sensitivity of index test (95% CI)a = 64.9% (61.9% to 68.0%) Specificity of index test (95% CI)a = 97.0% (95.5% to 98.4%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.28 Helb, 2010

Bibliographic reference	**Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, Kop J, Owens MR, Rodgers R, Banada P, Safi H, Blakemore R, Lan NT, Jones-López EC, Levi M, Burday M, Ayakaka I, Mugerwa RD, McMillan B, Winn-Deen E, Christel L, Dailey P, Perkins MD, Persing DH and Alland D (2010) Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. Journal of Clinical Microbiology 48(1): 229-37**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, Kop J, Owens MR, Rodgers R, Banada P, Safi H, Blakemore R, Lan NT, Jones-López EC, Levi M, Burday M, Ayakaka I, Mugerwa RD, McMillan B, Winn-Deen E, Christel L, Dailey P, Perkins MD, Persing DH and Alland D (2010) Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. Journal of Clinical Microbiology 48(1): 229-37**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? unclear
Number of patients	107
Patient characteristics	Inclusion Patients suspected of having tuberculosis Characteristics  TB incidence rate: 199 per 100,000 Proportion of TB cases in the study: 76.6%
Index test	Microscopy (type unspecified)

Characteristic	Vietnamese patients (n = 107)[a]
Patient characteristics	
Median age (yr [range])	34 (18–76)
No. of males (%)	74 (69)
No. of HIV-positive patients (%)	1 (0.9)[b]
No. of unavailable HIV result(s)	0
No. of previous TB episodes (no. of patients [%])	
1	2 (1.9)
2–3	0
4–5	0
Median duration of cough (days [range]	28 (14–336)

Bibliographic reference	**Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, Kop J, Owens MR, Rodgers R, Banada P, Safi H, Blakemore R, Lan NT, Jones-López EC, Levi M, Burday M, Ayakaka I, Mugerwa RD, McMillan B, Winn-Deen E, Christel L, Dailey P, Perkins MD, Persing DH and Alland D (2010) Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. Journal of Clinical Microbiology 48(1): 229-37**
Reference standard	Löwenstein-Jensen culture and MGIT 960 Positive cultures were confirmed to contain M. tuberculosis by MPT64 antigen detection using the Capilia TB test
Location	Vietnam World Bank Income Classification: middle-income
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 29, FP 0 Index test – Negative: FN 53, TN 25 Sensitivity of index test (95% CI)a = 35.4% (25.0% to 45.7%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	Supported by grants from the National Institutes of Health and a grant from the Foundation for Innovative New Diagnostics
Comments	Data for Xpert MTB/RIF included in the Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.29 Hengstler, 1996

Bibliographic reference	**Hengstler M, P Klavehn, Glockner G and Fahr AM (1996) Evaluation of the Amplicor Mycobacterium tuberculosis amplification and detection kit in a clinical laboratory: results and experiences. Clinical Laboratory 42: 387-93**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection

Bibliographic reference	Hengstler M, P Klavehn, Glockner G and Fahr AM (1996) Evaluation of the Amplicor Mycobacterium tuberculosis amplification and detection kit in a clinical laboratory: results and experiences. Clinical Laboratory 42: 387-93
	Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although the information provided was limited Is there concern that the included patients do not match the review question? it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear risk of bias Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? • Was there an appropriate interval between index test(s) and reference standard? yes

Bibliographic reference	**Hengstler M, P Klavehn, Glockner G and Fahr AM (1996) Evaluation of the Amplicor Mycobacterium tuberculosis amplification and detection kit in a clinical laboratory: results and experiences. Clinical Laboratory 42: 387-93**
	• Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	564 samples
Patient characteristics	Inclusion No details given Sample characteristics Respiratory tract samples – sputa, bronchoalveolar washings, tracheobronchial secretions
Index test	Fluorescence microscopy Decontaminated by the N-acetyl-L-cystein-NaOH method Heat fixation Auramine-rhodamine stainig
Reference standard	Löwenstein-Jensen (solid) and BACTEC 460 (BACTEC 12B liquid) culture Decontaminated by the N-acetyl-L-cystein-NaOH method
Location	Germany
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 8, FP 0 Index test – Negative: FN 11, TN 545 Sensitivity of index test (95% CI)a = 42.1% (19.9% to 64.4%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	No details given

Bibliographic reference	Hengstler M, P Klavehn, Glockner G and Fahr AM (1996) Evaluation of the Amplicor Mycobacterium tuberculosis amplification and detection kit in a clinical laboratory: results and experiences. Clinical Laboratory 42: 387-93
Comments	Data for Amplicor included in the Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.30 Hoffner, 1996

Bibliographic reference	Hoffner SE, Norberg R, Carlos Toro J, Winqvist N, Koivula T, Dias F, Svenson SB and Källenius G (1996) Direct detection of Mycobacterium tuberculosis in sputum samples from Guinea Bissau by an rRNA target-amplified test system. Tubercle and Lung Disease 77(1):67-70
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes

Bibliographic reference	**Hoffner SE, Norberg R, Carlos Toro J, Winqvist N, Koivula T, Dias F, Svenson SB and Källenius G (1996) Direct detection of Mycobacterium tuberculosis in sputum samples from Guinea Bissau by an rRNA target-amplified test system. Tubercle and Lung Disease 77(1):67-70**
	• Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	274 specimens from 247 participants
Patient characteristics	Inclusion Patients referred for examination on the suspicion of tuberculosis, either from peripheral health care centers, or from hospitals in Bissau Sample characteristics Sputum
Index test	Ziehl-Neelson microscopy
Reference standard	Löwenstein-Jensen culture
Location	Bissau, Guinea Bissau
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 36 / FP 2

Bibliographic reference	**Hoffner SE, Norberg R, Carlos Toro J, Winqvist N, Koivula T, Dias F, Svenson SB and Källenius G (1996) Direct detection of Mycobacterium tuberculosis in sputum samples from Guinea Bissau by an rRNA target-amplified test system. Tubercle and Lung Disease 77(1):67-70**
	Negative: FN 46, TN 190 Sensitivity of index test (95% CI)a = 43.9% (33.2% to 54.6%) Specificity of index test (95% CI)a = 99.0% (97.5% to 100%)
Source of funding	Supported by the Swedish Agency for research cooperation with developing countries (SAREC) and King Oscar II Jubilee Foundation
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.31 Holst, 1959

Bibliographic reference	**Holst E, Mitchison DA and Radhakrishna S (1959) Examination of smears for tubercle bacilli by fluorescence microscopy. Indian Journal of Medical Research 47(5): 495-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? sample contains 402 (29.1%) patients in their first 6 months of chemotherapy, almost all with isoniazid and para-aminosalicylic acid; it is unclear how many patients, if any, were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	Holst E, Mitchison DA and Radhakrishna S (1959) Examination of smears for tubercle bacilli by fluorescence microscopy. Indian Journal of Medical Research 47(5): 495-9
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? 29 (2.1%) excluded as the specimens were contaminated Other The technicians who carried out the examinations had some experience of Ziehl-Neelsen stains, but little of fluorescence microscopy
Number of patients	1383 specimens examined, data available for 1354 specimens; remaining 29 (2.1%) excluded as the specimens were contaminated
Patient characteristics	Sample characteristics Sputum

Bibliographic reference	**Holst E, Mitchison DA and Radhakrishna S (1959) Examination of smears for tubercle bacilli by fluorescence microscopy. Indian Journal of Medical Research 47(5): 495-9**
	Patient characteristics 981 (70.9%) were from patients who were not receiving chemotherapy; the remaining 402 (29.1%) were from patients during their first 6 months of chemotherapy, almost all with isoniazid and para-aminosalicylic acid
Index tests	Fluorescence microscopy Heat fixation Auramine-phenol staining A smear was called positive when it contained a minimum of 3 or 4 acid-fast bacilli of typical morphology
	Ziehl-Neelson microscopy A smear was called positive when it contained a minimum of 3 or 4 acid-fast bacilli of typical morphology
Reference standard	Löwenstein-Jensen culture NaOH treatment Incubation for 8 to 9 weeks
Location	Tuberculosis Chemotherapy Centre, Madras
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative Index test – Positive: TP 441, FP 15 Index test – Negative: FN 214, TN 684 Sensitivity of index test (95% CI)a = 67.3% (63.7% to 70.9%) Specificity of index test (95% CI)a = 97.9% (96.8% to 98.9%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative

Bibliographic reference	**Holst E, Mitchison DA and Radhakrishna S (1959) Examination of smears for tubercle bacilli by fluorescence microscopy. Indian Journal of Medical Research 47(5): 495-9**
	Index test Positive: TP 433, FP 14 Negative: FN 222, TN 685 Sensitivity of index test (95% CI)a = 66.1% (62.5% to 69.7%) Specificity of index test (95% CI)a = 98.0% (97.0% to 99.0%)
Source of funding	Conducted under the joint auspices of the Indian Council of Medical Research, the Madras Government, the World Health Organization, and the British Medical Research Council
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.32 Huang, 2003

Bibliographic reference	**Huang TS, Huang WK, Lee SS, Tu HZ, Chang SH and Liu YC (2003) Rapid detection of pulmonary tuberculosis using the BDProbeTEC ET Mycobacterium tuberculosis Complex Direct Detection Assay (DTB). Diagnostic Microbiology and Infectious Disease 46(1): 29-33**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, athough details provided were limited Is there concern that the included patients do not match the review question? unclear how many patients, if any, were under 18

Bibliographic reference	Huang TS, Huang WK, Lee SS, Tu HZ, Chang SH and Liu YC (2003) Rapid detection of pulmonary tuberculosis using the BDProbeTEC ET Mycobacterium tuberculosis Complex Direct Detection Assay (DTB). Diagnostic Microbiology and Infectious Disease 46(1): 29-33
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? yes Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	267 specimens from 89 patients
Patient characteristics	Inclusion Patients suspected of having tuberculosis and not on antituberculosis treatment Sample characteristics

Bibliographic reference	**Huang TS, Huang WK, Lee SS, Tu HZ, Chang SH and Liu YC (2003) Rapid detection of pulmonary tuberculosis using the BDProbeTEC ET Mycobacterium tuberculosis Complex Direct Detection Assay (DTB). Diagnostic Microbiology and Infectious Disease 46(1): 29-33**
	Respiratory specimens, including 245 sputa, 8 bronchial washings, and 14 gastric lavages
Index tests	Kinyoun microscopy Specimens that could not be processed immediately upon receipt were stored at 2-6°C for up to 48 hours
	BDProbeTEC ET Mycobacterium tuberculosis Complex Direct Detection Assay Specimens that could not be processed immediately upon receipt were stored at 2-6°C for up to 48 hours
Reference standard	MGIT 960 Negative cultures were reported at 6 weeks Positive cultures confirmed with BACTEC 460 using 12B vials Specimens that could not be processed immediately upon receipt were stored at 2-6°C for up to 48 hours A decreasing or unchanging growth index was considered to presumptively identify the M. tuberculosis complex
Location	Kaohsiung Veterans General Hospital, Taiwan
Outcomes measures and effect size	Diagnostic test accuracy – Kinyoun microscopy Reference standard Positive Negative Index test Positive: TP 33, FP 3 Negative: FN 45, TN 186 Sensitivity of index test (95% CI)a = 42.3% (31.3% to 53.3%) Specificity of index test (95% CI)a = 98.4% (96.6% to 100%)
	Diagnostic test accuracy – BDProbeTEC ET Reference standard Positive Negative

Bibliographic reference	**Huang TS, Huang WK, Lee SS, Tu HZ, Chang SH and Liu YC (2003) Rapid detection of pulmonary tuberculosis using the BDProbeTEC ET Mycobacterium tuberculosis Complex Direct Detection Assay (DTB). Diagnostic Microbiology and Infectious Disease 46(1): 29-33**
	Index test: Positive — TP 70, FP 12; Negative — FN 8, TN 177 Sensitivity of index test (95% CI)a = 89.7% (83.0 to 96.5%) Specificity of index test (95% CI)a = 93.7% (90.2% (97.1%)
Source of funding	Supported by a grant from Kaoshiung Veterans General Hospital
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.33 Hur, 2011

Bibliographic reference	**Hur M, Moon HW, Yun YM, Kang TY, Kim HS, Kim HS, Lee KM, Kang SH and Lee EH (2011) Detection of tuberculosis using artus M. tuberculosis PCR Kit and COBAS AMPLICOR Mycobacterium tuberculosis Test. International Journal of Tuberculosis and Lung Disease 15(6): 795-8**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no

Bibliographic reference	**Hur M, Moon HW, Yun YM, Kang TY, Kim HS, Kim HS, Lee KM, Kang SH and Lee EH (2011) Detection of tuberculosis using artus M. tuberculosis PCR Kit and COBAS AMPLICOR Mycobacterium tuberculosis Test. International Journal of Tuberculosis and Lung Disease 15(6): 795-8**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? unclear • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	Included = 238 Data available = 221 (no culture result for 17)
Patient characteristics	Inclusion Patients clinically suspected of having tuberculosis

Bibliographic reference	**Hur M, Moon HW, Yun YM, Kang TY, Kim HS, Kim HS, Lee KM, Kang SH and Lee EH (2011) Detection of tuberculosis using artus M. tuberculosis PCR Kit and COBAS AMPLICOR Mycobacterium tuberculosis Test. International Journal of Tuberculosis and Lung Disease 15(6): 795-8**
	Sample characteristics The enrolled specimens consisted of expectorated and induced sputum, bronchial washings and bronchoalveolar lavage 154 males and 84 females Median age of 49 years (5–85)
Index test	Cobas Amplicor Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	BacT/Alert MB, Ogawa and Middlebrook 7H10 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Seoul, Korea
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 134, FP 12 Negative: FN 0, TN 75 Sensitivity of index test (95% CI)a = 100% (100% to 100%) Specificity of index test (95% CI)a = 86.2% (79.0% to 93.5%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.34 Ichiyama, 1996

Bibliographic reference	Ichiyama S, Iinuma Y, Tawada Y, Yamori S, Hasegawa Y, Shimokata K and Nakashima N (1996) Evaluation of Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche PCR-microwell plate hybridization method (AMPLICOR MYCOBACTERIUM) for direct detection of mycobacteria. Journal of Clinical Microbiology 34(1): 130-3
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Ichiyama S, Iinuma Y, Tawada Y, Yamori S, Hasegawa Y, Shimokata K and Nakashima N (1996) Evaluation of Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche PCR-microwell plate hybridization method (AMPLICOR MYCOBACTERIUM) for direct detection of mycobacteria. Journal of Clinical Microbiology 34(1): 130-3**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	422 specimens from 170 participants
Patient characteristics	Inclusion Patients suspected of mycobacterial infection of the lung or those being followed during antituberculosis chemotherapy Sample characteristics Sputum
Index test	Fluorescence microscopy Auramine-rhodamine staining Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Septi-Chek AFB culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks Confirmation with Ziehl-Neelson microscopy
Location	Chubu National Hospital, Japan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive TP 74 FP 6

Bibliographic reference	**Ichiyama S, Iinuma Y, Tawada Y, Yamori S, Hasegawa Y, Shimokata K and Nakashima N (1996) Evaluation of Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche PCR-microwell plate hybridization method (AMPLICOR MYCOBACTERIUM) for direct detection of mycobacteria. Journal of Clinical Microbiology 34(1): 130-3**
	Negative: FN 47, TN 278 Sensitivity of index test (95% CI)a = 61.2% (52.5% to 69.8%) Specificity of index test (95% CI)a = 97.9% (96.2% to 99.6%)
Source of funding	Chugai Pharmaceutical Company Ltd, Nippon Roche Company Ltd and Nippon Becton Dickinson Company Ltd supplied the Amplified Mycobacterium Tuberculosis Direct Test, the Amplicor test kit and Septi-Chek kit
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test and Amplicor are included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.35 Iinuma, 2003

Bibliographic reference	**Iinuma Y, Senda K, Fujihara N, Saito T, Takakura S, Shimojima M, Kudo T and Ichiyama S (2003) Comparison of the BDProbeTec ET system with the Cobas Amplicor PCR for direct detection of Mycobacterium tuberculosis in respiratory samples. European Journal of Clinical Microbiology and Infectious Diseases 22(6): 368-71**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	Iinuma Y, Senda K, Fujihara N, Saito T, Takakura S, Shimojima M, Kudo T and Ichiyama S (2003) Comparison of the BDProbeTec ET system with the Cobas Amplicor PCR for direct detection of Mycobacterium tuberculosis in respiratory samples. European Journal of Clinical Microbiology and Infectious Diseases 22(6): 368-71
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	411 specimens included, data available for 397
Patient characteristics	Inclusion Patients suspected of mycobacterial infection of the lung or those being followed during antituberculosis chemotherapy Sample characteristics Respiratory specimens: 383 sputum and 28 bronchoalveolar lavage
Index test	Ziehl-Neelson microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide

Bibliographic reference	**Iinuma Y, Senda K, Fujihara N, Saito T, Takakura S, Shimojima M, Kudo T and Ichiyama S (2003) Comparison of the BDProbeTec ET system with the Cobas Amplicor PCR for direct detection of Mycobacterium tuberculosis in respiratory samples. European Journal of Clinical Microbiology and Infectious Diseases 22(6): 368-71**
Reference standard	MGIT 960 liquid culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks
Location	Japan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 83, FP 0 Index test – Negative: FN 10, TN 304 Sensitivity of index test (95% CI)a = 89.3% (83.0% to 95.5%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	No details provided
Comments	Data for Cobas Ampicor and BDProbeTec ET included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.36 Jonas, 1993

Bibliographic reference	**Jonas V, Alden MJ, Curry JI, Kamisango K, Knott CA, Lankford R, Wolfe JM and Moore DF (1993) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by amplification of rRNA. Journal of Clinical Microbiology 31(9): 2410-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias

Bibliographic reference	Jonas V, Alden MJ, Curry JI, Kamisango K, Knott CA, Lankford R, Wolfe JM and Moore DF (1993) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by amplification of rRNA. Journal of Clinical Microbiology 31(9): 2410-6
	• Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes

Bibliographic reference	**Jonas V, Alden MJ, Curry JI, Kamisango K, Knott CA, Lankford R, Wolfe JM and Moore DF (1993) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by amplification of rRNA. Journal of Clinical Microbiology 31(9): 2410-6**
	• Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	758 specimens from 235 participants; data available for 754 specimens
Patient characteristics	Inclusion Specimens were collected from patients being screened for tuberculosis or other mycobacterial infections or being followed during antituberculosis therapy At least 3 specimens per participant Sample characteristics Induced sputum
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks
Location	California, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 67, FP 7 Index test – Negative: FN 52, TN 628 Sensitivity of index test (95% CI)a = 56.3% (47.4% to 65.2%) Specificity of index test (95% CI)a = 98.9% (98.1% to 99.7%)

Bibliographic reference	Jonas V, Alden MJ, Curry JI, Kamisango K, Knott CA, Lankford R, Wolfe JM and Moore DF (1993) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by amplification of rRNA. Journal of Clinical Microbiology 31(9): 2410-6
Source of funding	No details provided
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.37 Jonsson and Ridell, 2003

Bibliographic reference	Jonsson B and Ridell M (2003) The Cobas Amplicor MTB test for detection of Mycobacterium tuberculosis complex from respiratory and non-respiratory clinical specimens. Scandinavian Journal of Infectious Diseases 35: 372–377
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

Bibliographic reference	Jonsson B and Ridell M (2003) The Cobas Amplicor MTB test for detection of Mycobacterium tuberculosis complex from respiratory and non-respiratory clinical specimens. Scandinavian Journal of Infectious Diseases 35: 372–377
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	877 specimens
Patient characteristics	Inclusion Suspected tuberculosis Exclusion Contaminated cultures Sample characteristics Respiratory specimens: expectorated and induced sputum (about 60%), bronchial washings (30%), bronchoalveolar lavage (10%) and transtracheal aspirates (1%)
Index test	Fluorescence microscopy Auramine-rhodamine staining Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	Sweden
Outcomes measures and	Diagnostic test accuracy

Bibliographic reference	**Jonsson B and Ridell M (2003) The Cobas Amplicor MTB test for detection of Mycobacterium tuberculosis complex from respiratory and non-respiratory clinical specimens. Scandinavian Journal of Infectious Diseases 35: 372–377**
effect size	Reference standard Positive Negative Index test Positive: TP 47, FP 17 Index test Negative: FN 61, TN 752 Sensitivity of index test (95% CI)a = 43.5% (34.2% to 52.9%) Specificity of index test (95% CI)a = 97.8% (96.8% to 98.8%)
Source of funding	
Comments	Data for Cobas Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.38 Kabeer, 2009

Bibliographic reference	**Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, et al (2009) Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals. PLoS ONE 4(5): e5718**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? yes

Bibliographic reference	Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, et al (2009) Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals. PLoS ONE 4(5): e5718
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	66 patients
Patient characteristics	Inclusion HIV-positive Exclusion Individuals with previous history of TB, silicosis, end stage renal disease, leukemia/lymphoma, who had a tuberculin skin test

Bibliographic reference	**Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, et al (2009) Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals. PLoS ONE 4(5): e5718**
	in the past 16 months, were receiving antituberculosis chemotherapy for more than two weeks, or were receiving antiretroviral therapy or immunosuppressive therapy Characteristics Adults Mostly male
Index tests	Tuberculin skin test – Mantoux Induration measured between 48 and 72 hrs after PPD injection by trained professionals Cut-off for positivity 5 mm
	Interferon gamma release assay – Quantiferon TB-Gold In-tube Positive: IFN-γ secretion in response to TB antigen ≥0.35 IU/ml Negative: IFN-γ secretion in response to TB antigen <0.35 IU/ml
Reference standard	Löwenstein-Jensen (solid) and MP BacT (liquid) culture Confirmation by GenProbe-based PCR
Location	Government Hospital of Thoracic Medicine, Tambaram, Chennai, India
Outcomes measures and effect size	Diagnostic test accuracy - TST Reference standard Positive Negative Index test – Positive: TP 11, FP 6 Index test – Negative: FN 33, TN 16 Sensitivity of index test (95% CI)a = 25.0% (12.2% to 37.8%) Specificity of index test (95% CI)a = 72.7% (54.1% to 91.3%)
	Diagnostic test accuracy - IGRA Reference standard Positive Negative

Bibliographic reference	**Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, et al (2009) Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals. PLoS ONE 4(5): e5718**
	Index test Positive: TP 29, FP 10 Negative: FN 5, TN 8 Indeterminate results = 12 Sensitivity of index test (95% CI)a = 85.3% (73.4% to 97.2%) Specificity of index test (95% CI)a = 44.4% (21.5% to 67.4%)
Source of funding	This project is financially supported by an NIH grant The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.39 Kambashi, 2001

Bibliographic reference	**Kambashi B, Mbulo G, McNerney R, Tembwe R, Kambashi A, Tihon V and Godfrey-Faussett P (2001) Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. International Journal of Tuberculosis and Lung Disease 5(4): 364-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many patients, if any,

Bibliographic reference	**Kambashi B, Mbulo G, McNerney R, Tembwe R, Kambashi A, Tihon V and Godfrey-Faussett P (2001) Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. International Journal of Tuberculosis and Lung Disease 5(4): 364-9**
	were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	171 specimens from 92 patients
Patient characteristics	Inclusion Adults

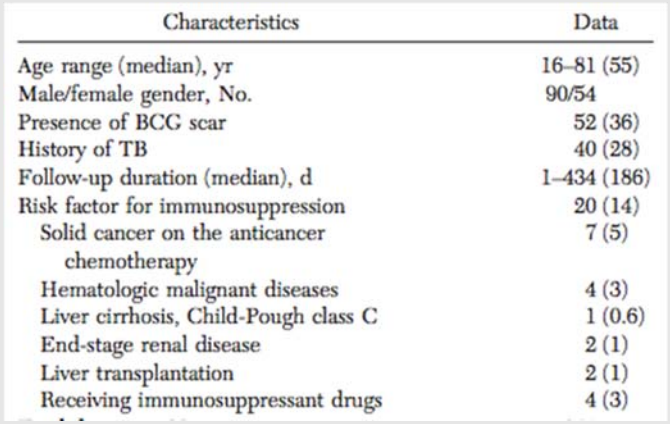
Bibliographic reference	**Kambashi B, Mbulo G, McNerney R, Tembwe R, Kambashi A, Tihon V and Godfrey-Faussett P (2001) Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. International Journal of Tuberculosis and Lung Disease 5(4): 364-9**
	Suspicion of pulmonary tuberculosis
Index tests	Fluorescence microscopy Decontamination with NaOH
	Enhanced Amplified Mycobactyerium Tuberculosis Direct Test Decontamination with NaOH
Reference standard	Löwenstein-Jensen culture Decontamination with NaOH
Location	Chest Clinic, University Teaching Hospital, Lusaka, Zambia
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Sensitivity of index test by specimen = 33% Sensitivity of index test by patient = 36%
	Diagnostic test accuracy – Enhanced Amplified Mycobactyerium Tuberculosis Direct Test Reference standard Positive / Negative Index test – Positive: TP 24 specimens; FP 24 specimens Index test – Negative: FN 9 specimens; TN 108 specimens Contaminated = 6 specimens Sensitivity of index test by specimen (95% CIa) = 72% (57.5% to 87.9%) Specificity of index test by specimen (95% CI)a = 81.8% (75.2% to 88.4%) Sensitivity of index test by patient = 84%
	Time to diagnosis Fluorescence microscopy = minimum of 1 day; routinely available within 3 days Enhanced Amplified Mycobactyerium Tuberculosis Direct Test = minimum of 1 day; routinely available within 3 days\ Löwenstein-Jensen culture = 4 to 8 weeks

Bibliographic reference	**Kambashi B, Mbulo G, McNerney R, Tembwe R, Kambashi A, Tihon V and Godfrey-Faussett P (2001) Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. International Journal of Tuberculosis and Lung Disease 5(4): 364-9**
Source of funding	This work was supported by the Department for International Development, UK AMTD kits and equipment were provided by GenProbe Inc
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.40 Kang, 2007

Bibliographic reference	**Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS and Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? moderate risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? patients with high clinical likelihood of active TB and a negative mycobacterial culture finding, but with good clinical and radiographic responses to anti-TB treatment during follow-up were excluded from the final analysis Is there concern that the included patients do not match the review question? age of included participants ranged from 16 to 60, though it is unclear how many patients were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes

Bibliographic reference	**Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS and Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? differs from the protocol-specified reference standard Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? reference standard was culture or histology plus radiology • Were all patients included in the analysis? no, results were missing for 3 TSTs and 3 IGRAs; plus, patients with high clinical likelihood of active TB and a negative mycobacterial culture finding, but with good clinical and radiographic responses to anti-TB treatment during follow-up were excluded from the final analysis
Number of patients	144 participants
Patient characteristics	Inclusion Suspicion of active pulmonary tuberculosis, based on clinical symptoms and a radiographic examination Sample characteristics HIV-negative

Bibliographic reference	**Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS and Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65**
	 (data presented as No. (%), unless otherwise indicated)
Index test	Tuberculin skin test – Mantoux Performed after IGRAs Cut-off value for a positive response was 10 mm induration
	Interferon gamma release assay – T-SPOT.TB 12 ml of peripheral blood Test wells were scored as positive if they contained at least five spot-forming cells more than the negative control well, and if this number was at least twice the number in the negative control well
	Interferon gamma release assay – Quantiferon TB-Gold 12 ml of peripheral blood Cut-off value for a positive response was 0.35 IU/ml of IFN-γ
Reference standard	Active pulmonary TB was confirmed by the culture of M tuberculosis from sputum (technique not specified) or by the presence of caseating granuloma in the lung tissues, obtained through the transthoracic needle biopsy, of patients in whom mass-like consolidation was evident from chest radiographs Patients with high clinical likelihood of active TB and a negative mycobacterial culture finding, but with good clinical and radiographic responses to anti-TB treatment during follow-up were excluded from the final analysis
Location	Seoul National University Hospital, South Korea
Outcomes measures and effect size	Diagnostic test accuracy - Mantoux Reference standard

Characteristics	Data
Age range (median), yr	16–81 (55)
Male/female gender, No.	90/54
Presence of BCG scar	52 (36)
History of TB	40 (28)
Follow-up duration (median), d	1–434 (186)
Risk factor for immunosuppression	20 (14)
Solid cancer on the anticancer chemotherapy	7 (5)
Hematologic malignant diseases	4 (3)
Liver cirrhosis, Child-Pough class C	1 (0.6)
End-stage renal disease	2 (1)
Liver transplantation	2 (1)
Receiving immunosuppressant drugs	4 (3)

Bibliographic reference	**Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS and Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65**

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 45	FP 37
	Negative	FN 21	TN 38

Sensitivity of index test (95% CI)a = 68.2% (56.9% to 79.4%)
Specificity of index test (95% CI)a = 50.7% (39.4% to 62.0%)

Diagnostic test accuracy – T-SPOT.TB

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 59	FP 39
	Negative	FN 5	TN 34

Sensitivity of index test (95% CI)a = 92.2% (85.6% to 98.8%)
Specificity of index test (95% CI)a = 46.6% (35.1% to 58.0%)

Diagnostic test accuracy – Quantiferon TB-Gold

Reference standard

Positive Negative

Bibliographic reference	**Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS and Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65**
	Index test: Positive — TP 58, FP 37; Negative — FN 7, TN 36 Sensitivity of index test (95% CI)a = 89.2% (81.7% to 96.8%) Specificity of index test (95% CI)a = 49.3% (37.9% to 60.8%)
Source of funding	T SPOT.TB test kits were donated by LK BioScience (Seoul, Republic of Korea), and part of the QuantiFERON-TB Gold assay kit was donated by Woongbee Meditech (Seoul, Republic of Korea)
Comments	Insufficient information provided to extract data for microscopy
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.41 Kim, 2004

Bibliographic reference	**Kim SY, Park YJ, Kang SJ, Kim BK and Kang CS (2004) Comparison of the BDProbeTec ET system with the roche COBAS AMPLICOR System for detection of Mycobacterium tuberculosis complex in the respiratory and pleural fluid specimens. Diagnostic Microbiology and Infectious Disease 49(1): 13-8**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear

Bibliographic reference	Kim SY, Park YJ, Kang SJ, Kim BK and Kang CS (2004) Comparison of the BDProbeTec ET system with the roche COBAS AMPLICOR System for detection of Mycobacterium tuberculosis complex in the respiratory and pleural fluid specimens. Diagnostic Microbiology and Infectious Disease 49(1): 13-8
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	152 specimens collected from 151 patients
Patient characteristics	Inclusion Specimens submitted for diagnosis of tuberculosis Sample characteristics

Bibliographic reference	**Kim SY, Park YJ, Kang SJ, Kim BK and Kang CS (2004) Comparison of the BDProbeTec ET system with the roche COBAS AMPLICOR System for detection of Mycobacterium tuberculosis complex in the respiratory and pleural fluid specimens. Diagnostic Microbiology and Infectious Disease 49(1): 13-8**
	Respiratory: bronchial washings
Index test	Ziehl-Neelson microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	MGIT 960 Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	South Korea
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 11, FP 1 Index test Negative: FN 13, TN 127 Sensitivity of index test (95% CI)a = 45.8% (25.9% to 65.8%) Specificity of index test (95% CI)a = 99.2% (97.7% to 100%)
Source of funding	
Comments	Data for Cobas Amplicor and BDProbeTec ET included in Ling et al (2008) meta-analysis
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.42 Kivihya-Ndugga, 2003

Bibliographic reference	**Kivihya-Ndugga LE, van Cleeff MR, Githui WA, Nganga LW, Kibuga DK, Odhiambo JA and Klatser PR (2003) A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. International Journal of Tuberculosis and Lung Disease 7(12): 1163-71**
Study type	Cross-sectional

Bibliographic reference	**Kivihya-Ndugga LE, van Cleeff MR, Githui WA, Nganga LW, Kibuga DK, Odhiambo JA and Klatser PR (2003) A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. International Journal of Tuberculosis and Lung Disease 7(12): 1163-71**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear; no data provided for 405 enrolled patients due to missing culture or x-ray results Is there concern that the included patients do not match the review question? age of included participants ranged from 16 to 60, though it is unclear how many patients were under 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Kivihya-Ndugga LE, van Cleeff MR, Githui WA, Nganga LW, Kibuga DK, Odhiambo JA and Klatser PR (2003) A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. International Journal of Tuberculosis and Lung Disease 7(12): 1163-71**
	Could the patient flow have introduced bias? • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? 405 enrolled patients were not includd due to missing culture or x-ray results
Number of patients	1398 suspects were enrolled, data provided for 993 patients (405 exclusions were due to missing data)
Patient characteristics	Inclusion New tuberculosis suspects Aged 15 to 65 years Sample characteristics Age: • male: median 30, range 16 to 65 • female: median 27, range 24 to 56 Male:female ratio = 3:2 HIV positivity: • male: 56% • female: 34%
Index test	Fluorescence microscopy Total of 3 smears
	Ziehl-Neelson microscopy Total of 3 smears
Reference standard	Löwenstein-Jensen culture 8 weeks of incubation
Location	Nairobi City Council Chest Clinic, Kenya
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard

Bibliographic reference	**Kivihya-Ndugga LE, van Cleeff MR, Githui WA, Nganga LW, Kibuga DK, Odhiambo JA and Klatser PR (2003) A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. International Journal of Tuberculosis and Lung Disease 7(12): 1163-71**
	Positive Negative Index test – Positive: TP 430, FP 7 Index test – Negative: FN 122, TN 434 Sensitivity of index test (95% CI)a = 77.9% (74.4% to 81.4%) Specificity of index test (95% CI)a = 98.4% (97.3% to 99.6%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test – Positive: TP 332, FP 8 Index test – Negative: FN 220, TN 433 Sensitivity of index test (95% CI)a = 60.1% (56.1% to 64.2%) Specificity of index test (95% CI)a = 98.2% (96.9% to 99.4%)
Source of funding	Supported by a grant from the Netherlands Ministry of Development Co-operation
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.43 Kurbatova, 2013

Bibliographic reference	**Kurbatova EV, Kaminski DA, Erokhin VV, Volchenkov GV, Andreevskaya SN, Chernousova LN, Demikhova OV, Ershova JV, Kaunetis NV, Kuznetsova TA, Larionova EE, Smirnova TG, Somova TR, Vasilieva IA, Vorobieva AV, Zolkina SS and Cegielski JP (2013) Performance of Cepheid ® Xpert MTB/RIF ® and TB-Biochip ® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(6): 735-43**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? yes

Bibliographic reference	**Kurbatova EV, Kaminski DA, Erokhin VV, Volchenkov GV, Andreevskaya SN, Chernousova LN, Demikhova OV, Ershova JV, Kaunetis NV, Kuznetsova TA, Larionova EE, Smirnova TG, Somova TR, Vasilieva IA, Vorobieva AV, Zolkina SS and Cegielski JP (2013) Performance of Cepheid ® Xpert MTB/RIF ® and TB-Biochip ® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(6): 735-43**
	Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	238 specimens from 201 consecutive patients Data available for: • Ziehl-Neelson microscopy = 238 • Fluorescence microscopy = 235 • TB-Biochip = 103 (only performed at the Central TB Research Institute of the Russian Academy of Medical Sciences, Moscow)
Patient characteristics	Inclusion Presumptive or recently diagnosed pulmonary tuberculosis Adults (≥18 years old) Exclusion Patients having received antituberculosis drugs within 60 days prior to specimen collection Sample characteristics Presenting signs and symptoms: presumptive or recently diagnosed TB Age: not stated Sex, female: not stated HIV infection: estimated < 5 % History of TB: not stated TB incidence rate: 97 per 100,000 Proportion of TB cases in the study: 46.9%

Bibliographic reference	**Kurbatova EV, Kaminski DA, Erokhin VV, Volchenkov GV, Andreevskaya SN, Chernousova LN, Demikhova OV, Ershova JV, Kaunetis NV, Kuznetsova TA, Larionova EE, Smirnova TG, Somova TR, Vasilieva IA, Vorobieva AV, Zolkina SS and Cegielski JP (2013) Performance of Cepheid ® Xpert MTB/RIF ® and TB-Biochip ® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(6): 735-43**
	Sputum samples of at least 5.0 ml
Index test	Ziehl-Neelson microscopy Decontaminated with N-acetyl-L-cysteine/sodium hydroxide Smears were scored using the World Health Organization scale
	Fluorescence microscopy Decontaminated with N-acetyl-L-cysteine/sodium hydroxide Auramine–rhodamine staining Smears were scored using the World Health Organization scale
	TB-Biochip Decontaminated with N-acetyl-L-cysteine/sodium hydroxide
Reference standard	Löwenstein-Jensen and MGIT 960 culture Decontaminated with N-acetyl-L-cysteine/sodium hydroxide
Location	Central TB Research Institute of the Russian Academy of Medical Sciences, Moscow, and the Regional TB Dispensary in Vladimir Oblast, Russia World Bank Income Classification: middle-income
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test – Positive: TP 65, FP 3 Index test – Negative: FN 44, TN 124 Sensitivity of index test (95% CI)a = 59.6% (50.4% to 68.8%) Specificity of index test (95% CI)a = 97.6% (95.0 to 100%)

Bibliographic reference	**Kurbatova EV, Kaminski DA, Erokhin VV, Volchenkov GV, Andreevskaya SN, Chernousova LN, Demikhova OV, Ershova JV, Kaunetis NV, Kuznetsova TA, Larionova EE, Smirnova TG, Somova TR, Vasilieva IA, Vorobieva AV, Zolkina SS and Cegielski JP (2013) Performance of Cepheid ® Xpert MTB/RIF ® and TB-Biochip ® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(6): 735-43**
	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative Index test Positive: TP 93, FP 12 Index test Negative: FN 16, TN 114 Sensitivity of index test (95% CI)a = 85.3% (78.7% to 92.0%) Specificity of index test (95% CI)a = 90.5% (85.4% to 95.6%)
	Diagnostic test accuracy – TB-Biochip Reference standard Positive Negative Index test Positive: TP 71, FP 7 Index test Negative: FN 2, TN 25 Sensitivity of index test (95% CI)a = 97.3% (93.5% to 100%) Specificity of index test (95% CI)a = 78.1% (63.8% to 92.5%)
Source of funding	Supported by the United States Agency for International Development (USAID) country mission in Russia
Comments	Data for Xpert MTB/RIF included in Steingart et al (2014) systematic review

Bibliographic reference	**Kurbatova EV, Kaminski DA, Erokhin VV, Volchenkov GV, Andreevskaya SN, Chernousova LN, Demikhova OV, Ershova JV, Kaunetis NV, Kuznetsova TA, Larionova EE, Smirnova TG, Somova TR, Vasilieva IA, Vorobieva AV, Zolkina SS and Cegielski JP (2013) Performance of Cepheid ® Xpert MTB/RIF ® and TB-Biochip ® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(6): 735-43**
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.44 Lawn, 2011

Bibliographic reference	**Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, et al (2011) Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Medicine 8(7): e1001067**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias

Bibliographic reference	Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, et al (2011) Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Medicine 8(7): e1001067
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no data for 69 of 514 enrolled participants due to missing or contaminated specimens
Number of patients	514 patients enrolled; data available for 778 samples from 445 patients (exclusions due to missing or contaminated specimens)
Patient characteristics	Inclusion Patients with advanced immunodeficiency being screened for TB (regardless of symptoms) prior to starting ART Aged 18 or older Sample characteristics Majority of first sputum samples (89%) were obtained by spontaneous expectoration, and the remainder of first samples and all second samples were induced using hypertonic saline Presenting signs and symptoms: HIV: the majority of patients had one or more of the following TB symptoms: current cough, fever, night sweats, or weight loss History of TB: 26.5% TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 18.3%

Bibliographic reference	**Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, et al (2011) Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Medicine 8(7): e1001067**
	Patient Characteristics[a] / **All Patients (*n*=468)** **Age, median (IQR)** 33.6 (27.8–40.7) **Female** 306 (65.4%) **BMI, median (IQR)** 23.5 (20.9–27.2) **History of previous TB** 124 (26.5%) **CD4 cell counts (cells/μl)** Median (IQR) 171 (102–236) CD4 <50 59 (12.6%) CD4 50–99 55 (11.8%) CD4 100–149 90 (19.2%) CD4 150–199 85 (18.2%) CD4 ≥200 179 (38.3%) **Baseline viral load, median (IQR) (log_{10} copies/ml)** 4.5 (4.0–5.0) **WHO stage at enrolment** 1 or 2 317 (67.7%) 3 or 4 151 (32.3%) **Positive WHO symptom screen** 328 (70.1%) **Current cough ≥2 wk** 103 (22.0%) **Radiological abnormality consistent with TB[c]** 170 (40.7%) [a]Data are number of patients (percent) unless otherwise indicated. [b]Comparison of characteristics of patients with and without TB. [c]Chest radiographs available for 418 patients. doi:10.1371/journal.pmed.1001067.t001
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Stained with auramine O Bacillary density was graded as scanty, 1+, 2+, and 3+, and all such smears were defined as positive
Reference standard	MGIT 960 liquid culture

Bibliographic reference	**Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, et al (2011) Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Medicine 8(7): e1001067**
	Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubated for up to 6 weeks
Location	Country: South Africa, Cape Town World Bank Income Classification: middle-income
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 21, FP 0 Index test – Negative: FN 54, TN 370 Sensitivity of index test (95% CI)a = 28.0% (17.8% to 38.2%) Specificity of index test (95% CI)a = 100% (100% to 100%)
	Time to diagnosis Time to diagnosis (median (interquartile range)) • index test = 3 (2 to 5) • reference standard (smear-positive) =12 (10 to 14) • reference standard (smear-negative) = 20 (17 to 27)
Source of funding	SDL, KK, and MN were funded by the Wellcome Trust, London, UK and MN also received funding from EDCTP; RW was funded in part by the US National Institutes of Health (NIH) through a CIPRA grant and an RO1 grant The authors are grateful to the Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland for providing access to the Xpert MTB/RIF assay cartridges with preferential pricing The funding sources played no role in study design, data collection and analysis, decision to publish or preparation of the manuscript
Comments	Data for Xpert MTB/RIF included in Steingart et al (2014) systematic review
a Calculated by reviewer	

Bibliographic reference	Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, et al (2011) Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Medicine 8(7): e1001067
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.45 Lawn, 2012

Bibliographic reference	Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear

Bibliographic reference	Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9
	Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	Among 602 patients recruited, 535 produced at least 1 sputum sample and a specimen of urine, and data was available for 516
Patient characteristics	Inclusion HIV-infected patients being screened for tuberculosis prior to starting antiretroviral therapy Age >18 years, Antiretroviral therapy-naïve No current diagnosis of tuberculosis Sample characteristics

Bibliographic reference	Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9
	All patients (n=516) Age 34·1 (28·6–41·3) Female 331 (64%) BMI 23·5 (20·9–27·1) CD4 counts (cells per μL)* 169·5 (100–233) <50 64 (12%) 50–99 64 (12%) 100–149 96 (19%) 150–199 101 (20%) ≥200 189 (37%) Baseline viral load (log copies per mL)† 4·6 (4·1–5·0) WHO stage at enrolment 1 or 2 346 (67%) 3 or 4 170 (33%) Positive WHO symptom screen 356 (69%) Previous history of tuberculosis 140 (27%) Current cough ≥2 weeks 104 (20%) Radiological abnormality consistent with tuberculosis‡ 235 (50%) (Data are median (interquartile range) or number (%))
Index tests	Sputum fluorescence microscopy Decontaminated with N-acetyl-L-cysteine and sodium hydroxide and concentrated by centrifugation Stained with auramine O

Bibliographic reference	**Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9**
	Sputum Xpert MTB/RIF Decontaminated with N-acetyl-L-cysteine and sodium hydroxide and concentrated by centrifugation
	Urine LAM – Clearview MTB
	Urine LAM – Determine TB-LAM point-of-care test strips
Reference standard	MGIT 960 liquid sputum culture Decontaminated with N-acetyl-L-cysteine and sodium hydroxide and concentrated by centrifugation Incubated for up to 6 weeks Confirmation using MTBDRplus
Location	Antiretroviral service, Gugulethu township, Cape Town, South Africa
Outcomes measures and effect size	Diagnostic test accuracy - fluorescence microscopy Reference standard Positive Negative Index test – Positive: TP 24, FP 1 Index test – Negative: FN 61, TN 430 Sensitivity of index test (95% CI)a = 28.2% (18.7% to 37.8%) Specificity of index test (95% CI)a = 99.8% (99.3% to 100%)
	Diagnostic test accuracy - Xpert MTB/RIF Reference standard Positive Negative Index test – Positive: TP 49, FP 4

Bibliographic reference	**Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9**

	Negative	FN 36	TN 427

Sensitivity of index test (95% CI)a = 57.7% (47.1% to 68.2%)
Specificity of index test (95% CI)a = 99.1% (98.2% to 100%)

Diagnostic test accuracy - Clearview MTB

		Reference standard	
		Positive	Negative
Index test	Positive	TP 23	FP 8
	Negative	FN 62	TN 423

Sensitivity of index test (95% CI)a = 27.1% (17.6% to 36.5%)
Specificity of index test (95% CI)a = 98.1% (96.9% to 99.4%)

Diagnostic test accuracy – Determine TB-LAM

		Reference standard	
		Positive	Negative
Index test	Positive	TP 24	FP 6
	Negative	FN 61	TN 425

Bibliographic reference	**Lawn SD, Kerkhoff AD, Vogt M and Wood R (2012) Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infectious Diseases 12(3): 201-9**
	Sensitivity of index test (95% CI)a = 28.2% (18.7% to 37.8%) Specificity of index test (95% CI)a = 98.6% (97.5% to 99.7%)
Source of funding	Wellcome Trust The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; LAM, lipoarabinomannan; TN, true negative; TP, true positive	

1.1.2.46 Lim, 2002

Bibliographic reference	**Lim TK, Gough A, Chin NK and Kumarasinghe G (2000) Relationship between estimated pretest probability and accuracy of automated Mycobacterium tuberculosis assay in smear-negative pulmonary tuberculosis. Chest 118(3): 641-7**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	Lim TK, Gough A, Chin NK and Kumarasinghe G (2000) Relationship between estimated pretest probability and accuracy of automated Mycobacterium tuberculosis assay in smear-negative pulmonary tuberculosis. Chest 118(3): 641-7
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	128 patients
Patient characteristics	Inclusion Smear-negative Adult patients (age >14 years) suspected of having pulmonary tuberculosis (patients were identified when a specimen from the respiratory tract with a request for a mycobacterium tuberculosis smear and culture was received by the microbiology laboratory) Exclusions Patients were excluded from the study if any of the following conditions were met: (1) if the results of any smears were reported as positive by the laboratory; (2) if the patient was already receiving anti-TB drugs; (3) if all cultures were contaminated; (4) if only MOTT was isolated in the culture; (5) if only pleural fluid was processed; (6) if laboratory data were incomplete; or (7) if clinical data were incomplete

Bibliographic reference	**Lim TK, Gough A, Chin NK and Kumarasinghe G (2000) Relationship between estimated pretest probability and accuracy of automated Mycobacterium tuberculosis assay in smear-negative pulmonary tuberculosis. Chest 118(3): 641-7**
	Sample characteristics Respiratory tract specimens included induced or spontaneously expectorated sputum, tracheal aspirates, and those obtained from bronchoscopy and biopsies
Index tests	Fluorescence smear Decontaminated and digested by N-acetyl-l-cysteine and NaOH Stained with auramine O Confirmation by Ziehl-Neelson microscopy
	Amplicor Decontaminated and digested by N-acetyl-l-cysteine and NaOH
Reference standard	BACTEC liquid Decontaminated and digested by N-acetyl-l-cysteine and NaOH
Location	National University Hospital, Singapore
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test Positive: TP 8; FP 2 Negative: FN 8; TN 110 Sensitivity of index test (95% CI)a = 50.0% (25.5% to 74.5%) Specificity of index test (95% CI)a = 98.2% (95.8% to 100%)
	Diagnostic test accuracy – Amplicor Reference standard Positive Negative

Bibliographic reference	**Lim TK, Gough A, Chin NK and Kumarasinghe G (2000) Relationship between estimated pretest probability and accuracy of automated Mycobacterium tuberculosis assay in smear-negative pulmonary tuberculosis. Chest 118(3): 641-7**

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 13	FP 3
	Negative	FN 3	TN 109

Sensitivity of index test (95% CI)a = 81.3% (62.1% to 100%)
Specificity of index test (95% CI)a = 97.3% (94.3% to 100%)

Smear-positive

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 8	FP 0
	Negative	FN 0	TN 2

Smear-negative

		Reference standard: Positive	Reference standard: Negative
Index test	Positive	TP 5	FP 3

Bibliographic reference	**Lim TK, Gough A, Chin NK and Kumarasinghe G (2000) Relationship between estimated pretest probability and accuracy of automated Mycobacterium tuberculosis assay in smear-negative pulmonary tuberculosis. Chest 118(3): 641-7**
	Negative: FN = 3; TN = 107 Sensitivity of index test (95% CI)a = 62.5% (29.0% to 96.1%) Specificity of index test (95% CI)a =97.3% (94.2% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.47 Lockman, 2003

Bibliographic reference	**Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L and Tappero JW (2003) Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. International Journal of Tuberculosis and Lung Disease 7(8): 714-23**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? yes Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	**Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L and Tappero JW (2003) Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. International Journal of Tuberculosis and Lung Disease 7(8): 714-23**
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	111 patients
Patient characteristics	Inclusion Adults (aged 18 years or more) Presenting with an abnormal chest X-ray and at least 1 of the following symptoms: 2 weeks or more of productive cough; 2 weeks or more of fever; 2 weeks or more of night sweats; 2 weeks or more of fatigue; haemoptysis for any duration; chest pain for any duration; weight loss for any duration Exclusion

Bibliographic reference	**Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L and Tappero JW (2003) Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. International Journal of Tuberculosis and Lung Disease 7(8): 714-23**
	Antibiotic use within the past 3 days Residence more than 30 minutes drive outside the study towns Antituberculosis chemotherapy within the past 6 months Sample characteristics Expectorated sputum samples were collected, with a goal of six sputum specimens per patient; patients whose first sputum was acid-fast bacilli-negative or who were unable to spontaneously expectorate sputum had sputum induced
Index tests	Microscopy (technique not specified) Any smear with at least two acid-fast bacilli per 300 high-powered field was considered positive
	Amplicor
Reference standard	Löwenstein-Jensen culture
Location	Princess Marina Hospital in Gaborone and Nyangabgwe Hospital in Francistown – referral hospitals for their surrounding districts - Botswana
Outcomes measures and effect size	Diagnostic test accuracy - microscopy Reference standard Positive Negative Index test Positive: TP 46, FP 12 Index test Negative: FN 16, TN 37 Sensitivity of index test (95% CI)a = 74.2% (63.3% to 85.1%) Specificity of index test (95% CI)a = 75.5% (63.5% to 87.6%)
	Diagnostic test accuracy - Amplicor Reference standard Positive Negative

Bibliographic reference	**Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L and Tappero JW (2003) Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. International Journal of Tuberculosis and Lung Disease 7(8): 714-23**

		TP	FP
Index test	Positive	48	5
	Negative	FN	TN
		14	44

Sensitivity of index test (95% CI)a = 77.4% (67.0% to 87.8%)
Specificity of index test (95% CI)a = 89.8% (81.3% 98.3%)
Diagnostic test accuracy – Amplicor – smear-positive

		Reference standard	
		Positive	Negative
Index test	Positive	TP	FP
		38	2
	Negative	FN	TN
		8	10

Sensitivity of index test (95% CI)a = 82.6% (71.7% to 93.6%)
Specificity of index test (95% CI)a = 83.3% (62.3% to 100%)
Diagnostic test accuracy – Amplicor – smear-negative

		Reference standard	
		Positive	Negative

Bibliographic reference	**Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L and Tappero JW (2003) Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. International Journal of Tuberculosis and Lung Disease 7(8): 714-23**
	Index test: Positive — TP 10, FP 3; Negative — FN 6, TN 34 Sensitivity of index test (95% CI)a = 62.5% (38.8% to 86.2%) Specificity of index test (95% CI)a = 91.9% (83.1% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.48 Lumb, 1999

Bibliographic reference	**Lumb R, Davies K, Dawson D, Gibb R, Gottlieb T, Kershaw C, Kociuba K, Nimmo G, Sangster N, Worthington M and Bastian I (1999) Multicenter evaluation of the Abbott LCx Mycobacterium tuberculosis ligase chain reaction assay. Journal of Clinical Microbiology 37(10): 3102-7**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear

Bibliographic reference	**Lumb R, Davies K, Dawson D, Gibb R, Gottlieb T, Kershaw C, Kociuba K, Nimmo G, Sangster N, Worthington M and Bastian I (1999) Multicenter evaluation of the Abbott LCx Mycobacterium tuberculosis ligase chain reaction assay. Journal of Clinical Microbiology 37(10): 3102-7**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	2,083 specimens
Patient characteristics	Inclusion Patients under investigation for tuberculosis
Index test	Fluorescence or Ziehl-Neelson microscopy

Bibliographic reference	**Lumb R, Davies K, Dawson D, Gibb R, Gottlieb T, Kershaw C, Kociuba K, Nimmo G, Sangster N, Worthington M and Bastian I (1999) Multicenter evaluation of the Abbott LCx Mycobacterium tuberculosis ligase chain reaction assay. Journal of Clinical Microbiology 37(10): 3102-7**
	Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen and/or BACTEC 12B and/or MB/BacT culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	Australia
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 66, FP 60 Index test – Negative: FN 65, TN 1856 Sensitivity of index test (95% CI)a = 50.5% (41.8% to 58.9%) Specificity of index test (95% CI)a = 96.9% (96.1% to 97.6%)
Source of funding	Abbott Diagnostics supplied the Ligase Chain Reaction assay kits
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.49 Majumdar, 2009

Bibliographic reference	**Majumdar A, Upadhye V and Harinath BC (2009) A prospective study of inhouse developed SEVA TB ELISA using cocktail of antigen and their immunoglobulins in the diagnosis of the tuberculosis suspected patients in a tertiary care hospital located in rural area. Biomedical Research 20(1): 59-63**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection

Bibliographic reference	Majumdar A, Upadhye V and Harinath BC (2009) A prospective study of inhouse developed SEVA TB ELISA using cocktail of antigen and their immunoglobulins in the diagnosis of the tuberculosis suspected patients in a tertiary care hospital located in rural area. Biomedical Research 20(1): 59-63
	Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? unclear • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? unclear – smear or clinical investigation alone (that is, without culture) would not match the specified reference standard Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes

Bibliographic reference	**Majumdar A, Upadhye V and Harinath BC (2009) A prospective study of inhouse developed SEVA TB ELISA using cocktail of antigen and their immunoglobulins in the diagnosis of the tuberculosis suspected patients in a tertiary care hospital located in rural area. Biomedical Research 20(1): 59-63**
	• Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	154 participants
Patient characteristics	Inclusion Suspicion of pulmonary tuberculosis based on clinical examination and laboratory investigation Sample characteristics All had a history of BCG vaccination
Index test	SEVA TB ELISA using ES-31, ES-43 and EST-6
Reference standard	Smear and(/or?) culture and(/or?) other clinical investigations
Location	Kasturba Hospital of Mahatma Gandhi Institute of Medical Sciences (tertiary hospital), Sevagram, in rural India
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 11, FP 68 Index test Negative: FN 0, TN 75 Sensitivity of index test (95% CI)a = 100% (100% to 100%) Specificity of index test (95% CI)a = 52.5% (44.3% to 60.6%)
Source of funding	Supported by a Tropical Disease Research grant from the Kasturba Health SOciety
Comments	
a Calculated by reviewer	

Bibliographic reference	Majumdar A, Upadhye V and Harinath BC (2009) A prospective study of inhouse developed SEVA TB ELISA using cocktail of antigen and their immunoglobulins in the diagnosis of the tuberculosis suspected patients in a tertiary care hospital located in rural area. Biomedical Research 20(1): 59-63
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.50 Malbruny, 2011

Bibliographic reference	Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease 15(4): 553-5
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease 15(4): 553-5**
	Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	91 specimens
Patient characteristics	Inclusion Clinically suspected respiratory tuberculosis Sample characteristics 18 sputum, 33 gastric aspirate, 31 bronchial aspirate and 9 bronchoalveolar lavage Early morning specimens
Index test	Fluorescence microscopy Digested and decontaminated with N-acetyl-cysteine-NaOH Stained with auramine-fluorochrome
Reference standard	Solid and MGIT 960 liquid culture Digested and decontaminated with N-acetyl-cysteine-NaOH Liquid culture incubated for up to 6 weeks, solid for up to 12 weeks Confirmation using TB Ag MPT64 Rapid
Location	University hospital of Caen, France
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease 15(4): 553-5**
	Index test: Positive — TP 11, FP 1; Negative — FN 6, TN 73 Sensitivity of index test (95% CI)a = 64.7% (42.0% to 87.4%) Specificity of index test (95% CI)a = 98.7% (96.0% to 100%)
Source of funding	No details provided
Comments	Data for Xpert MTB/RIF included in Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.51 Michos, 2006

Bibliographic reference	**Michos AG, Daikos GL, Tzanetou K, Theodoridou M, Moschovi M, Nicolaidou P, Petrikkos G, Syriopoulos T, Kanavaki S and Syriopoulou VP (2006) Detection of Mycobacterium tuberculosis DNA in respiratory and nonrespiratory specimens by the Amplicor MTB PCR. Diagnostic Microbiology and Infectious Disease 54(2):121-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no – includes children

Bibliographic reference	**Michos AG, Daikos GL, Tzanetou K, Theodoridou M, Moschovi M, Nicolaidou P, Petrikkos G, Syriopoulos T, Kanavaki S and Syriopoulou VP (2006) Detection of Mycobacterium tuberculosis DNA in respiratory and nonrespiratory specimens by the Amplicor MTB PCR. Diagnostic Microbiology and Infectious Disease 54(2):121-6**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	650 specimens
Patient characteristics	Inclusion Adult and paediatric patients with suspected tuberculosis Exclusion

Bibliographic reference	**Michos AG, Daikos GL, Tzanetou K, Theodoridou M, Moschovi M, Nicolaidou P, Petrikkos G, Syriopoulos T, Kanavaki S and Syriopoulou VP (2006) Detection of Mycobacterium tuberculosis DNA in respiratory and nonrespiratory specimens by the Amplicor MTB PCR. Diagnostic Microbiology and Infectious Disease 54(2):121-6**
	Lack of adequate clinical information Initiation of antituberculosis treatment for more than 2 weeks before the specimen collection Sample characteristics Respiratory specimens: 457 were sputum and 193 were bronchoalveolar lavage fluid
Index test	Ziehl-Neelsen microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 10 weeks
Location	Athens, Greece
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 16, FP 3 Index test Negative: FN 17, TN 614 Sensitivity of index test (95% CI)a = 48.5% (31.4% to 65.5%) Specificity of index test (95% CI)a = 99.5% (99.0% to 100%)
Source of funding	No details provided
Comments	Data for Amplicor included in Ling et al (2008) meta-analysis
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.52 Moore & Curry, 1995

Bibliographic reference	Moore DF and Curry JI (1995) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by Amplicor PCR. Journal of Clinical Microbiology 33(10): 2686-91
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	Moore DF and Curry JI (1995) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by Amplicor PCR. Journal of Clinical Microbiology 33(10): 2686-91
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? 20 specimens excluded as they were contaminated
Number of patients	1009 specimens included (301 retrospective, 708 prospective), data reported for 989 (exclusions were made due to contamination)
Patient characteristics	Inclusion Patients being screened for tuberculosis or other pulmonary mycobacterial infections Patients being followed during antituberculosis chemotherapy Sample characteristics 914 specimens were induced sputum samples
Index test	Fluorescence microscopy Digested and decontaminated with N-acetyl-cysteine-NaOH Stained with auramine-fluorochrome
Reference standard	Löwenstein-Jensen and BACTEC 12B culture Digested and decontaminated with N-acetyl-cysteine-NaOH Incubation for 6 weeks
Location	Orange County Health Care Agency Pulmonary Disease Clinic, California, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive TP 83 FP 8

Bibliographic reference	Moore DF and Curry JI (1995) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by Amplicor PCR. Journal of Clinical Microbiology 33(10): 2686-91
	Negative: FN 79; TN 819 Sensitivity of index test (95% CI)a = 51.2% (43.5% to 58.9%) Specificity of index test (95% CI)a = 99.0% (98.4% to 99.7%)
Source of funding	Supported by Roche Molecular Systems
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.53 Moore and Curry, 1998

Bibliographic reference	Moore DF and Curry JI (1998) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by ligase chain reaction. Journal of Clinical Microbiology 36(4): 1028-31
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	Moore DF and Curry JI (1998) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by ligase chain reaction. Journal of Clinical Microbiology 36(4): 1028-31
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	493 specimens collected from 205 participants
Patient characteristics	Inclusion Specimens collected for the initial diagnosis of tuberculosis Exclusion Specimens submitted for the follow-up of patients on antimicrobial therapy for tuberculosis Sample characteristics Majority of specimens were induced sputum samples
Index test	Fluorescence microscopy Auramine staining Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen and selective Middlebrook 7H11culture

Bibliographic reference	**Moore DF and Curry JI (1998) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by ligase chain reaction. Journal of Clinical Microbiology 36(4): 1028-31**
	Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks
Location	California, US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 13, FP 8 Index test Negative: FN 21, TN 451 Sensitivity of index test (95% CI)a = 38.2% (21.9% to 54.6%) Specificity of index test (95% CI)a = 98.3% (97.1% to 99.5%)
Source of funding	Supported by Abbott Laboratories
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.54 Mukhopadhyay, 2006

Bibliographic reference	**Mukhopadhyay A, Guan M, Chen HY, Lu Y and Lim TK (2006) Prospective study of a new serological test (ASSURE TB Rapid Test) for the diagnosis of pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 10(6): 620-4**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes

Bibliographic reference	Mukhopadhyay A, Guan M, Chen HY, Lu Y and Lim TK (2006) Prospective study of a new serological test (ASSURE TB Rapid Test) for the diagnosis of pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 10(6): 620-4
	• Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? 22 patients excluded (cultures revealed non-tuberculous mycobacteria for 9

Bibliographic reference	**Mukhopadhyay A, Guan M, Chen HY, Lu Y and Lim TK (2006) Prospective study of a new serological test (ASSURE TB Rapid Test) for the diagnosis of pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 10(6): 620-4**
	patients, were contaminated for 7 patients and were not done for 6 patients)
Number of patients	238 patients included, data available for 216 (cultures revealed non-tuberculous mycobacteria for 9 patients, were contaminated for 7 patients and were not done for 6 patients)
Patient characteristics	Inclusion Adult (18 years or older) in-patients suspected of having active pulmonary tuberculosis Exclusions Cultures revealed non-tuberculous mycobacteria for 9 patients, were contaminated for 7 patients and were not done for 6 patients Sample characteristics Microscopy and culture: respiratory secretions included spontaneously expectorated sputum and tracheal aspirates from intubated patients; additional specimens, such as induced sputum and bronchoscopy, were performed at the discretion of the attending physician ASSURE TB Rapid Test: blood sample drawn within 3 days of the respiratory samples 171 male : 67 female Age (mean (range)) = 56.6 (18–96) years
Index tests	Fluorescence microscopy Digested and decontaminated with N-acetyl-cysteine-NaOH Auramine O staining Confirmation using Ziehl-Neelson microscopy
	ASSURE TB Rapid Test (IgG)
Reference standard	BACTEC liquid culture Digested and decontaminated with N-acetyl-cysteine-NaOH
Location	National University Hospital, Singapore
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive / Negative Index test – Positive: TP 54 / FP 3

Bibliographic reference	**Mukhopadhyay A, Guan M, Chen HY, Lu Y and Lim TK (2006) Prospective study of a new serological test (ASSURE TB Rapid Test) for the diagnosis of pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 10(6): 620-4**
	Negative: FN 23, TN 136 Sensitivity of index test (95% CI)a = 70.1% (59.9% to 80.4%) Specificity of index test (95% CI)a = 97.8% (95.4% to 100%)
	Diagnostic test accuracy – ASSURE TB Rapid Test (IgG) Reference standard: Positive / Negative Index test – Positive: TP 50, FP 32 Index test – Negative: FN 27, TN 107 Sensitivity of index test (95% CI)a = 64.9% (54.3% to 75.6%) Specificity of index test (95% CI)a = 77.0% (70.0% to 84.0%)
Source of funding	ASSURE TB Rapid Test was performed courtesy of Genelabs Diagnostics, Singapore
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.55 Mutetwa, 2009

Bibliographic reference	**Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, Mungofa S, Butterworth AE, Mason PR and Corbett EL (2009) Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. International Journal of Tuberculosis and Lung Disease 13(10): 1253-9**
Study type	Cross-sectional

Bibliographic reference	**Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, Mungofa S, Butterworth AE, Mason PR and Corbett EL (2009) Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. International Journal of Tuberculosis and Lung Disease 13(10): 1253-9**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? yes – 23 of 397 included participants were adolescents Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	**Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, Mungofa S, Butterworth AE, Mason PR and Corbett EL (2009) Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. International Journal of Tuberculosis and Lung Disease 13(10): 1253-9**
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	Of 427 participants, complete data were available for 397
Patient characteristics	Inclusion Ambulant primary care TB suspects with a cough of more than 3 weeks duration attending to submit sputum specimens to the microscopy Patients admitted with a febrile or respiratory illness Exclusion Individuals on antituberculosis treatment for >24 hours Sample characteristics Urine specimens
Index test	Chemogen LAM test on urine specimens
Reference standard	Löwenstein-Jensen culture of sputum specimen
Location	Harare, Zimbabwe
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 71, FP 26 Index test – Negative: FN 90, TN 210

Bibliographic reference	Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, Mungofa S, Butterworth AE, Mason PR and Corbett EL (2009) Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. International Journal of Tuberculosis and Lung Disease 13(10): 1253-9
	Sensitivity of index test (95% CI)a = 44.1% (36.4% to 51.8%) Specificity of index test (95% CI)a = 89.0% (85.0% to 93.0%) HIV-positive Sensitivity of index test (95% CI) = 52% (43% to 62%) Specificity of index test (95% CI) = 86% (77% to 93%) HIV-negative Sensitivity of index test (95% CI) = 21% (9% to 37%) Specificity of index test (95% CI) = 93% (53% to 76%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.56 Myneedu, 2011

Bibliographic reference	Myneedu VP, Verma AK, Sharma PP and Behera D (2011) A pilot study of same day sputum smear examination, its feasibility and usefulness in diagnosis of pulmonary TB. Indian Journal of Tuberculosis 58(4): 160-7
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? no, though details were limited Is there concern that the included patients do not match the review question? unclear how many participants, if any, are under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	Myneedu VP, Verma AK, Sharma PP and Behera D (2011) A pilot study of same day sputum smear examination, its feasibility and usefulness in diagnosis of pulmonary TB. Indian Journal of Tuberculosis 58(4): 160-7
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	330 participants
Patient characteristics	Inclusion Suspicion of tuberculosis Sample characteristics

Bibliographic reference	**Myneedu VP, Verma AK, Sharma PP and Behera D (2011) A pilot study of same day sputum smear examination, its feasibility and usefulness in diagnosis of pulmonary TB. Indian Journal of Tuberculosis 58(4): 160-7**

Demographic/Clinical features		No. (%)
Total No. of Pulmonary suspects		330
Sex	Male patients	233 (70.60)
	Female patients	97 (29.4)
Mean age	Male patients	43.5
	Female patients	40.5
Cough	>2 weeks	291 (88.18)
	<2 weeks	39(11.2)
Fever for	>2 weeks	182(55.15)
	< 2weeks	48(14.54)
Chest pain		235(71.21)
Breathlessness		73(22.12)
Hemoptysis		106(32.12)
History of contact		93(28.18)
Preference of sputum submission on same day		307(93.03)
Loss of appetite		142(43.03)

Index test	Ziehl-Neelson microscopy Comparison of two approaches to sample collection: • two samples from consecutive mornings • two samples from the same morning, 1 hour apart Smear positive = a single bacillus seen in any of the samples
Reference standard	Löwenstein-Jensen culture
Location	New Delhi, India
Outcomes measures and effect size	Diagnostic test accuracy – two consecutive morning samples Reference standard Positive Negative

Bibliographic reference	**Myneedu VP, Verma AK, Sharma PP and Behera D (2011) A pilot study of same day sputum smear examination, its feasibility and usefulness in diagnosis of pulmonary TB. Indian Journal of Tuberculosis 58(4): 160-7**
	Index test / Positive: TP 60, FP 1 Index test / Negative: FN 43, TN 226 Sensitivity of index test (95% CI)a = 58.3% (48.7% to 67.8%) Specificity of index test (95% CI)a = 99.6% (98.7% to 100%)
	Diagnostic test accuracy – two same-morning samples Reference standard: Positive / Negative Index test / Positive: TP 42, FP 1 Index test / Negative: FN 61, TN 226 Sensitivity of index test (95% CI)a = 40.8% (31.3% to 50.3%) Specificity of index test (95% CI)a = 99.6% (98.7% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.57 O'Sullivan, 2002

Bibliographic reference	O'Sullivan CE, Miller DR, Schneider PS and Roberts GD (2002) Evaluation of Gen-Probe amplified mycobacterium tuberculosis direct test by using respiratory and nonrespiratory specimens in a tertiary care center laboratory. Journal of Clinical Microbiology 40(5): 1723-7
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	O'Sullivan CE, Miller DR, Schneider PS and Roberts GD (2002) Evaluation of Gen-Probe amplified mycobacterium tuberculosis direct test by using respiratory and nonrespiratory specimens in a tertiary care center laboratory. Journal of Clinical Microbiology 40(5): 1723-7
	Could the patient flow have introduced bias? moderate risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	391 specimens, data available for 336
Patient characteristics	Sample characteristics Respiratory
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine staining
Reference standard	MGIT 960 or Middlebrook 7H10 and 7H11 selective culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 30, FP 62 Index test Negative: FN 4, TN 240 Sensitivity of index test (95% CI)a = 88.2% (77.4% to 99.1%)

Bibliographic reference	O'Sullivan CE, Miller DR, Schneider PS and Roberts GD (2002) Evaluation of Gen-Probe amplified mycobacterium tuberculosis direct test by using respiratory and nonrespiratory specimens in a tertiary care center laboratory. Journal of Clinical Microbiology 40(5): 1723-7
	Specificity of index test (95% CI)a = 79.5% (74.9% to 84.0%)
Source of funding	No details provided
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.58 Reischl, 1998

Bibliographic reference	Reischl U, Lehn N, Wolf H and Naumann L (1998) Clinical evaluation of the automated COBAS AMPLICOR MTB assay for testing respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 36(10): 2853-60
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? it is unclear how many patients, if any, were under the age of 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	Reischl U, Lehn N, Wolf H and Naumann L (1998) Clinical evaluation of the automated COBAS AMPLICOR MTB assay for testing respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 36(10): 2853-60
	Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	643 specimens
Patient characteristics	Inclusion Patients with clinical signs or symptoms of pulmonary tuberculosis Sample characteristics Sputa, bronchial and tracheal aspirates, bronchial secretions, bronchial washings, and bronchoalveolar lavages
Index tests	Fluorescence microscopy Decontamination using N-acetyl-L-cysteine-NaOH method Stained using auramine-rhodamine fluorochrome Confirmation using Ziehl-Neelson
	Cobas Amplicor Decontamination using N-acetyl-L-cysteine-NaOH method
Reference standard	Culture Decontamination using N-acetyl-L-cysteine-NaOH method Major portion of the processed sediment cultivated by the radiometric BACTEC technique with the BACTEC 460 instrument;

Bibliographic reference	**Reischl U, Lehn N, Wolf H and Naumann L (1998) Clinical evaluation of the automated COBAS AMPLICOR MTB assay for testing respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 36(10): 2853-60**
	in addition, sediment was inoculated onto Kirchner medium, Löwenstein-Jensen medium and Stonebrink medium Occasionally, MB-Redox medium, ESP MycoII medium or MGIT medium was used instead of Kirchner medium Slants and vials were incubated for up to 8 weeks
Location	Germany
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test: Positive — TP 44, FP 11 Index test: Negative — FN 13, TN 575 Sensitivity of index test (95% CI)a = 77.2% (66.3% to 88.1%) Specificity of index test (95% CI)a = 98.1% (97.0% to 99.2%)
	Diagnostic test accuracy – Cobas Amplicor Reference standard Positive Negative Index test: Positive — TP 48, FP 5 Index test: Negative — FN 9, TN 581 Sensitivity of index test (95% CI)a = 84.2% (74.7% to 93.7%) Specificity of index test (95% CI)a = 99.2% (98.4% to 99.9%) Smear-positive

Bibliographic reference	**Reischl U, Lehn N, Wolf H and Naumann L (1998) Clinical evaluation of the automated COBAS AMPLICOR MTB assay for testing respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 36(10): 2853-60**
	Reference standard Positive Negative Index test Positive: TP 42, FP 1 Negative: FN 2, TN 10 Sensitivity of index test (95% CI)a = 95.5% (89.3% to 100%) Specificity of index test (95% CI)a = 90.9% (73.9% to 100%) Smear-negative Reference standard Positive Negative Index test Positive: TP 6, FP 4 Negative: FN 7, TN 571 Sensitivity of index test (95% CI)a = 46.2% (19.1% to 73.3%) Specificity of index test (95% CI)a = 99.3% (98.6% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.59 Ribeiro, 2004

Bibliographic reference	Ribeiro FK, Dettoni Vdo V, Peres RL, Vinhas SA, Có TR, Dietze R and Palaci M (2004) Evaluation of a commercial test based on ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Revista da Sociedade Brasileira de Medicina Tropical 37(6): 431-5
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Ribeiro FK, Dettoni Vdo V, Peres RL, Vinhas SA, Có TR, Dietze R and Palaci M (2004) Evaluation of a commercial test based on ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Revista da Sociedade Brasileira de Medicina Tropical 37(6): 431-5**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	297 specimens from 193 participants
Patient characteristics	Inclusion Patients being screened or under treatment for tuberculosis Exclusion Sample characteristics Respiratory: sputum and bronchial lavage
Index test	Fluorescent and/or Ziehl-Neelsen microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	Löwenstein-Jensen and BACTEC 460 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks
Location	Pneumology Clinic of Hospital Universitário Cassiano Antônio Moraes, Espírito Santo, Brazil
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive TP 26 FP 1

Bibliographic reference	**Ribeiro FK, Dettoni Vdo V, Peres RL, Vinhas SA, Có TR, Dietze R and Palaci M (2004) Evaluation of a commercial test based on ligase chain reaction for direct detection of Mycobacterium tuberculosis in respiratory specimens. Revista da Sociedade Brasileira de Medicina Tropical 37(6): 431-5**
	Negative: FN 16, TN 254 Sensitivity of index test (95% CI)a = 61.9% (47.2% to 76.6%) Specificity of index test (95% CI)a = 99.6% (98.8% to 100%)
Source of funding	Abbott Laboratórios do Brasil supplied the LCx MTB Assay kits
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.60 Rohner, 1998

Bibliographic reference	**Rohner P, Jahn EI, Ninet B, Ionati C, Weber R, Auckenthaler R and Pfyffer GE (1998) Rapid diagnosis of pulmonary tuberculosis with the LCx Mycobacterium tuberculosis assay and comparison with conventional diagnostic techniques. Journal of Clinical Microbiology 36(10): 3046-7**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	Rohner P, Jahn EI, Ninet B, Ionati C, Weber R, Auckenthaler R and Pfyffer GE (1998) Rapid diagnosis of pulmonary tuberculosis with the LCx Mycobacterium tuberculosis assay and comparison with conventional diagnostic techniques. Journal of Clinical Microbiology 36(10): 3046-7
	• If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	2001 specimens obtained from 1130 patients
Patient characteristics	Sample characteristics Respiratory: 1108 sputum, 540 bronchial aspirate, 320 bronchoalveolar lavage, 21 gastric fluid, and 12 tracheal aspirate specimens
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	BACTEC 12B vial, Löwenstein-Jensen and Middlebrook 7H10 and selective 7H11 Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 to 9 weeks

Bibliographic reference	**Rohner P, Jahn EI, Ninet B, Ionati C, Weber R, Auckenthaler R and Pfyffer GE (1998) Rapid diagnosis of pulmonary tuberculosis with the LCx Mycobacterium tuberculosis assay and comparison with conventional diagnostic techniques. Journal of Clinical Microbiology 36(10): 3046-7**
Location	Switzerland
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 58, FP 10 Index test Negative: FN 20, TN 1913 Sensitivity of index test (95% CI)a = 74.4% (64.7% to 84.1%) Specificity of index test (95% CI)a = 99.5% (99.2% to 99.8%)
Source of funding	No details provided
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.61 Rusch-Gerdes and Richter, 2004

Bibliographic reference	**Rusch-Gerdes S and Richter E (2004) Clinical evaluation of the semiautomated BDProbeTec ET System for the detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Diagnostic Microbiology and Infectious Disease 48: 265–270**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear

Bibliographic reference	Rusch-Gerdes S and Richter E (2004) Clinical evaluation of the semiautomated BDProbeTec ET System for the detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Diagnostic Microbiology and Infectious Disease 48: 265–270
	• Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes

Bibliographic reference	**Rusch-Gerdes S and Richter E (2004) Clinical evaluation of the semiautomated BDProbeTec ET System for the detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Diagnostic Microbiology and Infectious Disease 48: 265–270**
	• Were all patients included in the analysis? yes
Number of patients	735 specimens
Patient characteristics	Inclusion Patients who were suspected or clinically diagnosed as having tuberculosis Sample characteristics Respiratory specimens: 527 sputa, 208 bronchial washings and bronchoalveolar lavage fluids
Index test	Microscopy
Reference standard	Löwenstein-Jensen, Stonebrink or MGIT 960 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 to 8 weeks
Location	Germany
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 36, FP 2 Index test – Negative: FN 62, TN 635 Sensitivity of index test (95% CI)a = 36.7% (27.2% to 46.3%) Specificity of index test (95% CI)a = 99.7% (99.3% to 100%)
Source of funding	No details provided
Comments	Data for BDProbeTec ET included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.62 Savić, 1992

Bibliographic reference	Savić B, Sjöbring U, Alugupalli S, Larsson L, Miörner H (1992) Evaluation of polymerase chain reaction, tuberculostearic acid analysis, and direct microscopy for the detection of Mycobacterium tuberculosis in sputum. Journal of Infectious Diseases 166(5):1177-80
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, were under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no

Bibliographic reference	**Savić B, Sjöbring U, Alugupalli S, Larsson L, Miörner H (1992) Evaluation of polymerase chain reaction, tuberculostearic acid analysis, and direct microscopy for the detection of Mycobacterium tuberculosis in sputum. Journal of Infectious Diseases 166(5):1177-80**
	Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	145 sputum samples from 115 patients
Patient characteristics	Inclusion Patients with suspected pulmonary tuberculosis based on clinical symptoms and chest radiographic findings
Index tests	Ziehl-Neelson microscopy Decontaminated with sodium lauryl sulphate and NaOH
	PCR for IS6110
	Gas chromatography mass spectrometry for tuberculostearic acid
Reference standard	Löwenstein-Jensen culture Decontaminated with sodium lauryl sulphate and NaOH
Location	Sweden
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard: Positive / Negative Index test – Positive: TP 25 / FP 0

Bibliographic reference	**Savić B, Sjöbring U, Alugupalli S, Larsson L, Miörner H (1992) Evaluation of polymerase chain reaction, tuberculostearic acid analysis, and direct microscopy for the detection of Mycobacterium tuberculosis in sputum. Journal of Infectious Diseases 166(5):1177-80**

	Negative	FN 13	TN 107

Sensitivity of index test (95% CI)a = 65.8% (50.7% to 80.9%)
Specificity of index test (95% CI)a = 100% (100% to 100%)

Diagnostic test accuracy – PCR for IS6110

		Reference standard	
		Positive	Negative
Index test	Positive	TP 36	FP 7
	Negative	FN 2	TN 100

Sensitivity of index test (95% CI)a = 94.7% (87.6% to 100%)
Specificity of index test (95% CI)a = 93.5% (88.8% to 98.1%)

Diagnostic test accuracy – gas chromatography mass spectrometry for tuberculostearic acid

		Reference standard	
		Positive	Negative
Index test	Positive	TP 21	FP 14
	Negative	FN 17	TN 93

Bibliographic reference	**Savić B, Sjöbring U, Alugupalli S, Larsson L, Miörner H (1992) Evaluation of polymerase chain reaction, tuberculostearic acid analysis, and direct microscopy for the detection of Mycobacterium tuberculosis in sputum. Journal of Infectious Diseases 166(5):1177-80**
	Sensitivity of index test (95% CI)a = 55.3% (39.5% to 71.1%) Specificity of index test (95% CI)a = 86.9% (80.5% to 93.3%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.63 Scott, 2011

Bibliographic reference	**Scott LE, McCarthy K, Gous N, Nduna M, Van Rie A, et al (2011) Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study. PLoS Medicine 8(7): e1001061**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no

Bibliographic reference	Scott LE, McCarthy K, Gous N, Nduna M, Van Rie A, et al (2011) Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study. PLoS Medicine 8(7): e1001061
	Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	311 participants enrolled, data available for 177
Patient characteristics	Inclusion Adults (over 18 years of age) Suspected pulmonary tuberculosis Cough of 2 weeks duration or more, with or without fever, night sweats, loss of weight, chest pain, and signs of extrapulmonary involvement (such as lymph nodes, pleural effusions, or abdominal tuberculosis) Independent of a history of antituberculosis treatment and acceptance of HIV testing Exclusion Those unable to produce sputum Symptoms only of extrapulmonary tuberculosis Already on antituberculosis treatment Requiring hospital admission

Bibliographic reference	**Scott LE, McCarthy K, Gous N, Nduna M, Van Rie A, et al (2011) Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study. PLoS Medicine 8(7): e1001061**
	Sample characteristics Sputum Presenting signs and symptoms: patients presumed to have TB, presenting with cough, fever, night sweats, and/or weight loss Age: mean 32 years; range 19 to 75 years Sex, female: 41.1% HIV infection: 69.0% History of TB: not stated TB incidence rate: 993 per 100,000 Proportion of TB cases in the study: 37.9%
Index tests	Fluorescence microscopy Decontamination using N-acetyl-L-cysteine-NaOH Stained with auramine Confirmation with Ziehl-Neelson microscopy
	MTBDRplus
	LightCycler Mycobacterium Detection
Reference standard	MGIT 960 Decontamination using N-acetyl-L-cysteine-NaOH
Location	Clinical setting: primary care clinic Laboratory level: intermediate Country: South Africa, Johannesburg World Bank Income Classification: middle-income
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive / Negative Index test – Positive: TP 49 / FP 0

Bibliographic reference	**Scott LE, McCarthy K, Gous N, Nduna M, Van Rie A, et al (2011) Comparison of Xpert MTB/RIF with Other Nucleic Acid Technologies for Diagnosing Pulmonary Tuberculosis in a High HIV Prevalence Setting: A Prospective Study. PLoS Medicine 8(7): e1001061**
	Negative FN 18 TN 107 Sensitivity of index test (95% CI) = 59% (47% to 71%) Specificity of index test (95% CI) = 100% (96% to 100%)
	Diagnostic test accuracy – MTBDRplus Sensitivity of index test (95% CI) = 76% (64% to 85%) Specificity of index test (95% CI) = 97% (92% to 99%) HIV-positive (n = 124) Sensitivity of index test (95% CI) = 70% (54% to 83%) Specificity of index test (95% CI) = 96% (89% to 99%) HIV-negative (n = 26) Sensitivity of index test (95% CI) = 75% (43% to 95%) Specificity of index test (95% CI) = 100% (76% to 100%)
	Diagnostic test accuracy – LightCycler Mycobacterium Detection Sensitivity of index test (95% CI)a = 76% (64% to 85%) Specificity of index test (95% CI)a = 98% (93% to 99%) HIV-positive (n = 124) Sensitivity of index test (95% CI) = 70% (54% to 83%) Specificity of index test (95% CI) = 98% (93% to 100%) HIV-negative (n = 26) Sensitivity of index test (95% CI) = 75% (42% to 94%) Specificity of index test (95% CI) = 100% (76% to 100%)
Source of funding	Supported by the US Agency for International Development and the South Africa Tuberculosis and AIDS Training (SATBAT) program The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Comments	Data for Xpert MTB/RIF included in the Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.64 Selvakumar, 2004

Bibliographic reference	Selvakumar N, Sudhamathi S, Duraipandian M, Frieden TR, Narayanan PR (2004) Reduced detection by Ziehl-Neelsen method of acid-fast bacilli in sputum samples preserved in cetylpyridinium chloride solution. International Journal of Tuberculosis and Lung Disease 8(2): 248-52
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, were under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Selvakumar N, Sudhamathi S, Duraipandian M, Frieden TR, Narayanan PR (2004) Reduced detection by Ziehl-Neelsen method of acid-fast bacilli in sputum samples preserved in cetylpyridinium chloride solution. International Journal of Tuberculosis and Lung Disease 8(2): 248-52**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	988 specimens, included in analyses: • Ziehl-Neelson: 967 • fluorescence: 970
Patient characteristics	Sample characteristics Sputum
Index tests	Ziehl-Neelson microscopy Samples stored in cetylpyridinium chloride solution
	Fluorescence microscopy Samples stored in cetylpyridinium chloride solution Stained with auramine-phenol
Reference standard	Löwenstein-Jensen culture Samples stored in cetylpyridinium chloride solution
Location	Tuberculosis Research Centre, Chennai, India
Outcomes measures and effect size	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test Positive TP 223 FP 20

Bibliographic reference	**Selvakumar N, Sudhamathi S, Duraipandian M, Frieden TR, Narayanan PR (2004) Reduced detection by Ziehl-Neelsen method of acid-fast bacilli in sputum samples preserved in cetylpyridinium chloride solution. International Journal of Tuberculosis and Lung Disease 8(2): 248-52**
	Negative: FN 248, TN 476 Sensitivity of index test (95% CI)a = 47.4% (42.8% to 51.9%) Specificity of index test (95% CI)a = 96.0% (94.2% to 97.7%)
	Diagnostic test accuracy – fluorescence microscopy Reference standard: Positive / Negative Index test – Positive: TP 329, FP 35 Index test – Negative: FN 142, TN 461 Sensitivity of index test (95% CI)a = 69.9% (65.7% to 74.0%) Specificity of index test (95% CI)a = 92.9% (90.7% to 95.2%)
Source of funding	Supported in part by the WHO, with funds from USAID, through SEARO, New Delhi
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.65 Shim, 2002

Bibliographic reference	**Shim TS, Chi HS, Lee SD, Koh Y, Kim WS, Kim DS and Kim WD (2002) Adequately washed bronchoscope does not induce false-positive amplification tests on bronchial aspirates in the diagnosis of pulmonary tuberculosis. Chest 121(3): 774-81**
Study type	Cross-sectional

Bibliographic reference	**Shim TS, Chi HS, Lee SD, Koh Y, Kim WS, Kim DS and Kim WD (2002) Adequately washed bronchoscope does not induce false-positive amplification tests on bronchial aspirates in the diagnosis of pulmonary tuberculosis. Chest 121(3): 774-81**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? unclear how many patients, if any, are under the age of 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Shim TS, Chi HS, Lee SD, Koh Y, Kim WS, Kim DS and Kim WD (2002) Adequately washed bronchoscope does not induce false-positive amplification tests on bronchial aspirates in the diagnosis of pulmonary tuberculosis. Chest 121(3): 774-81**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	392 specimens from 331 patients
Patient characteristics	Sample characteristics Bronchial aspirate collected by bronchoscope
Index test	Ziehl-Neelson microscopy Decontamination using N-acetyl-L-cysteine-NaOH
Reference standard	Ogawa culture or histology Decontamination using N-acetyl-L-cysteine-NaOH Culture incubated for 8 weeks Accuprobe confirmation
Location	Asan Medical Center, Korea
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 13, FP 3 Index test Negative: FN 36, TN 340 Sensitivity of index test (95% CI)a = 26.5% (14.2% to 38.9%)

Bibliographic reference	**Shim TS, Chi HS, Lee SD, Koh Y, Kim WS, Kim DS and Kim WD (2002) Adequately washed bronchoscope does not induce false-positive amplification tests on bronchial aspirates in the diagnosis of pulmonary tuberculosis. Chest 121(3): 774-81**
	Specificity of index test (95% CI)a = 99.1% (98.1% to 100%)
Source of funding	No details provided
Comments	Data for Cobas Amplicor included in the Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.66 Smith, 1997

Bibliographic reference	**Smith MB, Bergmann JS, Harris SL and Woods GL (1997) Evaluation of the Roche AMPLICOR MTB assay for the detection of Mycobacterium tuberculosis in sputum specimens from prison inmates. Diagnostic Microbiology and Infectious Disease 27(4): 113-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	Smith MB, Bergmann JS, Harris SL and Woods GL (1997) Evaluation of the Roche AMPLICOR MTB assay for the detection of Mycobacterium tuberculosis in sputum specimens from prison inmates. Diagnostic Microbiology and Infectious Disease 27(4): 113-6
	Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	569 specimens from 287 participants
Patient characteristics	Sample characteristics Expectorated sputum specimens Prison inmates
Index test	Kinyoun microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Reference standard	BACTEC 460 (12B) and Middlebrook 7H10/ and 7H11 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	Texas
Outcomes measures and effect size	Diagnostic test accuracy Reference standard

Bibliographic reference	**Smith MB, Bergmann JS, Harris SL and Woods GL (1997) Evaluation of the Roche AMPLICOR MTB assay for the detection of Mycobacterium tuberculosis in sputum specimens from prison inmates. Diagnostic Microbiology and Infectious Disease 27(4): 113-6**
	Index test: Positive — TP 24, FP 22; Negative — FN 12, TN 511 Sensitivity of index test (95% CI)a = 66.7% (51.3% to 82.1%) Specificity of index test (95% CI)a = 95.9% (94.2% to 97.6%)
Source of funding	Supported in part by an educational grant from Rocke Diagnostic Systems
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.67 Smith, 1999

Bibliographic reference	**Smith MB, Bergmann JS, Onoroto M, Mathews G and Woods GL (1999) Evaluation of the enhanced amplified Mycobacterium tuberculosis direct test for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Archives of Pathology & Laboratory Medicine 123(11): 1101-3**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear

Bibliographic reference	Smith MB, Bergmann JS, Onoroto M, Mathews G and Woods GL (1999) Evaluation of the enhanced amplified Mycobacterium tuberculosis direct test for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Archives of Pathology & Laboratory Medicine 123(11): 1101-3
	Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	274 specimens from 151 participants
Patient characteristics	Inclusion

Bibliographic reference	**Smith MB, Bergmann JS, Onoroto M, Mathews G and Woods GL (1999) Evaluation of the enhanced amplified Mycobacterium tuberculosis direct test for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Archives of Pathology & Laboratory Medicine 123(11): 1101-3**
	Patients in respiratory isolation Sample characteristics Respiratory specimens: 231 sputum and 43 bronchial washes/lavages
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine O staining
Reference standard	Middlebrook selective 7H11 and BACTEC 12B culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	US
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test – Positive: TP 16, FP 7 Index test – Negative: FN 5, TN 246 Sensitivity of index test (95% CI)a = 76.2% (58.0% to 94.4%) Specificity of index test (95% CI)a = 97.2% (95.2% to 99.3%)
Source of funding	No details provided
Comments	Data for Amplified and Enhanced Amplified Mycobacterium Tuberculosis Direct Test included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.68 Soini, 1996

Bibliographic reference	Soini H, Agha SA, El-Fiky A and Viljanen MK (1996) Comparison of amplicor and 32-kilodalton PCR for detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 34(7): 1829-30
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	Soini H, Agha SA, El-Fiky A and Viljanen MK (1996) Comparison of amplicor and 32-kilodalton PCR for detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 34(7): 1829-30
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	76 specimens from 74 participants
Patient characteristics	Inclusion Patients with suspected tuberculosis Sample characteristics Sputum
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine staining
Reference standard	Löwenstein-Jensen culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 10 weeks
Location	Finland
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 13, FP 12 Index test – Negative: FN 2, TN 49 Sensitivity of index test (95% CI)a = 86.7% (69.5% to 100%)

Bibliographic reference	Soini H, Agha SA, El-Fiky A and Viljanen MK (1996) Comparison of amplicor and 32-kilodalton PCR for detection of Mycobacterium tuberculosis from sputum specimens. Journal of Clinical Microbiology 34(7): 1829-30
	Specificity of index test (95% CI)a = 80.3% (70.4% to 90.3%)
Source of funding	Supported by the Finnish Antituberculosis Foundation, the Tampere Tuberculosis Foundation, and the Foundation of Vaino and Laina Kivi
Comments	Data for Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.69 Su, 2000

Bibliographic reference	Su WJ, Tsou AP, Yang MH, Huang CY, Perng RP. Clinical experience in using polymerase chain reaction for rapid diagnosis of pulmonary tuberculosis. Zhonghua Yi Xue Za Zhi (Taipei) 63(7): 521-6
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many patients, if any, were under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	Su WJ, Tsou AP, Yang MH, Huang CY, Perng RP. Clinical experience in using polymerase chain reaction for rapid diagnosis of pulmonary tuberculosis. Zhonghua Yi Xue Za Zhi (Taipei) 63(7): 521-6
	Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? unclear risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	327 specimens from 275 patients
Patient characteristics	Inclusion Patients suspected of having pulmonary tuberculosis Sample characteristics Sputum specimens
Index tests	Ziehl-Neelson microscopy Decontamination using N-acetyl-L-cysteine-NaOH
Reference standard	Culture with Löwenstein-Jensen solid and liquid media and Middlebrook 7H9 Decontamination using N-acetyl-L-cysteine-NaOH
Location	Taipei Veterans General Hospital, Taiwan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative

Bibliographic reference	**Su WJ, Tsou AP, Yang MH, Huang CY, Perng RP. Clinical experience in using polymerase chain reaction for rapid diagnosis of pulmonary tuberculosis. Zhonghua Yi Xue Za Zhi (Taipei) 63(7): 521-6**
	Index test: Positive — TP 150, FP 0; Negative — FN 30, TN 147 Sensitivity of index test (95% CI)a = 83.3% (77.9% to 88.8%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	Partly supported by a research grant from the National Scientific Council, Taiwan
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; PCR, polymerase chain reaction; TN, true negative; TP, true positive	

1.1.2.70 Swindells, 2013

Bibliographic reference	**Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, Gupta A, Veloso VG, Asmelash A, Omoz-Oarhe AE, Gengiah S, Lalloo U, Allen R, Shiboski C, Andersen J, Qasba SS and Katzenstein DK; AIDS Clinical Trials Group 5253 Study Team (2013) Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. International Journal of Tuberculosis and Lung Disease 17(4): 532-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, are under 18 years old

Bibliographic reference	**Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, Gupta A, Veloso VG, Asmelash A, Omoz-Oarhe AE, Gengiah S, Lalloo U, Allen R, Shiboski C, Andersen J, Qasba SS and Katzenstein DK; AIDS Clinical Trials Group 5253 Study Team (2013) Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. International Journal of Tuberculosis and Lung Disease 17(4): 532-9**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	445 participants
Patient characteristics	Inclusion HIV-infected

Bibliographic reference	**Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, Gupta A, Veloso VG, Asmelash A, Omoz-Oarhe AE, Gengiah S, Lalloo U, Allen R, Shiboski C, Andersen J, Qasba SS and Katzenstein DK; AIDS Clinical Trials Group 5253 Study Team (2013) Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. International Journal of Tuberculosis and Lung Disease 17(4): 532-9**
	≥13 years old Exclusion Receipt of antiretroviral within 90 days Diagnosis of active tuberculosis within 90 days Current or recent receipt of medications with antituberculous activity Pregnancy – chest X-ray was performed in pregnant women if the site clinician considered that the potential benefits outweighed the potential risks, and if shielding was available Sample characteristics TB prevalence of ≥60 per 100,000 population Characteristic: n (%) or median [interquartile range] Age, years: 33 [28-39] Sex, male: 130 (29%) Ethnic origin: 444 (100) Black African: 1 (0) Asian: 0 White: 0 Other: CD4+, cell count/mm3: 259 [155-435] Body mass index: 23.48 [20.14-27.99] Karnofsky score: 90 [90-100]
Index test	Symptoms plus microscopy plus chest X-ray Algorithm of symptoms: • current cough, fever, night sweats and/or weight loss occurring in the previous 30 days Microscopy: • sputum • Ziehl-Neelsen • decontamination using NaCl and NaOH Chest X-ray: • findings were categorized as consistent with TB if any of the following were recorded: infiltrates, cavitary lesions, miliary

Bibliographic reference	**Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, Gupta A, Veloso VG, Asmelash A, Omoz-Oarhe AE, Gengiah S, Lalloo U, Allen R, Shiboski C, Andersen J, Qasba SS and Katzenstein DK; AIDS Clinical Trials Group 5253 Study Team (2013) Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. International Journal of Tuberculosis and Lung Disease 17(4): 532-9**
	patterns, pleural or pericardial effusions or adenopathy
Reference standard	Löwenstein-Jensen and/or MGIT 960 culture
Location	Botswana, Malawi, South Africa, Zimbabwe
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 29, FP 93 Index test Negative: FN 25, TN 298 Sensitivity of index test (95% CI)a = 53.7% (40.4% to 67.0%) Specificity of index test (95% CI)a = 76.2% (72.0 to 80.4%)
Source of funding	Supported by grants from the National Institutes for Health
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.71 Tansuphasiri and Kladphuang, 2002

Bibliographic reference	**Tansuphasiri U and Kladphuang B (2002) Evaluation of sputum staining by modified cold method and comparison with Ziehl-Neelsen and fluorochrome methods for the primary diagnosis of tuberculosis. Southeast Asian Journal of Tropical Medicine and Public Health 33(1): 128-35**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias

Bibliographic reference	Tansuphasiri U and Kladphuang B (2002) Evaluation of sputum staining by modified cold method and comparison with Ziehl-Neelsen and fluorochrome methods for the primary diagnosis of tuberculosis. Southeast Asian Journal of Tropical Medicine and Public Health 33(1): 128-35
	• Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, were under the age of 18 Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? unclear risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes

Bibliographic reference	**Tansuphasiri U and Kladphuang B (2002) Evaluation of sputum staining by modified cold method and comparison with Ziehl-Neelsen and fluorochrome methods for the primary diagnosis of tuberculosis. Southeast Asian Journal of Tropical Medicine and Public Health 33(1): 128-35**
	• Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	406 participants; data available for 392 (14 contaminated)
Patient characteristics	Inclusion Newly suspected tuberculosis based on chest symptoms Over 15 years old Sample characteristics Sputum specimens Collected prior to the administration of medication
Index test	Fluorescence microscopy Staining with auramine O
	Ziehl-Neelson microscopy
	Modified cold stain microscopy
Reference standard	Löwenstein-Jensen culture Incubated for 8 weeks
Location	Thailand
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard: Positive / Negative Index test – Positive: TP 71, FP 5 Index test – Negative: FN 48, TN 268 Sensitivity of index test (95% CI)a = 59.7% (50.9% to 68.5%)

Bibliographic reference	**Tansuphasiri U and Kladphuang B (2002) Evaluation of sputum staining by modified cold method and comparison with Ziehl-Neelsen and fluorochrome methods for the primary diagnosis of tuberculosis. Southeast Asian Journal of Tropical Medicine and Public Health 33(1): 128-35**
	Specificity of index test (95% CI)a = 98.2% (96.6% to 99.8%)
	Diagnostic test accuracy – Ziehl-Neelson microscopy Reference standard Positive Negative Index test Positive: TP 82, FP 7 Index test Negative: FN 37, TN 266 Sensitivity of index test (95% CI)a = 68.9% (60.6% to 77.2%) Specificity of index test (95% CI)a = 97.4% (95.6% to 99.3%)
	Diagnostic test accuracy – modified cold stain microscopy Reference standard Positive Negative Index test Positive: TP 84, FP 6 Index test Negative: FN 35, TN 267 Sensitivity of index test (95% CI)a = 70.6% (62.4% to 78.8%) Specificity of index test (95% CI)a = 97.8% (96.1% to 99.5%)
Source of funding	No details provided
Comments	

Bibliographic reference	Tansuphasiri U and Kladphuang B (2002) Evaluation of sputum staining by modified cold method and comparison with Ziehl-Neelsen and fluorochrome methods for the primary diagnosis of tuberculosis. Southeast Asian Journal of Tropical Medicine and Public Health 33(1): 128-35
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.72 Teo, 2011

Bibliographic reference	Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? unclear how many participants, if any, are under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? moderate risk of bias

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? no Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	131 specimens
Patient characteristics	Sample characteristics 124 sputum, 5 bronchoalveolar lavage fluid, and 2 tracheal aspirate specimens Presenting signs and symptoms: Patients thought to have TB based on symptoms and radiographic findings Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated TB incidence rate: 37 per 100,000 Proportion of TB cases in the study: 58.5%
Index tests	Ziehl-Neelson microscopy Decontaminated using N-acetyl-l-cysteine–sodium hydroxide
	Amplified Mycobacterium Tuberculosis Direct Test Decontaminated using N-acetyl-l-cysteine–sodium hydroxide

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
Reference standard	Löwenstein-Jensen or MGIT 960 culture Decontaminated using N-acetyl-l-cysteine–sodium hydroxide Incubated for 56 days
Location	Clinical setting: university hospital Laboratory level: central Country: Singapore World Bank Income Classification: high-income
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test Positive: TP 45, FP 9 Index test Negative: FN 22, TN 55 Sensitivity of index test (95% CI)a = 67.2% (55.9% to 78.4%) Specificity of index test (95% CI)a = 85.9% (77.4% to 94.5%)
	Diagnostic test accuracy – Amplified Mycobacterium Tuberculosis Direct Test Reference standard Positive Negative Index test Positive: TP 61, FP 5

Bibliographic reference	Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62

		Reference standard: Positive	Reference standard: Negative
Index test: Negative		FN 2	TN 52

Indeterminate = 11
Sensitivity of index test (95% CI)a = 96.8% (92.5% to 100%)
Specificity of index test (95% CI)a = 91.2% (83.9% to 98.6%)
Smear-negative

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 17	FP 3
Index test: Negative		FN 2	TN 46

Indeterminate = 9
Sensitivity of index test (95% CI)a = 89.5% (75.7% to 100%)
Specificity of index test (95% CI)a = 93.9% (87.2% to 100%)
Smear-positive

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 44	FP 2

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
	Negative: FN 0, TN 6 Indeterminate = 2 Sensitivity of index test (95% CI)a = 100% (100% to 100%) Specificity of index test (95% CI)a = 75.0% (45.0% to 100%)
Source of funding	Supported by a Health Service Development Programme grant provided by the Ministry of Health, Singapore
Comments	Data for Xpert MTB/RIF is included in Steingart et al (2014) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.73 Viveiros, 1999

Bibliographic reference	**Viveiros M, Pinheiro S, Moreira P, Pacheco T and Brum L (1999) Evaluation of a commercial ligase chain reaction assay for the diagnosis of pulmonary and extra-pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 3(6): 508-14**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	**Viveiros M, Pinheiro S, Moreira P, Pacheco T and Brum L (1999) Evaluation of a commercial ligase chain reaction assay for the diagnosis of pulmonary and extra-pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 3(6): 508-14**
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	93 specimens
Patient characteristics	Inclusion Patients with suspected pulmonary tuberculosis Sample characteristics Bronchopulmonary secretions
Index test	Ziehl-Neelsen microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide

Bibliographic reference	**Viveiros M, Pinheiro S, Moreira P, Pacheco T and Brum L (1999) Evaluation of a commercial ligase chain reaction assay for the diagnosis of pulmonary and extra-pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 3(6): 508-14**
Reference standard	Löwenstein-Jensen and Middlebrook 7H12 for BACTEC 460 culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 8 weeks
Location	Lisbon, Portugal
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 20, FP 8 Index test – Negative: FN 9, TN 56 Sensitivity of index test (95% CI)a = 69.0% (52.1% to 85.8%) Specificity of index test (95% CI)a = 87.5% (79.4% to 95.6%)
Source of funding	Supported by a grant from Comissão Nacional de Luta Contra a SIDA Abbott LCx® Mycobacterium tuberculosis Assay was supplied by Abbott Laboratories, Illinois, USA
Comments	Data for Ligase Chain Reaction included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.74 Vlaspolder, 1995

Bibliographic reference	**Vlaspolder F, Singer P and Roggeveen C (1995) Diagnostic value of an amplification method (Gen-Probe) compared with that of culture for diagnosis of tuberculosis. Journal of Clinical Microbiology 33(10): 2699-703**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection

Bibliographic reference	Vlaspolder F, Singer P and Roggeveen C (1995) Diagnostic value of an amplification method (Gen-Probe) compared with that of culture for diagnosis of tuberculosis. Journal of Clinical Microbiology 33(10): 2699-703
	Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear how many participants, if any, are under 18 years old Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes

Bibliographic reference	Vlaspolder F, Singer P and Roggeveen C (1995) Diagnostic value of an amplification method (Gen-Probe) compared with that of culture for diagnosis of tuberculosis. Journal of Clinical Microbiology 33(10): 2699-703
	• Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	412 specimens
Patient characteristics	Inclusion Specimens giving a positive smear result or high degree of suspicion that a patient with a negative smear results have tuberculosis Sample characteristics Sputa, bronchial and tracheal aspirates, and bronchoalveolar lavages
Index test	Amplified Mycobacterium Tuberculosis Direct Test Decontaminated using N-acetyl-l-cysteine–sodium hydroxide
Reference standard	Löwenstein-Jensen culture Decontaminated using N-acetyl-l-cysteine–sodium hydroxide Incubation for 8 weeks Confirmation by Accuprobe
Location	Alkmaar and Haarlem, The Netherlands
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 59 / FP 8 Index test – Negative: FN 2 / TN 343 Sensitivity of index test (95% CI)a = 96.7% (92.3% to 100%) Specificity of index test (95% CI)a = 97.7% (96.2% to 99.3%)

Bibliographic reference	Vlaspolder F, Singer P and Roggeveen C (1995) Diagnostic value of an amplification method (Gen-Probe) compared with that of culture for diagnosis of tuberculosis. Journal of Clinical Microbiology 33(10): 2699-703
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.75 Vuorinen, 1995

Bibliographic reference	Vuorinen P, Miettinen A, Vuento R and Hällström O (1995) Direct detection of Mycobacterium tuberculosis complex in respiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche Amplicor Mycobacterium Tuberculosis Test. Journal Clinical Microbiology 33(7): 1856-9
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? *** risk of bias • Was a consecutive or random sample of patients enrolled? • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? *** risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? • If a threshold was used, was it pre-specified? Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? *** risk of bias

Bibliographic reference	**Vuorinen P, Miettinen A, Vuento R and Hällström O (1995) Direct detection of Mycobacterium tuberculosis complex in respiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche Amplicor Mycobacterium Tuberculosis Test. Journal Clinical Microbiology 33(7): 1856-9**
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? *** risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis?
Number of patients	256 specimens from 243 participants enrolled; data available for 249
Patient characteristics	Sample characteristics Respiratory specimens: 132 sputum, 17 bronchoalveolar lavage, and 107 bronchial and tracheal aspirate specimens
Index test	Fluorescence microscopy Auramine staining Decontamination with N-acetyl-L-cysteine and sodium hydroxide Ziehl-Neelson confirmation
Reference standard	Löwenstein-Jensen and BACTEC 460 (12B) culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks A growth index of >100 was considered positive
Location	Tampere, Finland
Outcomes measures and effect size	Diagnostic test accuracy Reference standard

Bibliographic reference	**Vuorinen P, Miettinen A, Vuento R and Hällström O (1995) Direct detection of Mycobacterium tuberculosis complex in respiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test and Roche Amplicor Mycobacterium Tuberculosis Test. Journal Clinical Microbiology 33(7): 1856-9**
	Index test: Positive — Positive: TP 21; Negative: FP 2 Index test: Negative — Positive: FN 5; Negative: TN 221 Sensitivity of index test (95% CI)a = 80.8% (65.6% to 95.9%) Specificity of index test (95% CI)a = 99.1% (97.9% to 100%)
Source of funding	Supported by the Tampere Tuberculosis Foundation and by the Medical Research Fund of Tampere University Hospital, Tampere, Finland
Comments	Data for Amplified Mycobacterium Tuberculosis Direct Test and Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.76 Wang and Tay, 1999

Bibliographic reference	**Wang SX and Tay L (1999) Evaluation of three nucleic acid amplification methods for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Journal of Clinical Microbiology 37(6): 1932-4**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear

Bibliographic reference	Wang SX and Tay L (1999) Evaluation of three nucleic acid amplification methods for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Journal of Clinical Microbiology 37(6): 1932-4
	Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	230 participants
Patient characteristics	Sample characteristics Respiratory specimens: 222 sputum specimens, 4 bronchoalveolar lavage fluid specimens, 2 laryngeal swabs, and 2

Bibliographic reference	**Wang SX and Tay L (1999) Evaluation of three nucleic acid amplification methods for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. Journal of Clinical Microbiology 37(6): 1932-4**
	endotracheal aspirates
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine O staining
Reference standard	BACTEC 460 (12B) culture Decontamination with N-acetyl-L-cysteine and sodium hydroxide Incubation for 6 weeks
Location	Singapore
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 66, FP 0 Index test Negative: FN 6, TN 158 Sensitivity of index test (95% CI)a = 91.7% (85.3% to 98.1%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	
Comments	Data for Ligase Chain Reaction, Amplified Mycobacterium Tuberculosis Direct Test and Cobas Amplicor included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.77 Wang, 2004

Bibliographic reference	**Wang JY, Lee LN, Chou CS, Huang CY, Wang SK, Lai HC, Hsueh PR and Luh KT (2004) Performance assessment of a nested-PCR assay (the RAPID BAP-MTB) and the BD ProbeTec ET system for detection of Mycobacterium tuberculosis in clinical specimens. Journal of Clinical Microbiology 42(10): 4599-603**

Bibliographic reference	**Wang JY, Lee LN, Chou CS, Huang CY, Wang SK, Lai HC, Hsueh PR and Luh KT (2004) Performance assessment of a nested-PCR assay (the RAPID BAP-MTB) and the BD ProbeTec ET system for detection of Mycobacterium tuberculosis in clinical specimens. Journal of Clinical Microbiology 42(10): 4599-603**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	**Wang JY, Lee LN, Chou CS, Huang CY, Wang SK, Lai HC, Hsueh PR and Luh KT (2004) Performance assessment of a nested-PCR assay (the RAPID BAP-MTB) and the BD ProbeTec ET system for detection of Mycobacterium tuberculosis in clinical specimens. Journal of Clinical Microbiology 42(10): 4599-603**
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	552 specimens from 299 patients
Patient characteristics	Sample characteristics Respiratory specimens: 527 sputum and 25 bronchial wash specimens
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine staining
Reference standard	Middlebrook 7H11 selective culture and MGIT 960 Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	National Taiwan University Hospital, Taiwan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 12, FP 9 Index test – Negative: FN 18, TN 513 Sensitivity of index test (95% CI)a = 40.0% (22.5% to 57.5%) Specificity of index test (95% CI)a = 98.3% (97.2% to 99.4%)
Source of funding	No details provided

Bibliographic reference	**Wang JY, Lee LN, Chou CS, Huang CY, Wang SK, Lai HC, Hsueh PR and Luh KT (2004) Performance assessment of a nested-PCR assay (the RAPID BAP-MTB) and the BD ProbeTec ET system for detection of Mycobacterium tuberculosis in clinical specimens. Journal of Clinical Microbiology 42(10): 4599-603**
Comments	Data for BDProbeTec ET included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.1.2.78 Wang, 2006

Bibliographic reference	**Wang JY, Lee LN, Hsu HL, Hsueh PR and Luh KT (2006) Performance assessment of the DR. MTBC Screen assay and the BD ProbeTec ET system for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 44(3): 716-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? unclear Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

Bibliographic reference	**Wang JY, Lee LN, Hsu HL, Hsueh PR and Luh KT (2006) Performance assessment of the DR. MTBC Screen assay and the BD ProbeTec ET system for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 44(3): 716-9**
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	1206 specimens collected from 548 patients; 117 specimens that were collected from 46 patients with old cases of pulmonary tuberculosis and 23 specimens that were collected from 8 patients under antituberculosis treatment were excluded
Patient characteristics	Inclusion Clinical respiratory samples Exclusion Old cases of pulmonary tuberculosis Patients under antituberculosis treatment
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine and sodium hydroxide Auramine-rhodamine stain Kinyoun confirmation
Reference standard	MGIT 960 with Middlebrook 7H11 selective medium Decontamination with N-acetyl-L-cysteine and sodium hydroxide
Location	National Taiwan University Hospital, Taiwan

Bibliographic reference	**Wang JY, Lee LN, Hsu HL, Hsueh PR and Luh KT (2006) Performance assessment of the DR. MTBC Screen assay and the BD ProbeTec ET system for direct detection of Mycobacterium tuberculosis in respiratory specimens. Journal of Clinical Microbiology 44(3): 716-9**
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 30, FP 12 Index test Negative: FN 50, TN 974 Sensitivity of index test (95% CI)a = 37.5% (26.9% to 48.1%) Specificity of index test (95% CI)a = 98.8% (98.1% to 99.5%)
Source of funding	No details provided
Comments	Data for BDProbeTec ET included in Ling et al (2008) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

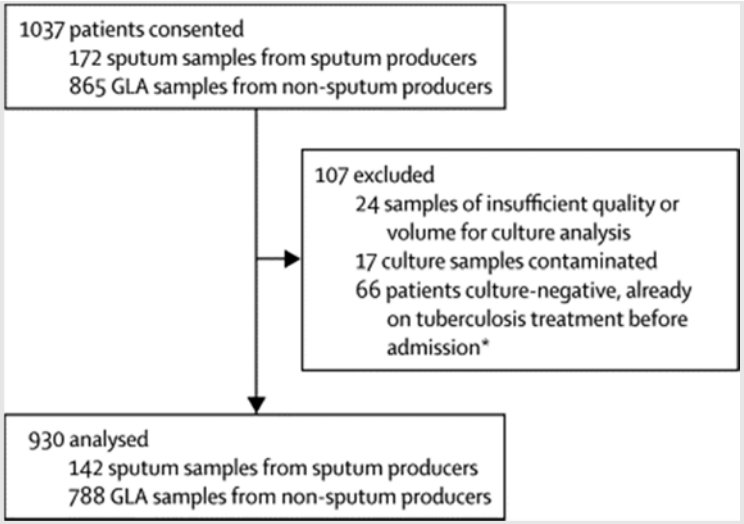
1.2 RQ D: Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in children and young people with suspected respiratory TB?

RQ E has been integrated into question this question.

1.2.1 Bates, 2013

Bibliographic reference	Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	930 participants

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**
	
Patient characteristics	Inclusion Children aged 15 years or younger Primary or secondary admission diagnosis of suspected tuberculosis based on a symptom-and-risk-factor screen (one or more of five factors: cough for more than 2 weeks, weight loss, malnutrition, HIV, or tuberculosis contact) Exclusion Poor prognosis Sample characteristics Sputum (142 specimens) or gastric lavage (788 specimens) HIV-positive = 279 (30%) Age: • <2 years = 462 (49.7%) • 2 to 4 years = 213 (22.9%) • 5 to 9 years = 124 (13.3%) • 10 to 15 years = 138 (14.8%)
Index tests	Fluorescence microscopy

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**
	Samples homogenised and digested in N-acetyl-L-cysteine-NaOH
	Xpert MTB/RIF assay Samples homogenised and digested in N-acetyl-L-cysteine-NaOH
Reference standard	MGIT 960 culture Samples homogenised and digested in N-acetyl-L-cysteine-NaOH
Location	University Teaching Hospital, Lusaka, Zambia
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test – Positive: TP 42, FP 7 Index test – Negative: FN 16, TN 865 Sensitivity of index test (95% CI)a = 72.4% (60.9% to 83.9%) Specificity of index test (95% CI)a = 99.2% (98.6% to 99.8%) Sputum specimens only Reference standard Positive Negative Index test – Positive: TP 9, FP 2

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

		FN	TN
	Negative	1	130

Sensitivity of index test (95% CI)a = 90.0% (71.4% to 100%)
Specificity of index test (95% CI)a = 98.5% (96.4% to 100%)
Gastric lavage specimens only

		Reference standard	
		Positive	Negative
Index test	Positive	TP 33	FP 5
	Negative	FN 15	TN 735

Sensitivity of index test (95% CI)a = 68.8% (55.6% to 81.9%)
Specificity of index test (95% CI)a = 99.3% (98.7% to 99.9%)

Diagnostic test accuracy – Xpert MTB/RIF assay

		Reference standard	
		Positive	Negative
Index test	Positive	TP 42	FP 7

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

			FN 16	TN 865

Negative

Sensitivity of index test (95% CI)a = 72.4% (60.9% to 83.9%)
Specificity of index test (95% CI)a = 99.2% (98.6% to 99.8%)
Smear-positive (n = 49)
TP = 14
FN = 1
Sensitivity of index test (95% CI)a = 93.3% (80.7% to 100%)
Smear-negative (n = 881)
TP = 28
FN = 15
Sensitivity of index test (95% CI)a = 65.1% (50.9% to 79.4%)
HIV-positive

		Reference standard	
		Positive	Negative
Index test	Positive	TP 16	FP 2
	Negative	FN 6	TN 255

Sensitivity of index test (95% CI)a = 72.7% (54.1% to 91.3%)
Specificity of index test (95% CI)a = 99.2% (98.2% to 100%)
HIV-positive – smear-positive
TP = 7
FN = 0

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

Sensitivity of index test (95% CI)a = 100% (100% to 100%)
HIV-positive – smear-negative
TP = 9
FN = 6
Sensitivity of index test (95% CI)a = 60.0% (35.2% to 84.8%)
HIV-negative

		Reference standard	
		Positive	Negative
Index test	Positive	TP 26	FP 5
	Negative	FN 9	TN 554

Sensitivity of index test (95% CI)a = 74.3% (59.8% to 88.8%)
Specificity of index test (95% CI)a = 99.1% (98.3% to 99.9%)
HIV-negative – smear-positive
TP = 7
FN = 1
Sensitivity of index test (95% CI)a = 87.5% (64.6% to 100%)
HIV-negative – smear-negative
TP = 19
FN = 8
Sensitivity of index test (95% CI)a = 70.4% (53.2% to 87.6%)
Sputum specimens only

	Reference standard	
	Positive	Negative

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

Index test	Positive	TP 9	FP 2
	Negative	FN 1	TN 130

Sensitivity of index test (95% CI)a = 90.0% (71.4% to 100%)
Specificity of index test (95% CI)a = 98.5% (96.4% to 100%)
Sputum specimens only – HIV-positive

		Reference standard	
		Positive	Negative
Index test	Positive	TP 6	FP 0
	Negative	FN 0	TN 38

Sensitivity of index test (95% CI)a = 100% (100% to 100%)
Specificity of index test (95% CI)a = 100% (100% to 100%)
Sputum specimens only – HIV-negative

		Reference standard	
		Positive	Negative

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

		TP	FP
Index test	Positive	3	2
	Negative	FN	TN
		1	84

Sensitivity of index test (95% CI)a = 75.0% (32.6% to 100%)
Specificity of index test (95% CI)a = 97.7% (94.5% to 100%)
Sputum specimens only – smear-positive (n = 11)
TP = 3
FN = 0
Sensitivity of index test (95% CI) = 100% (31.0% to 100%)
Sputum specimens only – smear-positive (n = 131)
TP = 6
FN = 1
Sensitivity of index test (95% CI) = 85.7% (42.0% to 99.2%)
Gastric lavage specimens only

		Reference standard	
		Positive	Negative
Index test	Positive	TP	FP
		33	5
	Negative	FN	TN
		15	735

Sensitivity of index test (95% CI)a = 68.8% (55.6% to 81.9%)

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

Specificity of index test (95% CI)a = 99.3% (98.7% to 99.9%)
Gastric lavage specimens only – HIV-positive

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 10	FP 2
Index test: Negative		FN 6	TN 217

Sensitivity of index test (95% CI)a = 62.5% (38.8% to 86.2%)
Specificity of index test (95% CI)a = 99.1% (97.8% to 100%)
Gastric lavage specimens only – HIV-negative

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 23	FP 3
Index test: Negative		FN 8	TN 470

Sensitivity of index test (95% CI)a = 74.2% (58.8% to 89.6%)
Specificity of index test (95% CI)a = 99.4% (98.7% to 100%)
Gastric lavage specimens only – smear-positive (n = 38)
TP = 11

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

FN = 1
Sensitivity of index test (95% CI) = 91.7% (59.7% to 99.6%)
Gastric lavage specimens only – smear-negative (n = 750)
TP = 22
FN = 14
Sensitivity of index test (95% CI) = 61.1% (43.5% to 76.4%)
<2 years old

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 12	FP 1
Index test: Negative		FN 7	TN 442

Sensitivity of index test (95% CI)a = 63.2% (41.5% to 84.9%)
Specificity of index test (95% CI)a = 99.8% (99.3% to 100%)
2 to 4 years old

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 12	FP 1

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**

	Negative	FN 6	TN 182

Sensitivity of index test (95% CI)a = 66.7% (44.9% to 88.4%)
Specificity of index test (95% CI)a = 99.5% (98.4% to 100%)
5 to 9 years old

		Reference standard	
		Positive	Negative
Index test	Positive	TP 3	FP 3
	Negative	FN 3	TN 115

Sensitivity of index test (95% CI)a = 50.0% (10.0% to 90.0%)
Specificity of index test (95% CI)a = 97.5% (94.6% to 100%)
10 to 15 years old

		Reference standard	
		Positive	Negative
Index test	Positive	TP 15	FP 2

Bibliographic reference	**Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, Kasonde R, Mulota P, Mzyece J, Chomba M, Mukonda L, Mumba M, Kapata N, Rachow A, Clowes P, Hoelscher M, Mwaba P and Zumla A (2013) Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. Lancet Infectious Diseases 13(1):36-42**
	Negative FN 0 TN 121 Sensitivity of index test (95% CI)a = 100% (100% to 100%) Specificity of index test (95% CI)a = 98.4% (96.1% to 100%)
Source of funding	Supported by the European Commission The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.2 El-Sayed Zaki, 2008

Bibliographic reference	**El-Sayed Zaki M and Abou-El Hassan S (2008) Clinical evaluation of Gen-Probe's amplified mycobacterium tuberculosis direct test for rapid diagnosis of Mycobacterium tuberculosis in Egyptian children at risk for infection. Archives of Pathology and Laboratory Medicine 132(2):244-7**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s)

Bibliographic reference	El-Sayed Zaki M and Abou-El Hassan S (2008) Clinical evaluation of Gen-Probe's amplified mycobacterium tuberculosis direct test for rapid diagnosis of Mycobacterium tuberculosis in Egyptian children at risk for infection. Archives of Pathology and Laboratory Medicine 132(2):244-7
	Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	60 participants
Patient characteristics	10 to 15 years of age From families with a positive history of tuberculosis Symptomatic with productive coughs Positive tuberculin skin test with a diameter of the induration of more than 10 mm

Bibliographic reference	**El-Sayed Zaki M and Abou-El Hassan S (2008) Clinical evaluation of Gen-Probe's amplified mycobacterium tuberculosis direct test for rapid diagnosis of Mycobacterium tuberculosis in Egyptian children at risk for infection. Archives of Pathology and Laboratory Medicine 132(2):244-7**
	Scars from a previous bacille Calmette-Guérin vaccination received within the past 2 years 3 consecutive sputum samples were taken from each patient, lumped together, and treated as 1 sample 43 boys and 7 girls Suspected lymphadenopathy was present in 20 patients (40%) by x-ray
Index test	Ziehl-Neelsen microscopy Sample decontamination by the NaOH and N-acetyl-l-cysteine method and then concentrated by centrifugation
	Amplified Mycobacterium Tuberculosis Direct Test Sample decontamination by the NaOH and N-acetyl-l-cysteine method and then concentrated by centrifugation
Reference standard	BACTEC 460 culture using 12B vials Sample decontamination by the NaOH and N-acetyl-l-cysteine method and then concentrated by centrifugation
Location	Mansoura University Children's Hospital, Egypt
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative Index test Positive: TP 25, FP 0 Index test Negative: FN 5, TN 20 Sensitivity of index test (95% CI)a = 83.3% (70.0% to 96.7%) Specificity of index test (95% CI)a = 100% (100% to 100%)
	Diagnostic test accuracy – Amplified M.TB Direct Test Reference standard Positive Negative

Bibliographic reference	El-Sayed Zaki M and Abou-El Hassan S (2008) Clinical evaluation of Gen-Probe's amplified mycobacterium tuberculosis direct test for rapid diagnosis of Mycobacterium tuberculosis in Egyptian children at risk for infection. Archives of Pathology and Laboratory Medicine 132(2):244-7
	Index test: Positive — TP 39, FP 0; Negative — FN 1, TN 20 Sensitivity of index test (95% CI)a = 97.5% (92.7% to 100%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.3 Iriso, 2005

Bibliographic reference	Iriso R, Mudido PM, Karamagi C and Whalen C (2005) The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. International Journal of Tuberculosis and Lung Disease 9(7): 716-26
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s)

Bibliographic reference	Iriso R, Mudido PM, Karamagi C and Whalen C (2005) The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. International Journal of Tuberculosis and Lung Disease 9(7): 716-26
	Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? chest X-ray, yes; other index tests unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	126 participants enrolled, data available for 110
Patient characteristics	Inclusion Children aged 2 months to 5 years Probable tuberculosis, based on the presence of the following: • chest X-ray showing unequivocal mediastinal lymphadenopathy or miliary tuberculosis, with appearance suggestive of tuberculosis (non-resolving or segmental/lobar opacification, cavitation or pleural effusion), or abnormal with no features

Bibliographic reference	Iriso R, Mudido PM, Karamagi C and Whalen C (2005) The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. International Journal of Tuberculosis and Lung Disease 9(7): 716-26
	suggestive of tuberculosis accompanied by loss of weight, cough and/or wheeze not responding to antibiotics for at least 2 weeks • significantly positive tuberculin skin test • histological appearance of biopsy suggestive of tuberculosis Exclusion Children who had been on antituberculosis treatment for 2 weeks or more Sample characteristics Expected prevalence: 5.2% Male:female raio = 1:1 Median duration of symptoms = 4 weeks History of BCG vaccination = 84% BCG scar = 40% History of tuberculosis contact = 40% Fever (>37.5°C) = 34% Local lymphadenopathy = 21% Oedema due to malnutrition = 11% Normal erythrocyte sedimentation rate (≤20 mm/hour)
Index test	Tuberculin skin test – Mantoux Result read after 72 hours
	Chest X-ray Anteroposterior with or without lateral chest radiographs Presence of unequivocal hilar or paratracheal adenopathy, miliary tuberculosis, lobar, segmental or bronchopneumonic opacification, cavitation or pleural effusion was noted Chest X-rays were classified as: • positive: showing unequivocal mediastinal lymphadenopathy or miliary tuberculosis, or appearance suggestive of tuberculosis (non-resolving or segmental/lobar opacification, cavitation or pleural effusion) • negative: abnormal but having no features suggestive of tuberculosis, or normal
	WHO scoring system Feature / 0 / 1 / 2 / 3 / 4 General Duration of illness, weeks / <2 / 2 to 4 / / >4 /

Bibliographic reference	Iriso R, Mudido PM, Karamagi C and Whalen C (2005) The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. International Journal of Tuberculosis and Lung Disease 9(7): 716-26				
	Nutrition, % weight for age	>80	60 to 80		<60
	Family history of tuberculosis	none	reported by family		proved sputum-positive
	Tuberculin skin test positive				positive
	Malnutrition				not improving after 4 weeks
	Unexplained fever and night sweats			no response to malaria treatment	
	Local				
					Lymph nodes
					Joint or bone swelling
					Abdominal mass or ascites
					Central nervous system signs, and usually abnormal cerebrospinal fluid findings
					Angle deformity of the spine
	Supportive of tuberculosis = score of ≥7				
Reference standard	Löwenstein-Jensen culture For a maximum of 8 weeks				
Location	Mulago Hospital, Kampala, Uganda				
Outcomes measures and effect size	Diagnostic test accuracy – Mantoux (n = 110) Sensitivity of index test = 47% Specificity of index test = 60%				
	Diagnostic test accuracy – X-ray (n = 110) Sensitivity of index test = 72%				

Bibliographic reference	Iriso R, Mudido PM, Karamagi C and Whalen C (2005) The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. International Journal of Tuberculosis and Lung Disease 9(7): 716-26
	Specificity of index test = 54%
	Diagnostic test accuracy – scoring system (n = 110) Sensitivity of index test = 86% Specificity of index test = 22%
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.4 Lodha, 2013

Bibliographic reference	Lodha R, Mukherjee A, Saini D, Saini S, Singh V, Singh S, Grewal HM and Kabra SK; Delhi TB Study Group (2013) Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis. International Journal of Tuberculosis and Lung Disease 17(11): 1383-8
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes

Bibliographic reference	Lodha R, Mukherjee A, Saini D, Saini S, Singh V, Singh S, Grewal HM and Kabra SK; Delhi TB Study Group (2013) Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis. International Journal of Tuberculosis and Lung Disease 17(11): 1383-8
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? yes Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	362 participants enrolled
Patient characteristics	Inclusion Children Cough and/or fever for >2 weeks with recent weight loss or history of contact with a tuberculosis patient in the past 2 years, in whom the diagnosis of intrathoracic tuberculosis was suspected HIV-negative Sample characteristics Gastric lavage for culture and microscopy

Bibliographic reference	**Lodha R, Mukherjee A, Saini D, Saini S, Singh V, Singh S, Grewal HM and Kabra SK; Delhi TB Study Group (2013) Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis. International Journal of Tuberculosis and Lung Disease 17(11): 1383-8**
	Characteristic — *n* (%) Age, months, median [IQR] — 115.5 [73–144] Females — 200 (55) Received BCG — 268 (74) History of contact with adult pulmonary tuberculosis case — 133 (37) Weight-for-age *Z*-score <−3 — 138 (38) Height-for-age *Z*-score <−3 — 47 (13) Chest X-ray findings Primary complex — 108 (30) Progressive disease — 204 (56) Pleural effusion — 50 (14) AFB-positive and/or *M. tuberculosis* culture-positive — 128 (35) IQR = interquartile range; BCG = bacille Calmette-Guérin; AFB = acid-fast bacilli.
Index tests	Tuberculin skin test 5 tuberculin units of purified protein derivative injected intradermally Cut-off: 10 mm induration after 49 to 72 hours
	Interferon-gamma release assay – QuantiFERON-TB Gold In-Tube test Performed within a week of the tuberculin skin test Cut-off: interferon-gamma ≥0.35 IU/ml and >25% of the nil control
Reference standard	MGIT 960 culture or Ziehl-Neelson microscopy
Location	New Delhi, India
Outcomes measures and effect size	Diagnostic test accuracy – tuberculin skin test Reference standard: Positive / Negative Index test, Positive: TP 115 / FP 222

Bibliographic reference	**Lodha R, Mukherjee A, Saini D, Saini S, Singh V, Singh S, Grewal HM and Kabra SK; Delhi TB Study Group (2013) Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis. International Journal of Tuberculosis and Lung Disease 17(11): 1383-8**
	Negative: FN 13, TN 12 Sensitivity of index test (95% CI)a = 89.8% (84.6% to 95.1%) Specificity of index test (95% CI)a = 5.1% (2.3% to 8.0%)
	Diagnostic test accuracy – interferon-gamma release assay Reference standard: Positive / Negative Index test – Positive: TP 102, FP 195 Index test – Negative: FN 26, TN 39 Sensitivity of index test (95% CI)a = 79.7% (72.7% to 86.7%) Specificity of index test (95% CI)a = 16.7% (11.9% to 21.4%)
Source of funding	Funded by the Norwegian Programme for Development, Research and Education and the Research Council of Norway
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.5 Nicol, 2011

Bibliographic reference	**Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24**
Study type	Cross-sectional

Bibliographic reference	Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	Enrolled = 492 Data available = 452 (40 did not have a suitable culture)
Patient characteristics	Inclusion Children aged 15 years or younger with suspected pulmonary tuberculosis on the basis of having a cough for more than 14 days and one of the following: a household contact infected with tuberculosis within the previous 3 months, loss of weight or failure to gain weight in the previous 3 months, a positive skin test to purified protein derivative, or a chest radiograph suggestive of pulmonary tuberculosis Exclusion Children who had received more than 72 hours of antituberculosis treatment or prophylaxis during their hospital admission Children in whom an induced sputum specimen could not be obtained Sample characteristics

Bibliographic reference	Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24

	All (n=452)	Definite (n=70)	Possible (n=216)	Not tuberculosis (n=166)
Median (IQR) age (months)	19·4 (11·1 to 46·2)	23·7 (15·2 to 59·5)	17·6 (10·6 to 40·6)	18·3 (10·9 to 39·9)
Sex (male)	250 (55%)	39 (56%)	116 (54%)	95 (57%)
HIV infection	108 (24%)	17 (24%)	55 (26%)	36 (22%)
WHO clinical staging				
Stage 1	15 (14%)	2 (13%)	7 (47%)	6 (40%)
Stage 2	43 (40%)	7 (16%)	20 (47%)	16 (37%)
Stage 3	27 (25%)	4 (15%)	13 (48%)	10 (37%)
Stage 4	23 (21%)	4 (17%)	15 (65%)	4 (17%)
HIV CDC immune suppression				
None	11 (10%)	2 (18%)	7 (64%)	2 (18%)
Moderate	34 (31%)	3 (9%)	16 (47%)	15 (44%)
Severe	54 (50%)	9 (17%)	28 (52%)	17 (32%)
Unknown	9 (8%)	3 (33%)	4 (44%)	2 (22%)
History of tuberculosis	51 (11%)	7 (10%)	23 (11%)	21 (13%)
Radiological changes suggestive of tuberculosis	274 (64%)	44 (68%)	139 (68%)	91 (57%)
Started on tuberculosis treatment	216 (48%)	69 (99%)	147 (68%)	0
Median (IQR) height for age Z score	−1·50 (−2·5 to −0·5)	−1·58 (−2·78 to −0·68)	−1·69 (−2·7 to −0·71)	−1·28 (−2·1 to −0·2)
Median (IQR) weight for age Z score	−1·5 (−2·3 to −0·6)	−1·77 (−2·86 to −0·89)	−1·52 (−2·37 to −0·65)	−1·24 (−2·16 to −0·43)
Median (IQR) weight for height Z score	−0·56 (−1·6 to 0·4)	−0·93 (−2·29 to −0·28)	−0·39 (−1·53 to 0·53)	−0·39 (−1·24 to 0·32)
Malnutrition (weight for age Z score <−2)	155 (34·3%)	31 (44·3%)	76 (35·2%)	48 (28·9%)
TST positive/TST result known (%)				
All children	128/372 (34%)	39/57 (68%)	78/176 (44%)	11/139 (8%)
HIV-infected	13/85 (15%)	3/11 (27%)	10/44 (23%)	0/30
HIV-uninfected	115/287 (40%)	36/46 (78%)	68/132 (52%)	11/109 (10%)

Bibliographic reference	**Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24**
Index test	Xpert 2 sequential induced sputum specimens using nebulised 3% hypertonic saline after 2 to 3 hours fast – the study participants underwent premedication with nebulised salbutamol prior to the administration of nebulised 3% hypertonic saline; a maximum of two attempts were conducted to obtain an adequate sample of at least 3 ml of sputum Digestion and decontamination of sputum by N-acetyl L-cysteine-sodium hydroxide method
	Fluorescence microscopy 2 sequential induced sputum specimens using nebulised 3% hypertonic saline after 2 to 3 hours fast – the study participants underwent premedication with nebulised salbutamol prior to the administration of nebulised 3% hypertonic saline; a maximum of two attempts were conducted to obtain an adequate sample of at least 3 ml of sputum Digestion and decontamination of sputum by N-acetyl L-cysteine-sodium hydroxide method
Reference standard	MGIT 960 culture 2 sequential induced sputum specimens using nebulised 3% hypertonic saline after 2 to 3 hours fast – the study participants underwent premedication with nebulised salbutamol prior to the administration of nebulised 3% hypertonic saline; a maximum of two attempts were conducted to obtain an adequate sample of at least 3 ml of sputum Digestion and decontamination of sputum by N-acetyl L-cysteine-sodium hydroxide method
Location	Cape Town, South Africa
Outcomes measures and effect size	Diagnostic test accuracy – Xpert Reference standard Positive Negative Index test – Positive: TP 52, FP 6 Index test – Negative: FN 18, TN 376 Sensitivity of index test (95% CI)a = 74.3% (64.1% to 84.5%) Specificity of index test (95% CI)a = 98.4% (97.2% to 99.7%)
	Diagnostic test accuracy – fluorescence Reference standard

Bibliographic reference	**Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, Boehme CC, Zemanay W and Zar HJ (2011) Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infectious Diseases 11(11): 819-24**
	Index test: Positive — TP 27, FP 0; Negative — FN 43, TN 382 Sensitivity of index test (95% CI)a = 38.6% (27.2% to 50.0%) Specificity of index test (95% CI)a = 100% (100% to 100%)
Source of funding	Funded by the National Institutes of Health, USA, the National Health Laboratory Service Research Trust, the Medical Research Council of South Africa and the Wellcome Trust
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.6 Sekadde, 2013

Bibliographic reference	**Sekadde MP, Wobudeya E, Joloba ML, Ssengooba W, Kisembo H, Bakeera-Kitaka S and Musoke P (2013) Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infectious Diseases 13: 33**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes

Bibliographic reference	**Sekadde MP, Wobudeya E, Joloba ML, Ssengooba W, Kisembo H, Bakeera-Kitaka S and Musoke P (2013) Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infectious Diseases 13: 33**
	Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	Enrolled 250; excluded data from 15 children (13 contaminated culture and 2 indeterminate MTB/RIF test results) and analysed 235

Bibliographic reference	Sekadde MP, Wobudeya E, Joloba ML, Ssengooba W, Kisembo H, Bakeera-Kitaka S and Musoke P (2013) Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infectious Diseases 13: 33
Patient characteristics	Inclusion Children aged 2 months to 12 years with suspected pulmonary tuberculosis Eligibility for enrolment was based on the WHO case definition for a tuberculosis suspect and included having a persistent cough of 2 weeks or more and one of the following: household tuberculosis contact, unexplained weight loss or failure to gain weight, and unexplained fever for 2 weeks or more Exclusion Children who were on antituberculosis therapy Children in whom sputum could not be obtained or sputum induction was contraindicated; the contraindications to sputum induction were adapted from the WHO guidelines for sputum induction and included: severe respiratory distress (including rapid breathing, wheezing, hypoxia); intubated patient; bleeding: low platelet count, bleeding tendency, severe nosebleeds (symptomatic or platelet count <50/ml blood); reduced level of consciousness and history of significant asthma (diagnosed and treated by a clinician) Sample characteristics

Bibliographic reference	**Sekadde MP, Wobudeya E, Joloba ML, Ssengooba W, Kisembo H, Bakeera-Kitaka S and Musoke P (2013) Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infectious Diseases 13: 33**
	Characteristic / **Frequency** / **Percentage** **Age** < 1 year 42 16.8 1-5 years 131 52.4 > 5 years 77 30.8 **Sex** Male 134 53.6 Female 116 46.4 **Patient status** Inpatient 211 84.4 Outpatient 39 15.6 **HIV status** Positive 104 41.6 Negative 146 58.4 **History of TB contact** Yes 86 34.4 No 164 65.6 **Prior TB diagnosis** Yes 18 7.2 No 232 92.8 **Previous pneumonia admission** Yes 66 26.4 No 184 73.6 **History of INH prophylaxis** Yes 1 0.4 No 249 99.6 **Tuberculin skin test** Positive 76 30.4 Negative 174 69.6 **Severe wasting*** Yes 68 27.2 No 182 72.8 **BCG scar** Yes 169 67.6 No 81 32.4 * Weight for height/length < 5 years, BMI/Age ≥ 5 years which was < −3SD.
Index test	Xpert Specimen: sputum induction using nebulised 3% hypertonic saline after a minimum of 3 hours fast – the study participants underwent premedication with nebulised salbutamol prior to the administration of nebulised 3% hypertonic saline; a maximum of two attempts were conducted to obtain an adequate sample of at least 3 ml of sputum Digestion and decontamination of sputum by N-acetyl L-cysteine-sodium hydroxide method
Reference standard	Löwenstein-Jensen (8 weeks) and MGIT 960 (6 weeks) culture Specimen: sputum induction using nebulised 3% hypertonic saline after a minimum of 3 hours fast – the study participants

Bibliographic reference	**Sekadde MP, Wobudeya E, Joloba ML, Ssengooba W, Kisembo H, Bakeera-Kitaka S and Musoke P (2013) Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infectious Diseases 13: 33**
	underwent premedication with nebulised salbutamol prior to the administration of nebulised 3% hypertonic saline; a maximum of two attempts were conducted to obtain an adequate sample of at least 3 ml of sputum Digestion and decontamination of sputum by N-acetyl L-cysteine-sodium hydroxide method
Location	Kampala, Uganda
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 27, FP 7 Index test – Negative: FN 7, TN 194 Sensitivity of index test (95% CI)a = 79.4% (65.8% to 93.0%) Specificity of index test (95% CI)a = 96.5% (94.0% to 99.1%)
Source of funding	European and Developing Countries Clinical Trials Partnership
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.7 Shata, 1996

Bibliographic reference	**Shata AM, Coulter JB, Parry CM, Ching'ani G and Broadhead RL and Hart CA (1996) Sputum induction for the diagnosis of tuberculosis. Archives of Disease in Childhood 74(6): 535-7**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias

Bibliographic reference	Shata AM, Coulter JB, Parry CM, Ching'ani G and Broadhead RL and Hart CA (1996) Sputum induction for the diagnosis of tuberculosis. Archives of Disease in Childhood 74(6): 535-7
	• Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes

Bibliographic reference	**Shata AM, Coulter JB, Parry CM, Ching'ani G and Broadhead RL and Hart CA (1996) Sputum induction for the diagnosis of tuberculosis. Archives of Disease in Childhood 74(6): 535-7**
	• Were all patients included in the analysis? yes
Number of patients	57 participants initially enrolled, samples collected for 29
Patient characteristics	Inclusion Children under the age of 15 suspected of having tuberculosis based on based on history, clinical examination, chest x ray, and a Mantoux test Sample characteristics Sputum was induced by nebulisation
Index test	Ziehl-Neelson and fluorescence microscopy
Reference standard	Löwenstein-Jensen culture Sputum was processed by the modified Petroff technique
Location	Queen Elizabeth Central Hospital, Blantyre, Malawi
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 3, FP 1 Index test – Negative: FN 4, TN 21 Sensitivity of index test (95% CI)a = 42.9% (6.2 to 79.5%) Specificity of index test (95% CI)a = 95.5% (86.8% to 100%)
Source of funding	No details provided
Comments	

a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.2.8 Zar, 2012

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias for Xpert, unclear risk of bias for microscopy • Were the index test results interpreted without knowledge of the results of the reference standard? yes for Xpert, unclear for microscopy • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95
	question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	674 participants enrolled, data available for 535
Patient characteristics	Inclusion Children under 15 years Suspected pulmonary tuberculosis based on cough for more than 14 days and one of the following conditions: a household tuberculosis contact within the preceding 3 months, weight loss or failure to gain weight within the preceding 3 months, a positive skin test to purified protein derivative, or a chest radiograph suggestive of pulmonary tuberculosis Exclusion Those who had received tuberculosis drug(s) for longer than 72 hours Sample characteristics

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95
	All Age (months; median and IQR) 19.0 (11.2–38.3) Male n (%) 294 (55.0) HIV infection n (%) 117 (21.9) HIV WHO clinical staging n (%) Stage 1 10 (8.6) Stage 2 35 (29.9) Stage 3 42 (35.9) Stage 4 30 (25.6) HIV CDC immune category n (%) None 23 (22.1) Moderate 35 (33.7) Severe 46 (44.2) History of prior tuberculosis N (%) 56 (10.4)
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine-NaOH
	Xpert MTB/RIF assay Decontamination with N-acetyl-L-cysteine-NaOH
Reference standard	MGIT 960 culture Decontamination with N-acetyl-L-cysteine-NaOH Incubation for 6 weeks Confirmation with MTBDRplus
Location	Cape Town, South Africa
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Induced sputum samples only Reference standard: Positive / Negative Index test – Positive: TP 28 / FP 0

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95

	Negative	FN 59	TN 448

Sensitivity of index test (95% CI) = 32.2% (22.2% to 42.2%)
Specificity of index test (95% CI) = 100% (99.2% to 100%)
Nasopharyngeal aspirate samples only

		Reference standard	
		Positive	Negative
Index test	Positive	TP 21	FP 0
	Negative	FN 66	TN 448

Sensitivity of index test (95% CI) = 24.1% (15.0% to 33.3%)
Specificity of index test (95% CI) = 100% (99.2% to 100%)

Diagnostic test accuracy – Xpert MTB/RIF assay
Induced sputum samples only

		Reference standard	
		Positive	Negative
Index test	Positive	TP 64	FP 5

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95

	Negative	FN 23	TN 443

Sensitivity of index test (95% CI) = 73.6% (64.1% to 83.0%)
Specificity of index test (95% CI) = 98.9% (97.9% to 99.9%)
Induced sputum samples only – smear-positive
TP = 29
FN = 1
Sensitivity of index test (95% CI) = 96.7% (89.9% to 100%)
Induced sputum samples only – smear-negative
TP = 35
FN = 22
Sensitivity of index test (95% CI) = 61.4% (48.4% to 74.4%)
Induced sputum samples only – HIV-positive

		Reference standard Positive	 Negative
Index test	Positive	TP 14	FP 0
	Negative	FN 1	TN 102

Sensitivity of index test (95% CI) = 93.3% (79.0% to 100%)
Specificity of index test (95% CI) = 100% (96.4% to 100%)
Induced sputum samples only – HIV-positive – smear-positive
TP = 9
FN = 0

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95

Sensitivity of index test (95% CI) = 100% (66.4% to 100%)
Induced sputum samples only – HIV-positive – smear-negative
TP = 5
FN = 1
Sensitivity of index test (95% CI) = 83.3% (40.5% to 100%)
Induced sputum samples only – HIV-negative

		Reference standard: Positive	Reference standard: Negative
Index test: Positive		TP 50	FP 5
Index test: Negative		FN 22	TN 340

Sensitivity of index test (95% CI) = 69.4% (58.5% to 80.3%)
Specificity of index test (95% CI) = 98.6% (97.3% to 99.8%)
Induced sputum samples only – HIV-negative – smear-positive
TP = 20
FN = 1
Sensitivity of index test (95% CI) = 95.2% (85.3% to 100%)
Induced sputum samples only – HIV-negative – smear-negative
TP = 30
FN = 21
Sensitivity of index test (95% CI) = 58.8% (44.8% to 72.8%)
Nasopharyngeal aspirate samples only

	Reference standard: Positive	Reference standard: Negative

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95

		TP	FP
Index test	Positive	49	8
	Negative	FN	TN
		38	440

Sensitivity of index test (95% CI) = 56.3% (45.7% to 67.0%)
Specificity of index test (95% CI) = 98.2% (97.0% to 99.5%)
Nasopharyngeal aspirate samples only – smear-positive
TP = 27
FN = 3
Sensitivity of index test (95% CI) = 90.0% (78.6% to 100%)
Nasopharyngeal aspirate samples only – smear-negative
TP = 22
FN = 35
Sensitivity of index test (95% CI) = 38.6% (25.6% to 51.6%)
Nasopharyngeal aspirate samples only – HIV-positive

		Reference standard	
		Positive	Negative
Index test	Positive	TP	FP
		10	2
	Negative	FN	TN
		5	100

Sensitivity of index test (95% CI) = 66.7% (39.6% to 93.7%)

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95

Specificity of index test (95% CI) = 98.0% (95.3% to 100%)
Nasopharyngeal aspirate samples only – HIV-positive – smear-positive
TP = 8
FN = 1
Sensitivity of index test (95% CI) = 88.9% (63.2% to 100%)
Nasopharyngeal aspirate samples only – HIV-positive – smear-negative
TP = 6
FN = 2
Sensitivity of index test (95% CI) = 33.3% (0% to 87.5%)
Nasopharyngeal aspirate samples only – HIV-negative

		Reference standard	
		Positive	Negative
Index test	Positive	TP 39	FP 6
	Negative	FN 33	TN 339

Sensitivity of index test (95% CI) = 54.2% (42.4% to 66.0%)
Specificity of index test (95% CI) = 98.3% (96.9% to 99.6%)
Nasopharyngeal aspirate samples only – HIV-negative – smear-positive
TP = 19
FN = 2
Sensitivity of index test (95% CI) = 90.5% (76.8% to 100%)
Nasopharyngeal aspirate samples only – HIV-negative – smear-negative
TP = 20
FN = 31
Sensitivity of index test (95% CI) = 39.2% (25.3% to 53.1%)

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clinical Infectious Diseases 55(8): 1088-95
	Time from obtaining specimen to reporting to clinician Median time (interquartile range), days • Xpert MTB/RIF assay = 0 (0 to 3) • culture = 15 (12 to 20)
Source of funding	Supported by the National Institutes of Health, USA, the National Health Laboratory Services Research Trust, the Medical Research Council of South Africa, and The Wellcome Trust
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.2.9 Zar, 2013

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias for Xpert, unclear risk of bias for microscopy

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health
	• Were the index test results interpreted without knowledge of the results of the reference standard? yes for Xpert, unclear for microscopy • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test?n unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	415 participants enrolled, data available for 384 (others did not have at least one induced sputum specimen and one nasopharyngeal aspirate)
Patient characteristics	Inclusion Children under 15 years Suspected pulmonary tuberculosis based on cough for more than 14 days and one of the following conditions: a household tuberculosis contact within the preceding 3 months, weight loss or failure to gain weight within the preceding 3 months, a positive skin test to purified protein derivative, or a chest radiograph suggestive of pulmonary tuberculosis

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health**
	Exclusion Those who had received tuberculosis drug(s) for longer than 72 hours Sample characteristics At least 1 induced sputum and nasopharyngeal aspirate **Overall (N=384)** Age in months (median [IQR]) 38·3 (21·2 to 56·5) Sex (male) 181 (47%) HIV infection 31 (8%) WHO HIV clinical staging Stage 1 11 (36%) Stage 2 1 (3%) Stage 3 19 (61%) Stage 4 0 HIV CDC immune category Mild 13 (46%) Moderate 11 (40%) Severe 4 (14%) History of tuberculosis 42 (11%) Radiological changes suggestive of tuberculosis* 314 (82%) Started on tuberculosis treatment 180 (47%) Z scores (median [IQR]) HAZ −0·8 (−1·7 to 0·1) WAZ −0·5 (−1·3 to 0·4) WHZ 0·2 (−0·9 to 1·1) Malnutrition† (a WAZ score less than −2) 50 (13%) Tuberculin skin positive‡ 259 (69%)
Index test	Fluorescence microscopy Decontamination with N-acetyl-L-cysteine-NaOH
	Xpert MTB/RIF assay Decontamination with N-acetyl-L-cysteine-NaOH
Reference standard	MGIT 960 culture

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health**
	Decontamination with N-acetyl-L-cysteine-NaOH Confirmation with MTBDRplus
Location	Nolungile primary care clinic, Khayelitsha, Cape Town, South Africa
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Induced sputum only Reference standard Positive Negative Index test Positive: TP 4, FP 1 Index test Negative: FN 26, TN 353 Sensitivity of index test (95% CI)a = 13.3% (1.1% to 25.5%) Specificity of index test (95% CI)a = 99.7% (99.2% to 100%) Amongst those with two paired induced sputum and nasopharyngeal aspirate specimens Reference standard Positive Negative Index test Positive: TP 3, FP 1 Index test Negative: FN 25, TN 280 Sensitivity of index test (95% CI)a = 10.7% (0.0% to 22.2%) Specificity of index test (95% CI)a = 99.6% (99.0% to 100%)

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health**
	Diagnostic test accuracy – Xpert MTB/RIF assay Induced sputum only Reference standard Positive Negative Index test Positive: TP 13, FP 3 Index test Negative: FN 17, TN 351 Sensitivity of index test (95% CI)a = 43.3% (25.6% to 61.1%) Specificity of index test (95% CI)a = 99.2% (98.2% to 100%) Nasopharyngeal aspirate only Reference standard Positive Negative Index test Positive: TP 9, FP 4 Index test Negative: FN 21, TN 350 Sensitivity of index test (95% CI)a = 30.0% (13.6% to 46.4%) Specificity of index test (95% CI)a = 98.9% (97.8% to 100.0%)
	Time from obtaining specimen to reporting to clinician Median time (interquartile range), days • Xpert MTB/RIF assay = 1 (1 to 1)

Bibliographic reference	Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W and Nicol MP (2013) Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Global Health
	• culture = 16 (13 to 19)
Source of funding	Funded by the National Institutes of Health, USA, the National Health Laboratory Services Research Trust, the Medical Research Council of South Africa, the National Research Foundation South Africa, and the European and Developing Countries Clinical Trials Partnership
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3 RQ G: Apart from culture, what other tests are effective in establishing an accurate diagnosis of active non-respiratory TB in people with suspected non-respiratory TB?

RQ H has been integrated into question this question.

1.3.1 Diagnosis of active bone and joint tuberculosis

1.3.1.1 Lai, 2011

Bibliographic reference	Lai CC, Tan CK, Liu WL, Lin SH, Huang YT, Liao CH and Hsueh PR (2011) Diagnostic performance of an enzyme-linked immunospot assay for interferon-γ in skeletal tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 30:767-71
Study type	Diagnostic cohort
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	**Lai CC, Tan CK, Liu WL, Lin SH, Huang YT, Liao CH and Hsueh PR (2011) Diagnostic performance of an enzyme-linked immunospot assay for interferon-γ in skeletal tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 30:767-71**
	Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? where culture-confirmed, yes; however, 3/15 cases of tuberculosis were only 'probable' (that is, not culture-confirmed) • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? yes
Number of patients	36 participants
Patient characteristics	Inclusion Patients with suspected skeletal tuberculosis Characteristics of included participants

Bibliographic reference	**Lai CC, Tan CK, Liu WL, Lin SH, Huang YT, Liao CH and Hsueh PR (2011) Diagnostic performance of an enzyme-linked immunospot assay for interferon-γ in skeletal tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 30:767-71**
	Variables / No (%) of patients with suspected genitourinary TB (*n*=36) Mean age ± standard deviation (years) — 62.0 ± 15.4 Male to female sex ratio — 17 : 19 Underlying condition Diabetes mellitus — 7 (19.4) Malignancy — 5 (13.9) Chronic kidney disease — 3 (8.3) Liver cirrhosis — 1 (2.7) HIV infection — 1 (2.7) Concomitant pulmonary TB — 3 (8.3) Positive ELISPOT assay — 21 (58.3) Diagnosis Confirmed TB — 12 (35.3) Probable TB — 3 (8.8) Not TB — 21 (58.3.) Bacterial osteoarthritis — 17 (47.2) Lymphoma — 2 (5.6) *Mycobacterium avium* complex infection — 1 (2.7) *Mycobacterium abscessus* infection — 1 (2.7) Suspect site of infection Spine — 20 (55.6) Knee — 9 (25.0) Hand — 6 (16.7) Hip — 1 (2.7)
Index test	T-SPOT.TB using whole blood Threshold for positivity: ≥8 spots more than the mean of the negative control wells, and at least twice the value found in the background control wells
Reference standard	Recovery of M. tuberculosis from a clinical specimen by Middlebrook 7H11 selective and MGIT 960 culture (‘confirmed’ tuberculosis) or histological findings of a biopsy specimen consistent with a diagnosis of tuberculosis (granulomatous

Bibliographic reference	**Lai CC, Tan CK, Liu WL, Lin SH, Huang YT, Liao CH and Hsueh PR (2011) Diagnostic performance of an enzyme-linked immunospot assay for interferon-γ in skeletal tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 30:767-71**
	inflammation and/or caseating necrosis) in a patient who responded clinically and radiologically to a full course of antituberculosis treatment ('probable' tuberculosis)
Location	Taiwan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive / Negative Index test – Positive: TP 13, FP 8 Index test – Negative: FN 2, TN 13 Sensitivity of index test (95% CI)a = 86.7% (69.5 to 100%) Specificity of index test (95% CI)a = 61.9% (41.1 to 82.7%)
Source of funding	Partly supported by the Institute for Biotechnology and Medicine Industry
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2 Diagnosis of active central nervous system tuberculosis

1.3.2.1 Denkinger, 2014

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
Study type	Systematic review

<table>
<tr><th>Bibliographic reference</th><th>Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. European Respiratory Journal 44(2): 435-46</th></tr>
<tr><td>Study quality</td><td>Does the review address an appropriate and clearly focused question that is relevant to the review question? yes
Does the review collect the type of studies considered relevant to the review question? yes
Is the literature search sufficiently rigorous to identify all the relevant studies? yes
Is study quality assessed and reported? yes
Is an adequate description of methodology included, and the methods used appropriate to the question? yes
Additional criteria
Is there concern that the included patients do not match the review question? no
Is there concern that the index test, its conduct, or interpretation differ from the review question? no
Is there concern that the target condition as defined by the reference standard does not match the review question? no
<table>
<tr><td>Study</td><td>Blinding</td><td>Selection</td><td>Prospective enrolment?</td></tr>
<tr><td>Armand, 2011</td><td>yes</td><td>convenience</td><td>no</td></tr>
<tr><td>Causse, 2011</td><td>yes</td><td>consecutive</td><td>yes</td></tr>
<tr><td>Hanif, 2011</td><td>no</td><td>consecutive</td><td>yes</td></tr>
<tr><td>Hillemann, 2011</td><td>yes</td><td>consecutive</td><td>yes</td></tr>
<tr><td>Moure, 2012</td><td>yes</td><td>convenience</td><td>no</td></tr>
<tr><td>Nhu, 2013</td><td>no</td><td>consecutive</td><td>yes</td></tr>
<tr><td>Patel, 2013</td><td>yes</td><td>consecutive</td><td>yes</td></tr>
<tr><td>Safianowska, 2012</td><td>no</td><td>consecutive</td><td>yes</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**

Tortoli, 2012	yes	convenience	no
Vadwai, 2011	yes	consecutive	yes
Zeka, 2011	yes	consecutive	no

Number of patients

Study	n
Armand, 2011	5
Causse, 2011	50
Hanif, 2011	5
Hillemann, 2011	19
Moure, 2012	14
Nhu, 2013	379
Patel, 2013	149
Safianowska, 2012	6
Tortoli, 2012	133
Vadwai, 2011	19
Zeka, 2011	31

Patient characteristics

Inclusion
Patients with suspected tuberculosis
Characteristics of included participants

Index test

Xpert MTB/RIF

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
Reference standard	Culture-based
Outcomes measures and effect size	Diagnostic test accuracy

Study	True positives	False positives	False negatives	True negatives
Armand, 2011	0	0	0	5
Causse, 2011	5	0	1	44
Hanif, 2011	1	0	0	4
Hillemann, 2011	0	0	0	19
Moure, 2012	2	0	0	12
Nhu, 2013	103	6	18	252
Patel, 2013	18	7	17	107
Safianowska, 2012	0	0	0	6
Tortoli, 2012	11	2	2	118
Vadwai, 2011	0	0	3	16
Zeka, 2011	3	0	0	28

Source of funding	No details provided
Comments	Data not extracted for duplicate studies
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.2 Al-Ateah, 2012

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**

Bibliographic reference	Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? details provided were limited Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	14 cerebrospinal fluid specimens
Patient characteristics	Clinically suspected tuberculosis Presenting signs and symptoms: not stated Age: not stated TB incidence rate: 17 per 100,000 Proportion of TB cases in the study: 25.6%
Index test	Fluorescence microscopy Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method; smears were prepared, fixed, and stained with auramine-rhodamine stain Suspected slides were confirmed by Ziehl-Neelson stain
Reference standard	Xpert MTB/RIF Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method
	Löwenstein-Jensen culture and MGIT 960 Specimen processing: N-acetyl-L-cysteine and sodium hydroxide method 6 to 8 weeks of incubation
Location	Saudi Arabia
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative

Bibliographic reference	**Al-Ateah SM, Al-Dowaidi MM and El-Khizzi NA(2012) Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Medical Journal 33(10): 1100-5**
	Index test / Positive: TP 0, FP 0; Negative: FN 0, TN 14
	Diagnostic test accuracy – Xpert MTB/RIF Reference standard: Positive / Negative Index test – Positive: TP 0, FP 0; Negative: FN 0, TN 14
Source of funding	This study was not funded by any pharmaceutical company or research organization
Comments	
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.3 Bonington, 2000

Bibliographic reference	**Bonington A, Strang JI, Klapper PE, Hood SV, Parish A, Swift PJ, Damba J, Stevens H, Sawyer L, Potgieter G, Bailey A and Wilkins EG (2000) TB PCR in the early diagnosis of tuberculous meningitis: evaluation of the Roche semi-automated COBAS Amplicor MTB test with reference to the manual Amplicor MTB PCR test. Tubercle and Lung Disease 80(4-5): 191-6**

Bibliographic reference	**Bonington A, Strang JI, Klapper PE, Hood SV, Parish A, Swift PJ, Damba J, Stevens H, Sawyer L, Potgieter G, Bailey A and Wilkins EG (2000) TB PCR in the early diagnosis of tuberculous meningitis: evaluation of the Roche semi-automated COBAS Amplicor MTB test with reference to the manual Amplicor MTB PCR test. Tubercle and Lung Disease 80(4-5): 191-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? *unclear risk of bias* • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? yes Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Bonington A, Strang JI, Klapper PE, Hood SV, Parish A, Swift PJ, Damba J, Stevens H, Sawyer L, Potgieter G, Bailey A and Wilkins EG (2000) TB PCR in the early diagnosis of tuberculous meningitis: evaluation of the Roche semi-automated COBAS Amplicor MTB test with reference to the manual Amplicor MTB PCR test. Tubercle and Lung Disease 80(4-5): 191-6**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no
Number of patients	114 cerebrospinal fluid specimens collected from 99 patients; data available for 83 specimens from 69 participants 30 patients were excluded from the study: 10 because sufficient clinical data were not available and a further 20 because culture results were not available
Patient characteristics	Inclusion Patients with suspected tuberculous meningitis Characteristics of included participants 31 males and 38 females Ages ranging from 1 year to 83 years (mean 29.7±17.4 (1 standard deviation) years)
Index test	Ziehl-Neelsen microscopy
Reference standard	BACTEC 12B culture Incubation for 6 weeks
Location	Eastern Cape, South Africa
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 3, FP 4

Bibliographic reference	**Bonington A, Strang JI, Klapper PE, Hood SV, Parish A, Swift PJ, Damba J, Stevens H, Sawyer L, Potgieter G, Bailey A and Wilkins EG (2000) TB PCR in the early diagnosis of tuberculous meningitis: evaluation of the Roche semi-automated COBAS Amplicor MTB test with reference to the manual Amplicor MTB PCR test. Tubercle and Lung Disease 80(4-5): 191-6**
	Negative FN 0 TN 62 Sensitivity (95% CI)a = 85.7% (49.1 to 100%) Specificity (95% CI)a = 93.9% (88.2 to 99.7%)
Source of funding	Supported by a grant from Roche Diagnostics Inc
Comments	Data for Cobas Amplicor included in the Pai (2003) systematic review
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.4 Chedore and Jamieson, 2002

Bibliographic reference	**Chedore P and Jamieson FB (2002) Rapid molecular diagnosis of tuberculous meningitis using the Gen-probe Amplified Mycobacterium Tuberculosis direct test in a large Canadian public health laboratory. International Journal of Tuberculosis and Lung Disease 6(10): 913-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? *unclear*

Bibliographic reference	Chedore P and Jamieson FB (2002) Rapid molecular diagnosis of tuberculous meningitis using the Gen-probe Amplified Mycobacterium Tuberculosis direct test in a large Canadian public health laboratory. International Journal of Tuberculosis and Lung Disease 6(10): 913-9
	• If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	311 specimens
Patient characteristics	Inclusion Clinical suspicion of tuberculous meningitis
Index test	Fluorescence microscopy Cerebrospinal fluid specimen
	Amplified M. Tuberculosis Direct test Cerebrospinal fluid specimen The cut-off value for a positive result was ≥500 000 relative light units

Bibliographic reference	**Chedore P and Jamieson FB (2002) Rapid molecular diagnosis of tuberculous meningitis using the Gen-probe Amplified Mycobacterium Tuberculosis direct test in a large Canadian public health laboratory. International Journal of Tuberculosis and Lung Disease 6(10): 913-9**
Reference standard	Löwenstein-Jensen solid and BACTEC MGIT 960 liquid culture Cerebrospinal fluid specimen Incubated for 6 to 7 weeks
Location	Toronto, Ontario
Outcomes measures and effect size	Diagnostic test accuracy – fluorescence microscopy Reference standard Positive Negative Index test Positive: TP 10, FP 0 Index test Negative: FN 19, TN 292 Sensitivity of index test (95% CI)a = 34.5% (17.2 to 51.8%) Specificity of index test (95% CI)a = 99.8% (99.4 to 100%)
	Diagnostic test accuracy – Amplified M. Tuberculosis Direct test Reference standard Positive Negative Index test Positive: TP 15, FP 2 Index test Negative: FN 1, TN 293 Sensitivity of index test (95% CI)a = 93.8% (81.9 to 100%) Specificity of index test (95% CI)a = 99.3% (98.4 to 100%)

Bibliographic reference	**Chedore P and Jamieson FB (2002) Rapid molecular diagnosis of tuberculous meningitis using the Gen-probe Amplified Mycobacterium Tuberculosis direct test in a large Canadian public health laboratory. International Journal of Tuberculosis and Lung Disease 6(10): 913-9**
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.5 Feng, 2014

Bibliographic reference	**Feng GD, Shi M, Ma L, Chen P, Wang BJ, Zhang M, Chang XL, Su XC, Yang YN, Fan XH, Dai W, Liu TT, He Y, Bian T, Duan LX, Li JG, Hao XK, Liu JY, Xue X, Song YZ, Wu HQ, Niu GQ, Zhang L, Han CJ, Lin H, Lin ZH, Liu JJ, Jian Q, Zhang JS, Tian Y, Zhou BY, Wang J, Xue CH, Han XF, Wang JF, Wang SL, Thwaites GE and Zhao G (2014) Diagnostic accuracy of intracellular mycobacterium tuberculosis detection for tuberculous meningitis. *American Journal of Respiratory and Critical Care Medicine* 189(4):475-81**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	**Feng GD, Shi M, Ma L, Chen P, Wang BJ, Zhang M, Chang XL, Su XC, Yang YN, Fan XH, Dai W, Liu TT, He Y, Bian T, Duan LX, Li JG, Hao XK, Liu JY, Xue X, Song YZ, Wu HQ, Niu GQ, Zhang L, Han CJ, Lin H, Lin ZH, Liu JJ, Jian Q, Zhang JS, Tian Y, Zhou BY, Wang J, Xue CH, Han XF, Wang JF, Wang SL, Thwaites GE and Zhao G (2014) Diagnostic accuracy of intracellular mycobacterium tuberculosis detection for tuberculous meningitis. *American Journal of Respiratory and Critical Care Medicine* 189(4):475-81**
	Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	281
Patient characteristics	*Inclusion* Children and adults with meningitis that was possibly, probably or definitely tuberculous, based on clinical and radiological examination, as well as examination of the cerebrospinal fluid Tuberculous meningitis was defined as “definite” if acid-fast bacilli were detected by cerebrospinal fluid culture *Exclusion* Patients infected with HIV *Baseline characteristics*

Bibliographic reference	**Feng GD, Shi M, Ma L, Chen P, Wang BJ, Zhang M, Chang XL, Su XC, Yang YN, Fan XH, Dai W, Liu TT, He Y, Bian T, Duan LX, Li JG, Hao XK, Liu JY, Xue X, Song YZ, Wu HQ, Niu GQ, Zhang L, Han CJ, Lin H, Lin ZH, Liu JJ, Jian Q, Zhang JS, Tian Y, Zhou BY, Wang J, Xue CH, Han XF, Wang JF, Wang SL, Thwaites GE and Zhao G (2014) Diagnostic accuracy of intracellular mycobacterium tuberculosis detection for tuberculous meningitis. *American Journal of Respiratory and Critical Care Medicine* 189(4):475-81**
	Variables / **Definite TBM (*n* = 37)** / **Probable TBM (*n* = 64)** / **Possible TBM (*n* = 139)** / **Not TBM (*n* = 40)***
	Age, yr: 29 (3–82) / 27 (2–73) / 36 (2–87) / 41 (3–38) Male sex: 15 (40.5) / 44 (68.8) / 86 (61.9) / 27 (67.5) Duration of symptoms, d: 6 (1–44) / 9 (1–205) / 7 (1–288) / 30 (1–92) Chest radiograph appearances of active tuberculosis: 4 (10.8) / 22 (34.4) / 5 (3.6) / 0 >1 d of antituberculosis treatment before CSF taken: 6 (16.2) / 18 (28.1) / 1 (0.7) / 0 MRC disease severity grade I: 21 (56.8) / 46 (71.9) / 95 (70.4) II: 11 (29.7) / 12 (18.8) / 31 (23.0) III: 5 (13.5) / 6 (9.4) / 9 (6.7) Glasgow Coma Score, /15: 15 (6–15) / 15 (8–15) / 15 (6–15) / 14 (8–15) CSF total white cell count, /mm^3: 140 (7–1,029) / 89 (0–3,208) / 41 (0–5,420) / 51 (0–3,208) CSF total neutrophils, /mm^3: 26 (0–387) / 1 (0–2,775) / 0 (0–4,688) / 4 (0–2,775) CSF total lymphocytes, /mm^3: 75 (3–993) / 45 (0–498) / 29 (0–995) / 26 (0–689) CSF total monocytes, /mm^3: 11 (1–63) / 7 (0–385) / 4 (0–583) / 6 (0–385) CSF glucose, mmol/L: 1.8 (0.4–2.1) / 2.5 (0.4–5.4) / 3.1 (0.61–6.8) / 2.1 (0.1–3.4) CSF protein, g/dl: 1.1 (0.2–2.1) / 1.0 (0.3–5.0) / 0.6 (0.04–6.5) / 1.0 (0.3–2.1) Death before discharge from hospital: 5 (13.5%) / 6 (9.4%) / 13 (9.4%) / 13 (32.5%) *Definition of abbreviations:* CSF = cerebrospinal fluid; MRC = Medical Research Council; TBM = tuberculous meningitis. Data are shown as n (%) (Death before discharge from hospital) or mean (95% confidence interval) (all other rows). *A total of 36 had cryptococcal meningitis (India ink positive CSF) and 4 had CSF culture-confirmed pyogenic bacterial meningitis.
Index test	Ziehl-Neelsen microscopy
	Modified Ziehl-Neelsen microscopy
Reference standard	MGIT 960
Location	China
Outcomes measures and effect size	Diagnostic test accuracy – modified Ziehl-Neelsen microscopy Reference standard Positive Negative

Bibliographic reference	**Feng GD, Shi M, Ma L, Chen P, Wang BJ, Zhang M, Chang XL, Su XC, Yang YN, Fan XH, Dai W, Liu TT, He Y, Bian T, Duan LX, Li JG, Hao XK, Liu JY, Xue X, Song YZ, Wu HQ, Niu GQ, Zhang L, Han CJ, Lin H, Lin ZH, Liu JJ, Jian Q, Zhang JS, Tian Y, Zhou BY, Wang J, Xue CH, Han XF, Wang JF, Wang SL, Thwaites GE and Zhao G (2014) Diagnostic accuracy of intracellular mycobacterium tuberculosis detection for tuberculous meningitis. *American Journal of Respiratory and Critical Care Medicine* 189(4):475-81**
	Index test: Positive — TP 37, FP 168; Negative — FN 0, TN 75
Source of funding	No details provided
Comments	
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.6 Kim, 2008

Bibliographic reference	**Kim SH, Chu K, Choi SJ, Song KH, Kim HB, Kim NJ, Park SH, Yoon BW, Oh MD and Choe KW (2008) Diagnosis of central nervous system tuberculosis by T-cell-based assays on peripheral blood and cerebrospinal fluid mononuclear cells. Clinical and Vaccine Immunology 15(9):1356-62**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s)

Bibliographic reference	Kim SH, Chu K, Choi SJ, Song KH, Kim HB, Kim NJ, Park SH, Yoon BW, Oh MD and Choe KW (2008) Diagnosis of central nervous system tuberculosis by T-cell-based assays on peripheral blood and cerebrospinal fluid mononuclear cells. Clinical and Vaccine Immunology 15(9):1356-62
	Could the conduct or interpretation of the index test have introduced bias? some risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? no • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? culture, yes; PCR, not yet an accepted reference standard • Were the reference standard results interpreted without knowledge of the results of the index test? no Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? some culture, some PCR • Were all patients included in the analysis? yes
Number of patients	37 participants
Patient characteristics	Inclusion Adult patients with suspected central nervous system tuberculosis Characteristics of included participants

Bibliographic reference	**Kim SH, Chu K, Choi SJ, Song KH, Kim HB, Kim NJ, Park SH, Yoon BW, Oh MD and Choe KW (2008) Diagnosis of central nervous system tuberculosis by T-cell-based assays on peripheral blood and cerebrospinal fluid mononuclear cells. Clinical and Vaccine Immunology 15(9):1356-62**
	Characteristic / **Patients with CNS TB (n = 12)[b]** / **Patients with not-active TB (n = 25)** Mean ± SD age (yr) / 45.5 ± 16.5 / 39.3 ± 16.5 Male sex / 5 (42) / 15 (60) Suspected infection and infection site Suspected TB meningitis[c] / 8 (67) / 23 (92) Suspected intracranial tuberculoma with disseminated TB / 4 (33) / 2 (8) Underlying condition or illness Human immunodeficiency virus infection / 1 (8) / 1 (4) Transplantation / 0 (0) / 2 (8) Hematologic malignancy / 0 (0) / 2 (8) Solid tumor / 0 (0) / 1 (4) Rheumatologic disease / 1 (8) / 1 (4) Diabetes / 1 (8) / 1 (4) No underlying illness / 8 (67) / 17 (68) Immunosuppressive condition[d] / 2 (17) / 7 (28) Prior latent tuberculosis treatment / 0 (0) / 0 (0) Prior active tuberculosis treatment / 2 (17) / 0 (0)
Index test	T-SPOT.TB Peripheral blood mononuclear cells
	Tuberculin skin test Mantoux Threshold for positivity = induration ≥10 mm
Reference standard	Culture of M. Tuberculosis-specific PCR assay
Location	Seoul, Korea
Outcomes measures and effect size	Diagnostic test accuracy – peripheral blood mononuclear cells Reference standard

Bibliographic reference	**Kim SH, Chu K, Choi SJ, Song KH, Kim HB, Kim NJ, Park SH, Yoon BW, Oh MD and Choe KW (2008) Diagnosis of central nervous system tuberculosis by T-cell-based assays on peripheral blood and cerebrospinal fluid mononuclear cells. Clinical and Vaccine Immunology 15(9):1356-62**
	Diagnostic test accuracy – PCR Reference standard Positive / Negative Index test – Positive: TP 10, FP 9 Index test – Negative: FN 1, TN 15 2 indeterminate results Sensitivity of index test (95% CI)a = 90.9% (73.9 to 100%) Specificity of index test (95% CI)a = 62.5% (43.1 to 81.9%)
	Diagnostic test accuracy – tuberculin skin test Reference standard Positive / Negative Index test – Positive: TP 5, FP 8 Index test – Negative: FN 6, TN 16 2 indeterminate results Sensitivity of index test (95% CI)a = 45.5% (16.0 to 74.9%) Specificity of index test (95% CI)a = 66.7% (47.8 to 85.5%)
Source of funding	No author received financial support
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; PCR, polymerase chain reaction; TN, true negative; TP, true positive	

1.3.2.7 Liao, 2009

Bibliographic reference	Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	20 participants
Patient characteristics	Inclusion Patients with suspected tuberculosis Adults
Index test	T.SPOT-TB using peripheral blood and 'body fluids' (cerebrospinal fluid?) Threshold: ≥10 pots per test well when the background control had a count of <5, or at least twice the value found in the background control wells, when the background control had a count of ≥5
Reference standard	'Recovery' of M. tuberculosis from a clinical specimen – i.e. fluorescence microscopy or culture (Middlebrook 7H11 selective agar, or BACTEC MGIT 960)
Location	Taiwan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 2, FP 8 Index test Negative: FN 0, TN 10 Sensitivity of index test (95% CI)a = 80.0% (30.4 to 100%)

Bibliographic reference	Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8
	Specificity of index test (95% CI)a = 55.6% (32.6 to 78.5%)
Source of funding	Supported by the Institute for Biotechnology and Medicine Industry, Taiwan
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.8 Malbruny, 2011

Bibliographic reference	Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? no, although details provided are limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard

Bibliographic reference	Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease
	Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? yes Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	15 participants
Patient characteristics	Inclusion Clinically suspected tuberculosis
Index test	Fluorescence microscopy Pleural fluid specimen
	Gene Xpert MTB/RIF Pleural fluid specimen
Reference standard	BACTEC MGIT 960 and Colestos culture Pleural fluid specimen Inoculation for 6 to 12 weeks Confirmation using TB Ag MPT64 Rapid
Location	Caen, France
Outcomes measures and	Diagnostic test accuracy – microscopy

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease**
effect size	Reference standard Positive Negative Index test Positive: TP 0, FP 0 Index test Negative: FN 1, TN 14
	Diagnostic test accuracy – Xpert MTB/RIF Reference standard Positive Negative Index test Positive: TP 1, FP 0 Index test Negative: FN 0, TN 14
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.9 Pai, 2003

Bibliographic reference	**Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infectious Diseases* 3(10): 633-43**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? *yes* Does the review collect the type of studies considered relevant to the review question? *yes, all cross-sectional* Is the literature search sufficiently rigorous to identify all the relevant studies? *yes* Is study quality assessed and reported? *yes* Is an adequate description of methodology included, and the methods used appropriate to the question? *yes* *Additional criteria* Is there concern that the included patients do not match the review question? *unclear* Is there concern that the index test, its conduct, or interpretation differ from the review question? *review included LCx, which is no longer available in the UK; reviewer did not extract this data* Is there concern that the target condition as defined by the reference standard does not match the review question? *no, although not all were culture-based reference standards*

Study	*Double or single blind*	*Consecutive or random sample*	*Reference standard*
Baker, 2002	Yes	No	Microbiological diagnosis
Bonington, 1998	Yes	Yes	Microbiological diagnosis
Bonington, 2000	Yes	Yes	Microbiological diagnosis
Brienze, 2001	Yes	Yes	Microbiological plus clinical diagnosis
D'Amato, 1996	Unknown	Unknown	Microbiological diagnosis
Ehlers, 1996	Yes	No	Clinical diagnosis, response to treatment and other laboratory tests
Gamboa, 1997	Yes	No	Microbiological diagnosis
Gamboa, 1997	Yes	No	Microbiological diagnosis

<table>
<tr><th>Bibliographic reference</th><th>Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. Lancet Infectious Diseases 3(10): 633-43</th></tr>
<tr><td></td><td>
<table>
<tr><td>Lang, 1998</td><td>Yes</td><td>No</td><td>Microbiological plus clinical diagnosis</td></tr>
<tr><td>Pfyffer, 1996</td><td>Unknown</td><td>Unknown</td><td>Microbiological plus clinical diagnosis</td></tr>
<tr><td>Reischl, 1998</td><td>Yes</td><td>Yes</td><td>Microbiological diagnosis</td></tr>
<tr><td>Shah, 1998</td><td>Yes</td><td>Yes</td><td>Microbiological diagnosis</td></tr>
</table>
</td></tr>
<tr><td>Number of patients</td><td>12 studies, 1607 participants
<table>
<tr><td>Study</td><td>n</td></tr>
<tr><td>Baker, 2002</td><td>29</td></tr>
<tr><td>Bonington, 1998</td><td>37</td></tr>
<tr><td>Bonington, 2000</td><td>37</td></tr>
<tr><td>Brienze, 2001</td><td>28</td></tr>
<tr><td>D'Amato, 1996</td><td>801</td></tr>
<tr><td>Ehlers, 1996</td><td>51</td></tr>
<tr><td>Gamboa, 1997</td><td>22</td></tr>
<tr><td>Gamboa, 1997</td><td>17</td></tr>
<tr><td>Lang, 1998</td><td>84</td></tr>
<tr><td>Pfyffer, 1996</td><td>54</td></tr>
<tr><td>Reischl, 1998</td><td>77</td></tr>
<tr><td>Shah, 1998</td><td>392</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. Lancet Infectious Diseases 3(10): 633-43</th></tr>
<tr><td>Study characteristics</td><td>The search strategy aimed to include all available studies on nucleic acid amplification tests for direct detection of M. tuberculosis in CSF specimens
For inclusion, the studies had to report a comparison of an nucleic acid amplification test against a reference standard, provide data necessary for the computation of both sensitivity and specificity, and include at least ten CSF specimens in the study (since very small studies may be vulnerable to selection bias)
Although no language restrictions were imposed, only English and Spanish articles were reviewed
Conference abstracts were excluded because they universally contained inadequate data to permit evaluation</td></tr>
<tr><td>Index test</td><td>Commercial nucleic acid amplification tests
<table><tr><th>Study</th><th>Index test</th></tr><tr><td>Bonington, 1998</td><td>Amplicor</td></tr><tr><td>Brienze, 2001</td><td>Amplicor</td></tr><tr><td>D'Amato, 1996</td><td>Amplicor</td></tr><tr><td>Shah, 1998</td><td>Amplicor</td></tr><tr><td>Baker, 2002</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Ehlers, 1996</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Gamboa, 1997</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Gamboa, 1997</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Lang, 1998</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Pfyffer, 1996</td><td>Amplified M. Tuberculosis Direct test</td></tr><tr><td>Bonington, 2000</td><td>Cobas Amplicor</td></tr><tr><td>Reischl, 1998</td><td>Cobas Amplicor</td></tr></table></td></tr>
</table>

Bibliographic reference	**Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infectious Diseases* 3(10): 633-43**
Reference standard	

Study	*Index test*
Bonington, 1998	Microbiological diagnosis
Brienze, 2001	Microbiological plus clinical diagnosis
D'Amato, 1996	Microbiological diagnosis
Shah, 1998	Microbiological diagnosis
Baker, 2002	Microbiological diagnosis
Ehlers, 1996	Clinical diagnosis, response to treatment and other laboratory tests
Gamboa, 1997	Microbiological diagnosis
Gamboa, 1997	Microbiological diagnosis
Lang, 1998	Microbiological plus clinical diagnosis
Pfyffer, 1996	Microbiological plus clinical diagnosis
Bonington, 2000	Microbiological diagnosis
Reischl, 1998	Microbiological diagnosis

Outcomes measures and effect size

Diagnostic test accuracy

Study	*Index test*	*Number of specimens with TB*	Number of specimens without TB	Sensitivity (95% CI)	Specificity (95% CI)

Bibliographic reference	Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infectious Diseases* 3(10): 633-43					
	Bonington, 1998	Amplicor	8	29	88 (47 to 99)	100 (88 to 100)
	Brienze, 2001	Amplicor	11	17	36 (13 to 68)	94 (69 to 100)
	D'Amato, 1996	Amplicor	2	799	50 (3 to 0.97)	99 (92 to 100)
	Shah, 1998	Amplicor	3	389	67 (13 to 98)	100 (98 to 100)
	Baker, 2002	Amplified M. Tuberculosis Direct test	5	24	100 (48 to 100)	100 (86 to 100)
	Ehlers, 1996	Amplified M. Tuberculosis Direct test	6	45	67 (24 to 94)	98 (87 to 100)
	Gamboa, 1997	Amplified M. Tuberculosis Direct test	8	14	63 (26 to 90)	100 (77 to 100)
	Gamboa, 1997	Amplified M. Tuberculosis Direct test	8	9	63 (26 to 90)	100 (66 to 100)
	Lang, 1998	Amplified M. Tuberculosis Direct test	24	60	33 (17 to 55)	100 (94 to 100)
	Pfyffer, 1996	Amplified M. Tuberculosis Direct test	6	48	100 (54 to 100)	96 (85 to 99)

Bibliographic reference	**Pai M, Flores LL, Pai N, Hubbard A, Riley LW and Colford JM Jr (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infectious Diseases* 3(10): 633-43**

	Bonington, 2000	Cobas Amplicor	8	29	50 (18 to 82)	100 (88 to 100)
	Reischl, 1998	Cobas Amplicor	3	74	67 (13 to 98)	99 (92 to 100)

Source of funding	Supported by the National Institutes of Health, Fogarty AIDS International Training Program and the Consejo Nacional de Ciencia y Tecnologia (CONACyT), National Council of Science and Technology, Mexico
Comments	Data for LCx not extracted as this test is not available in the UK

a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.3.2.10 Patel, 2010

Bibliographic reference	**Patel VB, Singh R, Connolly C, Coovadia Y, Peer AK, Parag P, Kasprowicz V, Zumla A, Ndung'u T and Dheda K (2010) Cerebrospinal T-cell responses aid in the diagnosis of tuberculous meningitis in a human immunodeficiency virus- and tuberculosis-endemic population. American Journal of Respiratory and Critical Care Medicine 182(4): 569-77**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias

Bibliographic reference	**Patel VB, Singh R, Connolly C, Coovadia Y, Peer AK, Parag P, Kasprowicz V, Zumla A, Ndung'u T and Dheda K (2010) Cerebrospinal T-cell responses aid in the diagnosis of tuberculous meningitis in a human immunodeficiency virus- and tuberculosis-endemic population. American Journal of Respiratory and Critical Care Medicine 182(4): 569-77**
	• Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although PCR is not yet a validated gold standard • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no, only compared definite and non-tuberculosis groups
Number of patients	150 participants; data only reported for definite and non-tuberculosis groups (86 participants)
Patient characteristics	Inclusion Suspected tuberculous meningitis Patients referred with a meningitic illness or with arachnoiditis and neck stiffness Characteristics of included participants

Bibliographic reference	Patel VB, Singh R, Connolly C, Coovadia Y, Peer AK, Parag P, Kasprowicz V, Zumla A, Ndung'u T and Dheda K (2010) Cerebrospinal T-cell responses aid in the diagnosis of tuberculous meningitis in a human immunodeficiency virus- and tuberculosis-endemic population. American Journal of Respiratory and Critical Care Medicine 182(4): 569-77

Characteristic	Definite TBM, n (%)	Non-TBM, n (%)
Mean age (± SD)	33.5 (9.5)	32.9 (9.7)
Age, yr		
<36	24 (61.5)	35 (64.8)
≥36	15 (38.5)	19 (35.2)
Sex		
Male	18 (46.1)	16 (29.6)
Female	21 (53.9)	38 (70.4)
Ethnic group		
Black African	38 (97.4)	53 (98.2)
Mixed race	1 (2.6)	0 (0.0)
European descent	0 (0.0)	0 (0.0)
Indian	0 (0.0)	1 (1.8)
HIV status		
Positive	34 (87.2)	47 (87.0)
Negative	4 (10.3)	6 (11.3)
Unknown/refused	1 (2.6)	1 (1.9)
Previous TB infection		
Yes	8 (20.5)	24 (44.4)
No	27 (69.2)	30 (55.6)
Unknown	4 (10.3)	0 (0.0)
TB contact (within 2 yr)		
Yes	9 (23.1)	14 (25.9)
No	26 (66.7)	40 (74.1)
Unknown	4 (10.3)	0 (0.0)
Duration of illness, d†		
<6	6 (16.2)	9 (16.7)
≥6	31 (83.8)	45 (83.3)
Steroid treatment at diagnosis		
Yes	12 (30.8)	8 (14.8)
No	27 (69.2)	46 (85.2)
CLAT		
Positive	4 (10.3)	27 (50.0)
Negative	35 (89.7)	27 (50.0)
Median CD4 (IQR) per μl	84 (53–173)	161 (54–261)
Hydrocephalus on CT or MRI		
Yes	17 (56.7)	10 (43.5)
No	13 (43.3)	13 (56.5)

Bibliographic reference	**Patel VB, Singh R, Connolly C, Coovadia Y, Peer AK, Parag P, Kasprowicz V, Zumla A, Ndung'u T and Dheda K (2010) Cerebrospinal T-cell responses aid in the diagnosis of tuberculous meningitis in a human immunodeficiency virus- and tuberculosis-endemic population. American Journal of Respiratory and Critical Care Medicine 182(4): 569-77**
Index test	T-SPOT.TB using cerebrospinal fluid cells Threshold for positivity: ≥20 spot-forming cells per million cells in the ESAT-6 or CFP-10 wells
Reference standard	Definite tuberculosis: cerebrospinal fluid culture or PCR positive Non-tuberculosis: an alternate definite cause for meningitis identified and response to appropriate non-tuberculosis therapy
Location	South Africa
Outcomes measures and effect size	Diagnostic test accuracy Reference standard: Positive / Negative Index test – Positive: TP 32, FP 13 Index test – Negative: FN 6, TN 35 Indeterminate results = 8 Sensitivity of index test (95% CI)a = 84.2% (72.6 to 95.8%) Specificity of index test (95% CI)a = 72.9% (60.3 to 85.5%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; PCR, polymerase chain reaction; TN, true negative; TP, true positive	

1.3.2.11 Teo, 2011

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
Study type	Cross-sectional

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? no Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
	• Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	7 specimens
Patient characteristics	Presenting signs and symptoms: patients thought to have tuberculosis based on symptoms and radiographic findings Age: not stated Sex, female: not stated HIV infection: not stated History of TB: not stated TB incidence rate: 37 per 100,000 Proportion of TB cases in the study: 58.5%
Index test	Ziehl-Neelson microscopy Decontaminated using N-acetyl-l-cysteine–sodium hydroxide
	Amplified Mycobacterium Tuberculosis Direct Test Decontaminated using N-acetyl-l-cysteine–sodium hydroxide
	Xpert MTB/RIF Decontaminated using N-acetyl-l-cysteine–sodium hydroxide
Reference standard	Löwenstein-Jensen or MGIT 960 culture Decontaminated using N-acetyl-l-cysteine–sodium hydroxide Incubated for 56 days
Location	Clinical setting: university hospital Laboratory level: central Country: Singapore World Bank Income Classification: high-income
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
	Positive Negative Index test: Positive — TP 1, FP 0 Index test: Negative — FN 2, TN 4 Sensitivity of index test (95% CI)a = 33.3% (0.0 to 86.7%) Specificity of index test (95% CI)a = 88.9% (59.9 to 100%)
	Diagnostic test accuracy – Amplified Mycobacterium Tuberculosis Direct Test Reference standard Positive Negative Index test: Positive — TP 2, FP 1 Index test: Negative — FN 0, TN 4 Sensitivity of index test (95% CI)a = 80.0% (30.4 to 100%) Specificity of index test (95% CI)a = 80.0% (44.9 to 100%)
	Diagnostic test accuracy – Xpert MTB/RIF Reference standard Positive Negative

Bibliographic reference	**Teo J, Jureen R, Chiang D, Chan D and Lin R (2011) Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified Mycobacterium Tuberculosis Direct assay, for detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. Journal of Clinical Microbiology 49(10): 3659-62**
	Index test: Positive — TP 2, FP 0; Negative — FN 1, TN 4 Sensitivity of index test (95% CI)a = 66.7% (13.3 to 100%) Specificity of index test (95% CI)a = 88.9% (59.9 to 100%)
Source of funding	Supported by a Health Service Development Programme grant provided by the Ministry of Health, Singapore
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.2.12 Tuon, 2010

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? no, includes some case-control Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes 8

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**

Additional criteria

Is there concern that the included patients do not match the review question? no

Is there concern that the index test, its conduct, or interpretation differ from the review question? no

Is there concern that the target condition as defined by the reference standard does not match the review question? not all were culture-based reference standards

4 prospective studies and 9 retrospective studies were included

3 studies included fewer than 10 patients with tuberculous meningitis

The technique used for ADA measurement was not described in 3 studies

3studies reported that ADA measurements were performed, but they did not report any clinical data

5 studies were classified low quality and 5 studies were classified as moderate quality

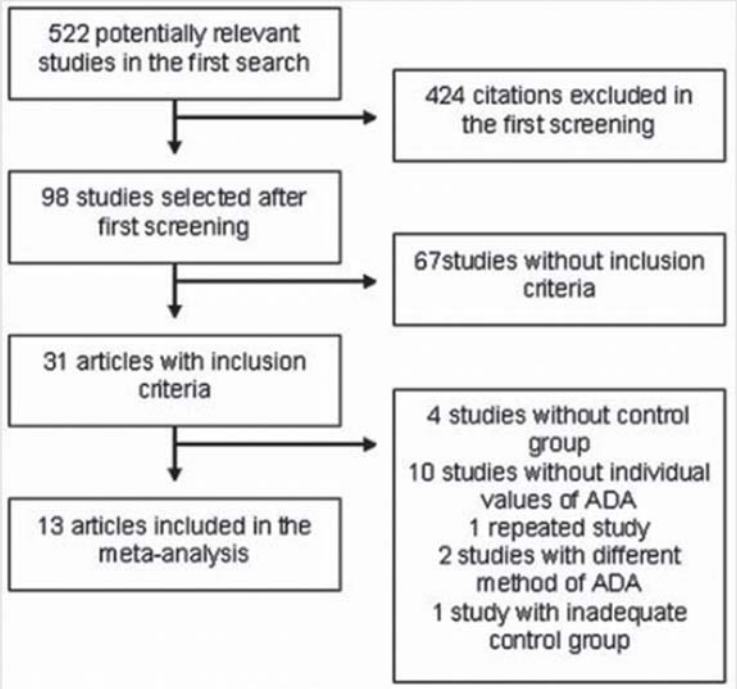
Study	Consecutive or random sample?	Blind test	Overall quality
Baro, 1996	Yes	No	low
Blake, 1982	Yes	No	low
Choi, 2002	Yes	No	moderate
Donald, 1986	Yes	No	moderate
Kaur, 1992	Yes	Yes	high
Lopez-Cortes, 1995	Yes	No	high
Malan, 1984	Yes	No	moderate
Mann, 1982	Yes	No	low

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**

Mishra, 1996	Yes	No	moderate
Pettersson, 1991	Yes	No	low
Ribera, 1987	Yes	Yes	high
Schutte, 2001	Yes	Yes	moderate
Zapata, 1996	Yes	No	low

Number of patients

13 studies, 1092 participants



Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**

Study	n
Baro, 1996	27
Blake, 1982	109
Choi, 2002	178
Donald, 1986	160
Kaur, 1992	52
Lopez-Cortes, 1995	141
Malan, 1984	96
Mann, 1982	60
Mishra, 1996	56
Pettersson, 1991	56
Ribera, 1987	96
Schutte, 2001	26
Zapata, 1996	35

Patient characteristics	There was no language restriction The ADA values from each patient with tuberculous meningitis (case) and controls (diagnosed with other types of meningitis) were present and could be extracted for calculation of sensitivity and specificity To avoid measurement bias, only papers evaluating total ADA were considered Cases of tuberculous meningitis were defined according to standardized criteria (see reference standard below)

Study	Age	HIV patients

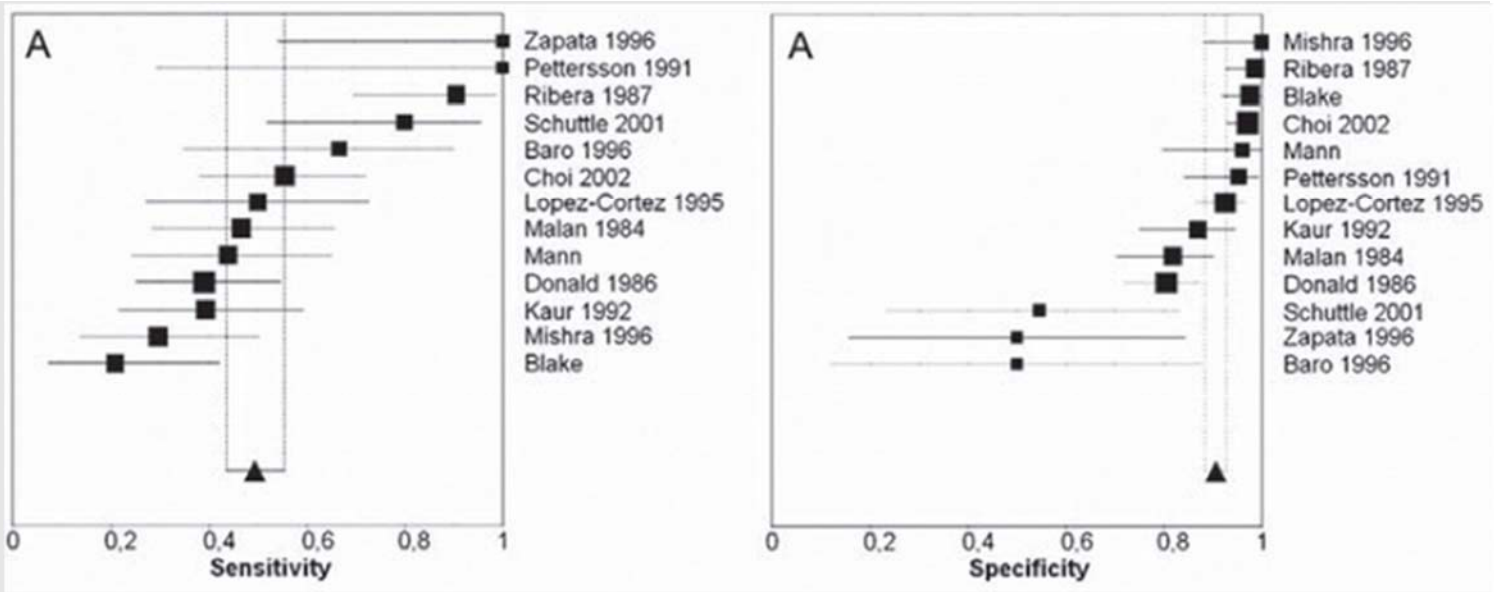
Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**

Baro, 1996	adults	no
Blake, 1982	all ages	no
Choi, 2002	adults	no
Donald, 1986	all ages	no
Kaur, 1992	adults	no
Lopez-Cortes, 1995	all ages	yes
Malan, 1984	all ages	no
Mann, 1982	children	no
Mishra, 1996	children	no
Pettersson, 1991	adults	no
Ribera, 1987	unknown	no
Schutte, 2001	adults	no
Zapata, 1996	adults	yes

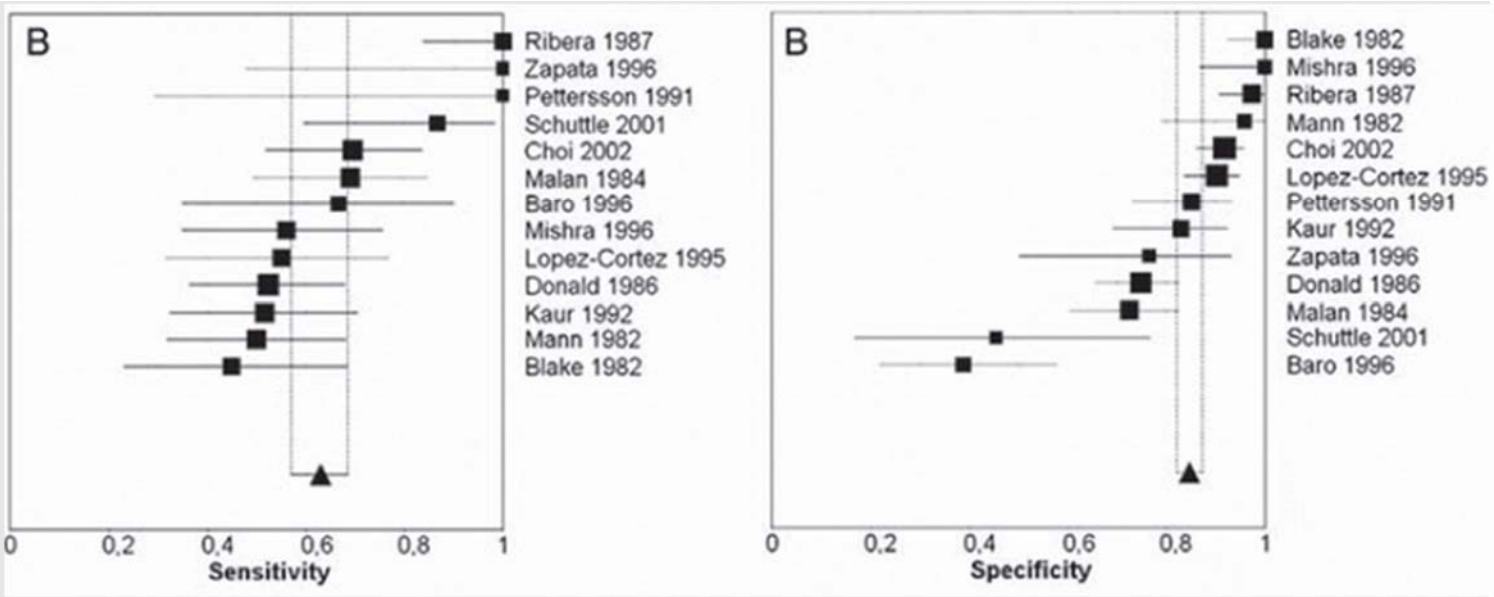
Index test

Study	ADA measurement assay and cut-off
Baro, 1996	Giusti 7.10 U/l
Blake, 1982	Unknown 6.00 U/l
Choi, 2002	Giusti 10.00 U/l
Donald, 1986	Giusti 6.00 U/l

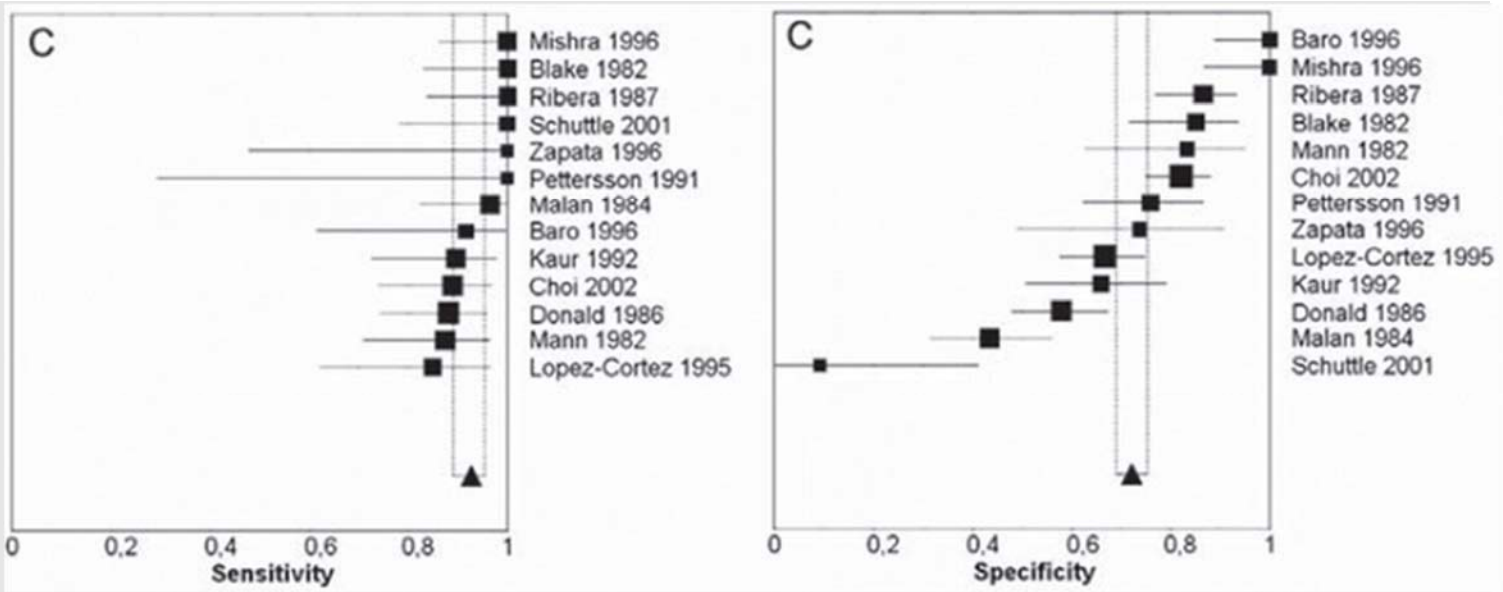
Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**
	Kaur, 1992 — Giusti 10.00 U/l Lopez-Cortes, 1995 — Giusti 10.00 U/l Malan, 1984 — Giusti 6.00 U/l Mann, 1982 — Unknown 5.00 U/l Mishra, 1996 — Giusti 5.00 U/l Pettersson, 1991 — Giusti 20.00 U/l Ribera, 1987 — Giusti 9.00 U/l Schutte, 2001 — Unknown 10.00 U/l Zapata, 1996 — Giusti 9.00 U/l
Reference standard	Tuberculous meningitis was defined by the presence of at least 1 of the following diagnostic criteria: (1) M. tuberculosis in cerebrospinal fluid culture; (2) meningitis and presence of acid-fast bacilli on CSF smear; (3) meningitis associated with tuberculosis in another organ; or (4) clinical and/or laboratory evidence of tuberculous meningitis, with improvement after empirical treatment for tuberculosis Patients with other types of infectious meningitis (viral, bacterial or fungal) as well as neoplasms were included as controls
Outcomes measures and effect size	Diagnostic test accuracy – ADA cut-off 10 U/l Pooled sensitivity of index test (95% CI) = 49.5% (43.6 to 55.4%) Pooled specificity of index test (95% CI) = 90.7% (88.5 to 92.7%)

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**
	 Diagnostic test accuracy – ADA cut-off 8 U/l Pooled sensitivity of index test (95% CI) = 63.0% (57.1 to 68.6%) Pooled specificity of index test (95% CI) = 84.8% (82.1 to 87.3%)

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**



Diagnostic test accuracy – ADA cut-off 4 U/l
Pooled sensitivity of index test (95% CI) = 92.7% (89.1 to 95.4%)
Pooled specificity of index test (95% CI) = 72.3% (69.0 to 75.4%)

Bibliographic reference	**Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L and Leite OM (2010) Adenosine deaminase and tuberculous meningitis--a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207**
	
Source of funding	There was no financial support for this study
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.3 Diagnosis of active genitourinary tuberculosis

1.3.3.1 Dinnes, 2007

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**
	Does the review collect the type of studies considered relevant to the review question? unclear Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? all except 2 studies explicitly include participants with suspected tuberculosis; data relating to final inclusions was not provided Is there concern that the index test, its conduct, or interpretation differ from the review question? no; data for LCx, which is not available in the UK, was not extracted Is there concern that the target condition as defined by the reference standard does not match the review question? no, all culture-based; however, reference standard varies across studies

Study	Reference standard	Index blinded	Reference standard blinded	Design	Representative sample
Gamboa, 1997	culture alone	unclear	unclear	unclear	unclear
Gamboa, 1998	culture plus x-ray	unclear	unclear	unclear	yes
Zambardi, 1995	culture plus clinical diagnosis	yes	yes	unclear	unclear

Number of patients	3 studies, 208 evaluations

Study	n
Gamboa, 1997	40
Gamboa, 1998	73

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)
	73 Zambardi, 1995 22
Patient characteristics	Inclusion Patients with suspected tuberculosis Characteristics of included participants Study / Prevalence of TB / Smear-positive Gamboa, 1997 0.45 - Gamboa, 1998 0.19 4.1% 0.19 5.9% Zambardi, 1995 0.05 -
Index test	Commercial nucleic acid amplification tests Study / Index test Gamboa, 1997 Amplified M. Tuberculosis Direct test - standard Gamboa, 1998 Amplified M. Tuberculosis Direct test - standard Amplified M. Tuberculosis Direct test - enhanced Zambardi, 1995 Amplicis Myco B
Reference standard	Reference standards for tests for detecting active tuberculosis can be defined as follows: A: culture and/or microscopy smear test B: very high clinical suspicion of TB, with or without a response to treatment C: clinical suspicion of TB, but it is not certain one way or the other Studies may use one or more of these reference tests either alone or in combination with each other as a reference strategy

<table>
<tr><th>Bibliographic reference</th><th colspan="4">Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)</th></tr>
<tr><td></td><td colspan="4">Strategy A alone, although previously considered good practice is now recognised as an inadequate reference standard, especially in smear-negative patients; although culture specificity is high, sensitivity is much poorer
Clinical diagnosis, although improving sensitivity, has a relatively low specificity for tuberculosis diagnosis

Study — Reference standard
Gamboa, 1997 — culture alone
Gamboa, 1998 — culture plus x-ray
Zambardi, 1995 — culture plus clinical diagnosis</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">Diagnostic test accuracy

<table>
<tr><th>Study</th><th>Index test</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>Gamboa, 1997</td><td>Amplified M. Tuberculosis Direct test - standard</td><td>50% (26 to 74%)</td><td>100% (85 to 100%)</td></tr>
<tr><td>Gamboa, 1998</td><td>Amplified M. Tuberculosis Direct test - standard</td><td>79% (49 to 95%)</td><td>100% (94 to 100%)</td></tr>
<tr><td></td><td>Amplified M. Tuberculosis Direct test - enhanced</td><td>64% (35 to 87%)</td><td>100% (94 to 100%)</td></tr>
<tr><td>Zambardi, 1995</td><td>Amplicis Myco B</td><td>0% (0 to 97%)</td><td>67% (43 to 85%)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td colspan="4">NIHR Health Technology Assessment Programme</td></tr>
<tr><td>Comments</td><td colspan="4">Data for LCx, which is not available in the UK, was not extracted
Other diagnostics for lymph node tuberculosis evaluated by the review were in-house and therefore not relevant
Data not extracted for duplicate studies</td></tr>
<tr><td colspan="5">a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.3.2 Hemal, 2000

Bibliographic reference	Hemal AK, Gupta NP, Rajeev TP, Kumar R, Dar L and Seth P (2000) Polymerase chain reaction in clinically suspected genitourinary tuberculosis: comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 56(4): 570-4
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? unclear • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? unclear *Domain 4: Flow and timing*

Bibliographic reference	**Hemal AK, Gupta NP, Rajeev TP, Kumar R, Dar L and Seth P (2000) Polymerase chain reaction in clinically suspected genitourinary tuberculosis: comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 56(4): 570-4**
	Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? *yes* • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? yes
Number of patients	42 participants
Patient characteristics	Inclusion Clinical suspicion of genitourinary tuberculosis Characteristics of included participants 25 men and 17 women Mean age 31.04 years, range 9 to 72 The most common presentation was irritative voiding symptoms (n = 37); other findings included sterile pyuria in 32, hematuria in 19, constitutional symptoms in 12, flank pain in 11, recurrent urinary infection in 8, and a scrotal mass in 1 patient
Index test	'Routine' microscopy on urine sample
	Radiologic evidence suggestive of tuberculosis Includes renal calcification, caliceal destruction, infundibular stenosis, cavitation, ureteral stricture, vesicoureteral reflux and small capacity bladder
Reference standard	Advanced and typical radiologic findings, positive urine smear or culture, and histologic examination of a biopsy or surgically resected specimen
Location	New Delhi, India
Outcomes measures and effect size	Diagnostic test accuracy – microscopy Reference standard Positive Negative

Bibliographic reference	**Hemal AK, Gupta NP, Rajeev TP, Kumar R, Dar L and Seth P (2000) Polymerase chain reaction in clinically suspected genitourinary tuberculosis: comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 56(4): 570-4**
	Index test: Positive — TP 10, FP 0; Negative — FN 25, TN 7 Sensitivity of index test (95% CI)a = 28.6% (13.6 to 43.5%) Specificity of index test (95% CI)a = 93.3% (75.5 to 100%)
	Diagnostic test accuracy – radiology Reference standard: Positive / Negative Index test: Positive — TP 32, FP 5; Negative — FN 3, TN 2 Sensitivity of index test (95% CI)a = 91.4% (82.2 to 100%) Specificity of index test (95% CI)a = 28.6% (0.0 to 62.0%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.3.3 Lai, 2010

Bibliographic reference	**Lai CC, Tan CK, Lin SH, Liao CH, Huang YT, Wang CY, Wang JY, Lin HI and Hsueh PR (2010) Diagnostic value of an enzyme-linked immunospot assay for interferon-γ in genitourinary tuberculosis. *Diagnostic Microbiology and Infectious Disease* 68(3): 247-50**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? microscopy, unclear; T.SPOT-TB, yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Lai CC, Tan CK, Lin SH, Liao CH, Huang YT, Wang CY, Wang JY, Lin HI and Hsueh PR (2010) Diagnostic value of an enzyme-linked immunospot assay for interferon-γ in genitourinary tuberculosis. *Diagnostic Microbiology and Infectious Disease* 68(3): 247-50**
	Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	30 participants
Patient characteristics	Inclusion Patients with clinically suspected genitourinary tuberculosis Characteristics of included participants Variables — No. (%) of patients with suspected genitourinary TB (n = 30) Mean age ± standard deviation (years) — 62.9 ± 12.4 Male-to-female sex ratio — 17:13 Underlying condition Diabetes mellitus — 12 (400.) Chronic kidney disease — 6 (20.0) Malignancy — 1 (3.3) HIV infection — 1 (3.3)
Index test	Fluorescence microscopy confirmed by Kinyoun staining
	T.SPOT-TB using whole blood A positive response was defined as ≥10 spots per test well (when the background control had a count <5) or at least twice the value found in the background control wells (when the background control had a count ≥5)
Reference standard	Subjects were categorized as having confirmed tuberculosis if M. tuberculosis was recovered from culture (Middlebrook 7H11 selective or BACTEC MGIT 960) or as not having confirmed tuberculosis if an alternative diagnosis was responsible for the clinical symptoms and signs or there was clinical improvement without antituberculosis therapy
Location	Taipei, Taiwan
Outcomes measures and	Diagnostic test accuracy – microscopy

Bibliographic reference	**Lai CC, Tan CK, Lin SH, Liao CH, Huang YT, Wang CY, Wang JY, Lin HI and Hsueh PR (2010) Diagnostic value of an enzyme-linked immunospot assay for interferon-γ in genitourinary tuberculosis. *Diagnostic Microbiology and Infectious Disease* 68(3): 247-50**
effect size	Reference standard Positive Negative Index test Positive: TP 6, FP 1 Index test Negative: FN 6, TN 17 Sensitivity of index test (95% CI)a = 50.0% (21.7 to 78.3%) Specificity of index test (95% CI)a = 94.4% (83.9 to 100%)
	Diagnostic test accuracy – T.SPOT-TB Reference standard Positive Negative Index test Positive: TP 11, FP 2 Index test Negative: FN 1, TN 16 Sensitivity of index test (95% CI)a = 91.7% (76.0 to 100%) Specificity of index test (95% CI)a = 88.9% (74.4 to 100%)
Source of funding	Partly supported by the Institute for Biotechnology and Medicine Industry (Taipei, Taiwan)
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4 Diagnosis of active gastrointestinal tuberculosis

1.3.4.1 Ng, 2014

Bibliographic reference	**Ng SC, Hirai HW, Tsoi KK, Wong SH, Chan FK, Sung JJ and Wu JC (2014) Systematic review with meta-analysisaccuracy of interferon-gamma releasing assay and anti-Saccharomyces cerevisiae antibody in differentiating intestinal tuberculosis from Crohn's disease in Asians. *Journal of Gastroenterology and Hepatology* 29(9): 1664-70**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes, all cross-sectional Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes, using QUADAS-2 Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? no Is there concern that the index test, its conduct, or interpretation differ from the review question? no Is there concern that the target condition as defined by the reference standard does not match the review question? reviewers do not specify the reference standard, but report that the risk of bias for this domain to be low

Study	*Patient selection*[1]	*Index test*[2]	*Reference standard*[3]	*Flow and timing*[4]
Kim, 2011	Low	Low	Low	Low

Bibliographic reference	**Ng SC, Hirai HW, Tsoi KK, Wong SH, Chan FK, Sung JJ and Wu JC (2014) Systematic review with meta-analysisaccuracy of interferon-gamma releasing assay and anti-Saccharomyces cerevisiae antibody in differentiating intestinal tuberculosis from Crohn's disease in Asians. *Journal of Gastroenterology and Hepatology* 29(9): 1664-70**

Lee, 2010	Low	Low	Low	Low
Lei, 2013	Low	Low	Low	Low
Li, 2012	Low	Low	Low	Low
Qui, 2012	Low	Low	Low	Low

Number of patients

Study	*n*
Kim, 2011	147
Lee, 2010	56
Lei, 2013	109
Li, 2012	84
Qui, 2012	33

Patient characteristics

Review inclusion

Studies including abstracts and/or full-text articles published in English and non-English language journals that have assessed the performance of either QuantiFERON-TB Gold and T-SPOT.TB in distinguishing intestinal tuberculosis from Crohn's disease

Review exclusion

Studies were excluded if they have (i) evaluated a noncommercial, in-house or older generation of test; (ii) reported insufficient data on desired outcomes (e.g. no sensitivities or specificities); (iii) had fewer than 10 Crohn's disease subjects; and (iv) were review articles or commentaries

In cases where there was a suspicion of overlapping study populations, the larger study population was selected for inclusion

<table>
<tr><th>Bibliographic reference</th><td>Ng SC, Hirai HW, Tsoi KK, Wong SH, Chan FK, Sung JJ and Wu JC (2014) Systematic review with meta-analysisaccuracy of interferon-gamma releasing assay and anti-Saccharomyces cerevisiae antibody in differentiating intestinal tuberculosis from Crohn's disease in Asians. Journal of Gastroenterology and Hepatology 29(9): 1664-70</td></tr>
<tr><td>Index test</td><td>Interferon gamma release assays
QuantiFERON-TB Gold or T-SPOT.TB</td></tr>
<tr><td>Reference standard</td><td>Culture-based</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><th>Study</th><th>Index test</th><th>True positives</th><th>False positives</th><th>False negatives</th><th>True negatives</th></tr>
<tr><td>Kim, 2011</td><td>QuantiFERON-TB Gold</td><td>50</td><td>7</td><td>25</td><td>65</td></tr>
<tr><td>Lee, 2010</td><td>T-SPOT.TB</td><td>12</td><td>6</td><td>0</td><td>38</td></tr>
<tr><td>Lei, 2013</td><td>T-SPOT.TB</td><td>36</td><td>5</td><td>6</td><td>62</td></tr>
<tr><td>Li, 2012</td><td>T-SPOT.TB</td><td>16</td><td>16</td><td>3</td><td>49</td></tr>
<tr><td>Qui, 2012</td><td>T-SPOT.TB</td><td>12</td><td>5</td><td>1</td><td>15</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>No details provided</td></tr>
<tr><td>Comments</td><td>Data not extracted for duplicate studies or studies reported only as an abstract</td></tr>
<tr><td colspan="2">[1] QUADAS-2 considerations: Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?
[2] QUADAS-2 considerations: Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre-specified?
[3] QUADAS-2 considerations: Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test? Could the reference standard, its conduct, or its interpretation have introduced bias?
[4] QUADAS-2 considerations: Was there an appropriate interval between index test(s) and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.4.2 Brant, 1995

Bibliographic reference	Brant CQ, Silva MR Jr, Macedo EP, Vasconcelos C, Tamaki N and Ferraz ML (1995) The value of adenosine deaminase (ADA) determination in the diagnosis of tuberculous ascites. Revista do Instituto de Medicina Tropical de São Paulo 37(5): 449-53
Study type	Diagnostic cohort
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although did not need to be culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

Bibliographic reference	**Brant CQ, Silva MR Jr, Macedo EP, Vasconcelos C, Tamaki N and Ferraz ML (1995) The value of adenosine deaminase (ADA) determination in the diagnosis of tuberculous ascites. Revista do Instituto de Medicina Tropical de São Paulo 37(5): 449-53**
	Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? unclear • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? no
Number of patients	53 participants; 43 completed study
Patient characteristics	Inclusion Patients with ascites Characteristics of included participants Tuberculosis cases (n = 8): positive smear and/or culture, or histology of a peritoneal fragment compatible with a diagnosis of tuberculosis Non-tuberculosis cases: malignant peritoneal infiltration (n = 13), spontaneous bacterial peritonitis (n = 6), pancreatic ascites (n = 2), decompensated chronic liver disease (n = 12), congestive heart failure (n = 1), chronic renal failure (n = 1) and pancreatitis with secondary bacterial peritonitis (n = 1)
Index test	Adenosine deanimase activity in ascetic fluid by Giusti's method Cut-off for positivity: 30 U/l
Reference standard	Microscopy and/or culture and/or histology of a peritoneal fragment compatible with a diagnosis of tuberculosis
Location	Sao Paolo, Brazil
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive TP 8 FP 3

Bibliographic reference	**Brant CQ, Silva MR Jr, Macedo EP, Vasconcelos C, Tamaki N and Ferraz ML (1995) The value of adenosine deaminase (ADA) determination in the diagnosis of tuberculous ascites. Revista do Instituto de Medicina Tropical de São Paulo 37(5): 449-53**
	Negative: FN 0, TN 32 Sensitivity of index test (95% CI)a = 94.1% (78.3 to 100%) Specificity of index test (95% CI)a = 91.4% (82.2 to 100%
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4.3 Cho, 2011

Bibliographic reference	**Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? *low risk of bias* • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71
	• If a threshold was used, was it pre-specified? T.SPOT-TB, yes; microscopy, unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes, though not all culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? no indeterminate results not included
Number of patients	Peripheral blood: 64 specimens Peritoneal fluid: 39 specimens Peritoneal biopsy: 21 specimens
Patient characteristics	Inclusion Patients with suspected tuberculous peritonitis, defined as patients who had clinical symptoms or signs compatible with tuberculous peritonitis and CT finding showing diffuse peritoneal infiltrations or peritoneal fluid changes (serum-ascites albumin gradient <1.1 g/dl and ascites protein >2.5 g/dl) Adults (16 years of age or older) Characteristics of included participants

Bibliographic reference	**Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71**

characteristic	TB Peritonitis[a] (*n* = 30)	Not active TB (*n* = 25)	Possible TB (*n* = 9)
Age, mean years ± SD	48.6 ± 19.6	49.9 ± 16.0	54.7 ± 17.1
Male sex	16 (53)	16 (64)	6 (67)
Clinical diagnosis			
Combined pulmonary TB	12 (40)	NA	NA
Disseminated TB	15 (50)	NA	NA
Bacterial peritonitis	NA	7 (28)	NA
Peritoneal seeding of malignancy	NA	7 (28)	NA
Other	NA	11 (44)[b]	NA
Underlying condition or illness			
HIV infection	1 (3)	0	0
Transplantation	2 (7)	3 (12)	1 (11)
Hematologic malignancy	2 (7)	4 (16)	1 (11)
Solid tumor	0	3 (12)	1 (11)
Liver cirrhosis	4 (13)	3 (12)	2 (22)
Rheumatic disease	1 (3)	2 (8)	0
Chronic renal failure	2 (7)	3 (12)	3 (33)
Diabetes	2 (7)	0	2 (22)
No underlying illness	19 (63)	8 (32)	3 (33)
Immunosuppressive condition[c]	8 (27)	13 (52)	5 (56)
Prior TB treatment	0	3 (12)	0

Data are positive patients over total patients (%), unless otherwise indicated. TB, tuberculosis; HIV, human immunodeficiency virus; NA, not applicable; SD, standard deviation.

[a] TB peritonitis includes confirmed (*n* = 27) and probable (*n* = 3) TB.

[b] These 11 cases include cases of lupus peritonitis (*n* = 1), polyarteritis nodosa (*n* = 1), sclerotic mesenteritis (*n* = 1), candida peritonitis (*n* = 1), rejection after kidney transplantation (*n* = 1), end stage renal disease (*n* = 1), portal hypertension (*n* = 3), and inflammatory bowel disease (*n* = 2).

[c] Immunosuppressive condition is defined as presence of underlying diseases, such as HIV infection, malignancy, liver cirrhosis, and chronic renal failure, and/or receipt of immunosuppressive treatment.

Index test	Microscopy Performed on peritoneal fluid and biopsy
	T-SPOT.TB Performed on peripheral blood mononuclear cells and mononuclear cells from peritoneal fluid Threshold for positivity: ≥6 spots
Reference standard	Cases: • patients in whom clinical specimens were found to be positive for M. tuberculosis in culture or by the M. tuberculosis polymerase chain reaction (PCR) assay • patients who presented a clinical picture of tuberculous peritonitis associated with peritoneal fluid changes consistent with tuberculous peritonitis, histologic biopsy showing caseating granuloma, and a successful response to antituberculosis therapy

Bibliographic reference	**Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71**
	Non-cases: • patients who did not fulfil the above criteria, but a diagnosis of active tuberculosis could not be excluded • patients in whom some other diagnosis was made, or when there was clinical improvement in the absence of antituberculosis therapy
Location	Seoul, South Korea
Outcomes measures and effect size	Diagnostic test accuracy – microscopy on peritoneal fluid Reference standard Positive Negative Index test – Positive: TP 10, FP 0 Index test – Negative: FN 20, TN 32 Sensitivity of index test (95% CI)a = 33.3% (16.5 to 50.2%) Specificity of index test (95% CI)a = 98.5% (94.2 to 100%)
	Diagnostic test accuracy – microscopy on peritoneal biopsy Reference standard Positive Negative Index test – Positive: TP 2, FP 0 Index test – Negative: FN 10, TN 9 Sensitivity of index test (95% CI)a = 16.7% (0.0 to 37.8%)

Bibliographic reference	**Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71**
	Specificity of index test (95% CI)a = 94.7% (80.5 to 100%)
	Diagnostic test accuracy – T.SPOT-TB on peripheral blood mononuclear cells Reference standard Positive Negative Index test Positive: TP 25, FP 15 Index test Negative: FN 4, TN 15 Indeterminate: 5 Sensitivity of index test (95% CI)a = 86.2% (73.7 to 98.8%) Specificity of index test (95% CI)a =50.0% (32.1 to 67.9%)
	Diagnostic test accuracy – T.SPOT-TB on peritoneal fluid mononuclear cells Reference standard Positive Negative Index test Positive: TP 12, FP 8 Index test Negative: FN 0, TN 12 Indeterminate: 7 Sensitivity of index test (95% CI)a = 96.0% (85.1 to 100%) Specificity of index test (95% CI)a = 60.0% (38.5 to 81.5%)
Source of funding	Supported by the Korea Research Foundation

Bibliographic reference	Cho OH, Park KH, Park SJ, Kim SM, Park SY, Moon SM, Chong YP, Kim MN, Lee SO, Choi SH, Woo JH, Kim YS and Kim SH (2011) Rapid diagnosis of tuberculous peritonitis by T cell-based assays on peripheral blood and peritoneal fluid mononuclear cells. Journal of Infection 62(6): 462-71
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4.4 Liao, 2009

Bibliographic reference	Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? *yes* • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

Bibliographic reference	**Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8**
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	16 specimens
Patient characteristics	Inclusion Patients with suspected tuberculosis Adults
Index test	T.SPOT-TB using peripheral blood and pleural effusion Threshold: ≥10 pots per test well when the background control had a count of <5, or at least twice the value found in the background control wells, when the background control had a count of ≥5
Reference standard	'Recovery' of M. tuberculosis from a clinical specimen – i.e. fluorescence microscopy or culture (Middlebrook 7H11 selective agar, or BACTEC MGIT 960)
Location	Taiwan
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative

Bibliographic reference	**Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8**
	Index test: Positive — TP 3, FP 3; Negative — FN 2, TN 8 Sensitivity of index test (95% CI)a = 60.0% (17.1 to 100%) Specificity of index test (95% CI)a = 72.7% (46.4 to 99.1%)
Source of funding	Supported by the Institute for Biotechnology and Medicine Industry, Taiwan
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4.5 Saleh, 2012

Bibliographic reference	**Saleh MA, Hammad E, Ramadan MM, Abd El-Rahman A and Enein AF (2012) Use of adenosine deaminase measurements and QuantiFERON in the rapid diagnosis of tuberculous peritonitis. Journal of Medical Microbiology 61(4): 514-9**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no

Bibliographic reference	**Saleh MA, Hammad E, Ramadan MM, Abd El-Rahman A and Enein AF (2012) Use of adenosine deaminase measurements and QuantiFERON in the rapid diagnosis of tuberculous peritonitis. Journal of Medical Microbiology 61(4): 514-9**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although not all tuberculosis cases were culture-confirmed (6/14), and 2 of these were 'probable' (that is, did not meet the complexity set by the GDG for a non-culture-confirmed reference standard) • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? 2 of the 14 tuberculosis cases were 'probable'; that is, did not meet the complexity set by the GDG for a non-culture-confirmed reference standard Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? yes
Number of patients	41 participants

Bibliographic reference	**Saleh MA, Hammad E, Ramadan MM, Abd El-Rahman A and Enein AF (2012) Use of adenosine deaminase measurements and QuantiFERON in the rapid diagnosis of tuberculous peritonitis. Journal of Medical Microbiology 61(4): 514-9**
Patient characteristics	Inclusion Patients with a presumptive diagnosis of tuberculous peritonitis with ascites HIV-negative
Index test	Ziehl-Neelsen microscopy of ascetic fluid
Reference standard	A final clinical diagnosis of tuberculous peritonitis was based on the following criteria A) fever, ascites and abdominal pain for more than 6 weeks B) M. tuberculosis-positive Löwenstein–Jensen culture from ascitic fluid C) ascitic fluid showing characteristics of exudate fluid with cell counts of 150–4000 mm−3 (predominantly lymphocytes) and protein concentrations ≥2.5 mg dl−1 D) abdominal computed tomography showing high-density ascites and abdominal lymphadenopathy, and radiological findings of pleural effusion or evidence of pulmonary tuberculosis Patients were categorized as: • ‘definite tuberculous peritonitis’ when criteria A and B were met • ‘highly probable tuberculous peritonitis’ when criterion A , C, and D were met • ‘probable tuberculous peritonitis’ when criterion A and any one of criteria C or D Patients with a presumptive clinical diagnosis of TB but who did not meet criteria B, C or D were classified as ‘definitely not TB peritonitis’, and they received other final clinical diagnoses
Location	Egypt
Outcomes measures and effect size	Diagnostic test accuracy Reference standard Positive Negative Index test Positive: TP 3, FP 11 Index test Negative: FN 0, TN 27 Sensitivity of index test (95% CI)a = 85.7% (49.1 to 100%)

Bibliographic reference	**Saleh MA, Hammad E, Ramadan MM, Abd El-Rahman A and Enein AF (2012) Use of adenosine deaminase measurements and QuantiFERON in the rapid diagnosis of tuberculous peritonitis. Journal of Medical Microbiology 61(4): 514-9**
	Specificity of index test (95% CI)a = 71.1% (56.6 to 85.5%)
Source of funding	No details provided
Comments	Data for the QuantiFERON-Gold assay is included in the Su (2013) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4.6 Shen, 2013

Bibliographic reference	**Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes, although more terms for 'peritonitis' could have been explored Is study quality assessed and reported? yes, using QUADAS (maximum score 14) Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? the threshold for positivity and assay method varies across the studies Is there concern that the target condition as defined by the reference standard does not match the review question? varies across the studies; plus, some do not meet the minimum requirements set by the GDG

Study	Reference standard	ADA assay method	Cut-off value (IU/l)	QUADAS	Study design

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7					
	Bandyopadhyay, 2006	bacteriology plus histopathology plus clinical diagnosis	Giusti	33	10	prospective
	Bhargava, 1990	histopathology	Giusti	36	9	prospective
	Burgess, 2001	bacteriology plus histopathology	Giusti	30	10	prospective
	Dwivedi, 1990	bacteriology plus histopathology	Giusti	33	9	prospective
	Fernandez-Rodriguez, 1991	bacteriology plus histopathology	Slaats	32	10	prospective
	Hillebrand, 1996	bacteriology plus histopathology	n/a	7	10	retrospective
	Hong, 2011	bacteriology plus histopathology	n/a	30	8	retrospective
	Kang, 2012	bacteriology plus histopathology	n/a	21	12	retrospective
	Martinez-Vazquez, 1986	bacteriology plus histopathology	Giusti	35	7	retrospective
	Ribera, 1991	bacteriology plus histopathology plus clinical diagnosis	Giusti	40	10	prospective
	Saleh, 2012	bacteriology plus clinical diagnosis	Giusti	35	11	prospective
	Sathar, 1995	bacteriology plus histopathology	Giusti	30	9	prospective

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7

Sathar, 1999	histopathology	Kinetic enzyme-coupled assay	30	9	prospective
Sharma, 2006	bacteriology plus histopathology	Giusti	37	11	prospective
Voigt, 1989	bacteriology	Giusti	32.3	11	retrospective
Voigt, 1989	bacteriology plus histopathology plus clinical diagnosis	Giusti	32.3	11	prospective

Number of patients

16 studies in 15 publications with 1574 participants

Study	n
Bandyopadhyay, 2006	96
Bhargava, 1990	87
Burgess, 2001	178
Dwivedi, 1990	49
Fernandez-Rodriguez, 1991	108
Hillebrand, 1996	368
Hong, 2011	52
Kang, 2012	52

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7
	Martinez-Vazquez, 1986 — 66 Ribera, 1991 — 86 Saleh, 2012 — 41 Sathar, 1995 — 81 Sathar, 1999 — 45 Sharma, 2006 — 119 Voigt, 1989 — 82 Voigt, 1989 — 64
Study characteristics	Inclusion Measurement of ascitic adenosine deanimase in human subjects Detailed diagnostic criteria for tuberculous peritonitis Studies provided both the sensitivity and specificity of adenosine deanimase assay At least 20 participants (10 patients and 10 controls) Exclusion No control group Limited participants Non-English publications Publications with limited information to calculate sensitivity and specificity of adenosine deanimase

Study	Tuberculous peritonitis	Non-tuberculous peritonitis
Bandyopadhyay, 2006	36	60

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7

Bhargava, 1990	17	70
Burgess, 2001	18	160
Dwivedi, 1990	19	30
Fernandez-Rodriguez, 1991	12	96
Hillebrand, 1996	17	351
Hong, 2011	35	17
Kang, 2012	27	25
Martinez-Vazquez, 1986	10	56
Ribera, 1991	16	70
Saleh, 2012	14	27
Sathar, 1995	28	53
Sathar, 1999	23	22
Sharma, 2006	31	88
Voigt, 1989	41	41
Voigt, 1989	11	53

Index test

Adenosine deanimase activity

Study	ADA assay method	Cut-off value (IU/l)

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7

Bandyopadhyay, 2006	Giusti	33
Bhargava, 1990	Giusti	36
Burgess, 2001	Giusti	30
Dwivedi, 1990	Giusti	33
Fernandez-Rodriguez, 1991	Slaats	32
Hillebrand, 1996	n/a	7
Hong, 2011	n/a	30
Kang, 2012	n/a	21
Martinez-Vazquez, 1986	Giusti	35
Ribera, 1991	Giusti	40
Saleh, 2012	Giusti	35
Sathar, 1995	Giusti	30
Sathar, 1999	Kinetic enzyme-coupled assay	30
Sharma, 2006	Giusti	37
Voigt, 1989	Giusti	32.3
Voigt, 1989	Giusti	32.3

Reference standard

Study	Reference standard

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7

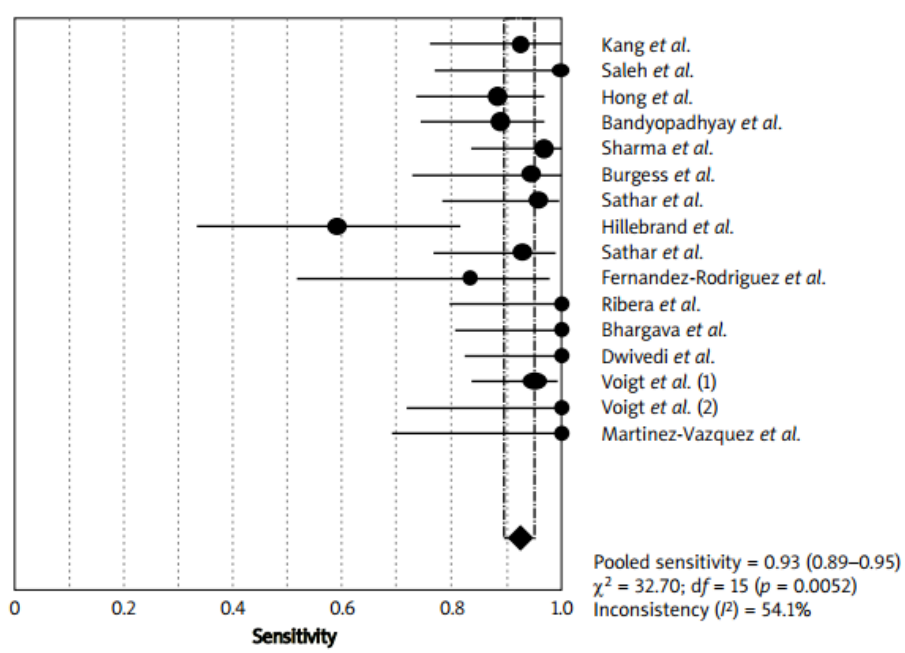
Bandyopadhyay, 2006	bacteriology plus histopathology plus clinical diagnosis
Bhargava, 1990	histopathology
Burgess, 2001	bacteriology plus histopathology
Dwivedi, 1990	bacteriology plus histopathology
Fernandez-Rodriguez, 1991	bacteriology plus histopathology
Hillebrand, 1996	bacteriology plus histopathology
Hong, 2011	bacteriology plus histopathology
Kang, 2012	bacteriology plus histopathology
Martinez-Vazquez, 1986	bacteriology plus histopathology
Ribera, 1991	bacteriology plus histopathology plus clinical diagnosis
Saleh, 2012	bacteriology plus clinical diagnosis
Sathar, 1995	bacteriology plus histopathology
Sathar, 1999	histopathology
Sharma, 2006	bacteriology plus histopathology
Voigt, 1989	bacteriology
Voigt, 1989	bacteriology plus histopathology plus clinical diagnosis

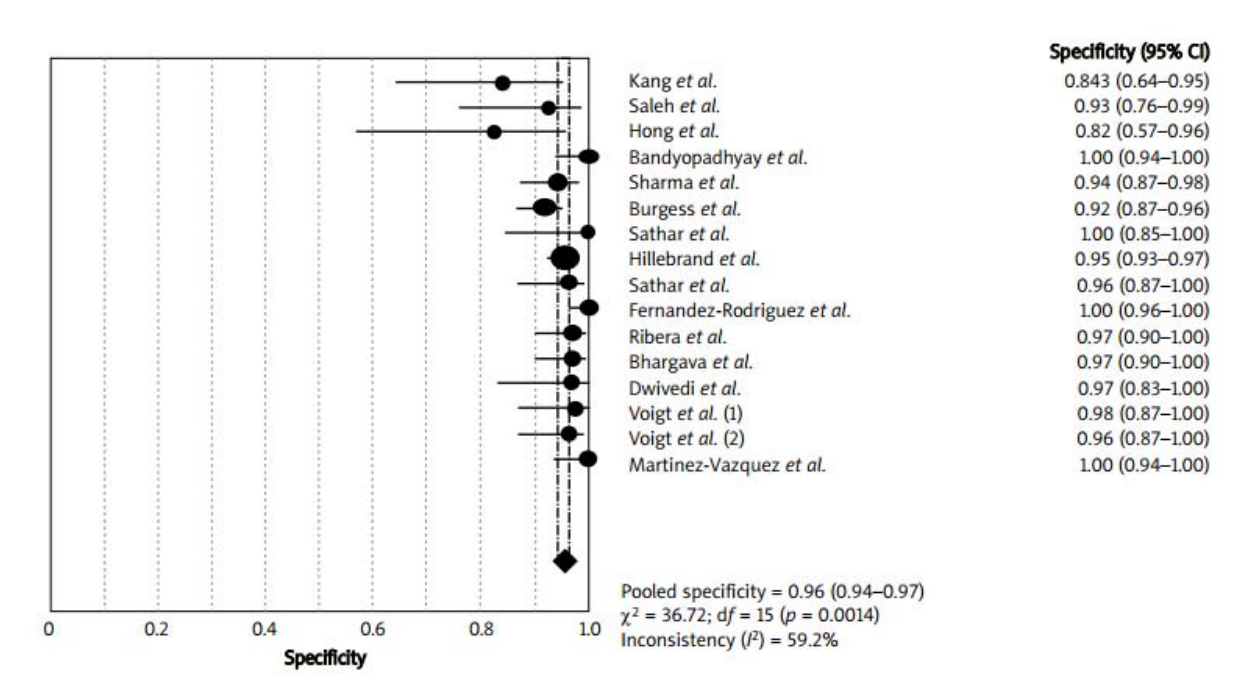
Bibliographic reference	**Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7**
Outcomes measures and effect size	Diagnostic test accuracy

Study	n	Tuberculous peritonitis	Non-tuberculous peritonitis	TP	FP	FN	TN
Bandyopadhyay, 2006	96	36	60	32	0	4	60
Bhargava, 1990	87	17	70	17	2	0	68
Burgess, 2001	178	18	160	17	13	1	147
Dwivedi, 1990	49	19	30	19	1	0	29
Fernandez-Rodriguez, 1991	108	12	96	10	0	2	96
Hillebrand, 1996	368	17	351	10	16	7	335
Hong, 2011	52	35	17	31	3	4	14
Kang, 2012	52	27	25	25	4	2	21
Martinez-Vazquez, 1986	66	10	56	10	0	0	56
Ribera, 1991	86	16	70	16	2	0	68
Saleh, 2012	41	14	27	14	2	0	25
Sathar, 1995	81	28	53	26	2	2	51
Sathar, 1999	45	23	22	22	0	1	22
Sharma, 2006	119	31	88	30	5	1	83
Voigt, 1989	82	41	41	39	1	2	40

Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7

Voigt, 1989	64	11	53	11	2	0	51



Bibliographic reference	Shen YC, Wang T, Chen L, Yang T, Wan C, Hu QJ and Wen FQ (2013) Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Archives of Medical Science 9(4): 601-7
	
Source of funding	Supported by the National Natural Science Foundation of China and the China Medical Board of New York
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.4.7 Su, 2013

Bibliographic reference	Su SB, Qin SY, Guo XY, Luo W and Jiang HX (2013) Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. World Journal of Gastroenterology 19(10): 1645-51
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes, although only 1 of

Bibliographic reference	Su SB, Qin SY, Guo XY, Luo W and Jiang HX (2013) Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. World Journal of Gastroenterology 19(10): 1645-51

the most appropriate study design (cross-sectional) was included

Is the literature search sufficiently rigorous to identify all the relevant studies? yes

Is study quality assessed and reported? yes, using STARD and QUADAS

Is an adequate description of methodology included, and the methods used appropriate to the question? yes

Additional criteria

Is there concern that the included patients do not match the review question? unclear

Is there concern that the index test, its conduct, or interpretation differ from the review question? unclear that all are commercially available interferon-gamma release assays; different interferon-gamma release assays with different thresholds for positivity used across the studies

Is there concern that the target condition as defined by the reference standard does not match the review question? yes, some cases could be diagnosed on clinical grounds alone (although authors state that 'diagnosis of peritoneal tuberculosis was confirmed in most of the tuberculous peritonitis patients based on the conventional "gold standard" which was a smear or a positive M. tuberculosis culture which was taken from ascitic fluid and/or histology showing a caseating granuloma'); plus, reference standards vary across studies

Study	*n*	*Reference standard*	*Cross-sectional design*	*Consecutive or random*	*Blinded design*	*Prospective*	*STARD*	*QUADAS*
Ribera, 1991	86	bacteriology, histology or clinical diagnosis	no	yes	no	yes	11	9
Saleh, 2012	41	bacteriology, histology or clinical diagnosis	no	yes	no	yes	16	11
Sathar, 1995	92	bacteriology or histology	no	yes	no	yes	13	10

Bibliographic reference	**Su SB, Qin SY, Guo XY, Luo W and Jiang HX (2013) Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. World Journal of Gastroenterology 19(10): 1645-51**

Sathar, 1999	52	bacteriology, histology or clinical diagnosis	no	yes	no	yes	14	12
Sharma, 2006	119	bacteriology or histology	yes	yes	yes	yes	18	13
Soliman, 1994	50	bacteriology, histology or clinical diagnosis	no	yes	yes	yes	15	12

Number of patients

6 studies, 440 participants

Study	*n*
Ribera, 1991	86
Saleh, 2012	41
Sathar, 1995	92
Sathar, 1999	52
Sharma, 2006	119
Soliman, 1994	50

Study characteristics

Inclusion

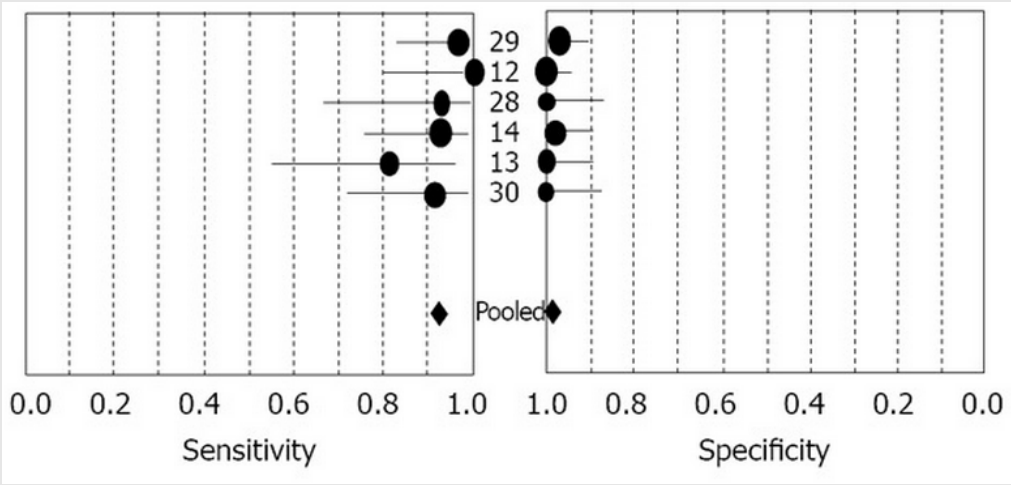
Although no language restrictions were imposed initially, our resources only permitted the review of articles published in the English language for the full text review and final analysis

A study was included when it provided both the sensitivity (true-positive rate) and specificity (false-positive rate) of interferon-gamma for tuberculous peritonitis diagnosis, or provided interferon-gamma values in a dot-plot form that allowed results to be extracted for individual study subjects

<table>
<tr><th>Bibliographic reference</th><th>Su SB, Qin SY, Guo XY, Luo W and Jiang HX (2013) Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. World Journal of Gastroenterology 19(10): 1645-51</th></tr>
<tr><td></td><td>Any age
Selected studies including at least 10 tuberculous peritonitis specimens which were eligible for inclusion in order to reduce selection bias due to a small number of participants
Exclusion
Conference abstracts and letters were excluded due to unavailable data</td></tr>
<tr><td>Index test</td><td>Interferon-gamma release assays
<table>
<tr><td>Study</td><td>Assay method</td><td>Cut-off</td></tr>
<tr><td>Ribera, 1991</td><td>RIA</td><td>3 U/ml or 9 U/ml</td></tr>
<tr><td>Saleh, 2012</td><td>ELISA</td><td>0.35 IU/ml</td></tr>
<tr><td>Sathar, 1995</td><td>RIA</td><td>3.2 U/ml</td></tr>
<tr><td>Sathar, 1999</td><td>ELISA</td><td>20 pg/ml</td></tr>
<tr><td>Sharma, 2006</td><td>ELISA</td><td>112 pg/ml</td></tr>
<tr><td>Soliman, 1994</td><td>ELISA</td><td>26 pg/ml</td></tr>
</table></td></tr>
<tr><td>Reference standard</td><td>Smear or culture of M. tuberculosis and/or histologic observation of peritoneal tissue, as well as clinical diagnosis, such as response to antituberculosis therapy
<table>
<tr><td>Study</td><td>Reference standard</td></tr>
<tr><td>Ribera, 1991</td><td>bacteriology, histology or clinical diagnosis</td></tr>
<tr><td>Saleh, 2012</td><td>bacteriology, histology or clinical diagnosis</td></tr>
<tr><td>Sathar, 1995</td><td>bacteriology or histology</td></tr>
<tr><td>Sathar, 1999</td><td>bacteriology, histology or clinical diagnosis</td></tr>
<tr><td>Sharma, 2006</td><td>bacteriology or histology</td></tr>
<tr><td>Soliman, 1994</td><td>bacteriology, histology or clinical diagnosis</td></tr>
</table></td></tr>
<tr><td>Outcomes measures and</td><td>Diagnostic test accuracy</td></tr>
</table>

Bibliographic reference	**Su SB, Qin SY, Guo XY, Luo W and Jiang HX (2013) Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. World Journal of Gastroenterology 19(10): 1645-51**
effect size	

Study	*n*	*TP*	*FP*	*FN*	*TN*
Ribera, 1991	86	16	0	0	70
Saleh, 2012	41	13	0	1	27
Sathar, 1995	92	25	1	2	54
Sathar, 1999	52	21	0	2	29
Sharma, 2006	119	30	3	1	85
Soliman, 1994	50	13	0	3	33



Source of funding	No details provided
Comments	

a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.3.5 Diagnosis of active lymph node tuberculosis

1.3.5.1 Dinnes, 2007

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? all except 1 study explicitly include participants with suspected tuberculosis; data relating to final inclusions was not provided Is there concern that the index test, its conduct, or interpretation differ from the review question? no; data for LCx, which is not available in the UK, was not extracted Is there concern that the target condition as defined by the reference standard does not match the review question? no

Study	Reference standard	Index blinded	Reference standard blinded	Design	Representative sample
Baek, 2000	histology plus response to treatment	unclear	no	unclear	yes
Bemer-Melchior, 1998	culture alone	unclear	unclear	retrospective	yes
Ehlers, 1996	culture alone	unclear	unclear	unclear	yes

Bibliographic reference	Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)

Gamboa, 1997	culture alone	unclear	unclear	unclear	unclear
Gamboa, 1998	culture plus x-ray	unclear	unclear	unclear	yes
Rimek, 2002	culture alone	unclear	unclear	unclear	yes
Shah, 1998	culture alone	unclear	unclear	unclear	yes

Overall, the studies were very poorly reported, especially in terms of study design and blinding of test interpretation

Number of patients

7 studies, 241 participants

Study	n
Baek, 2000	29
Bemer-Melchior, 1998	33
Ehlers, 1996	29
Gamboa, 1997	28
Gamboa, 1998	38
Rimek, 2002	39
Shah, 1998	45

Patient characteristics

Inclusion
Patients with suspected tuberculosis
Characteristics of included participants

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**

Study	Prevalence of TB	Smear-positive
Baek, 2000	0.59	-
Bemer-Melchior, 1998	0.33	8%
Ehlers, 1996	0.48	-
Gamboa, 1997	0.61	-
Gamboa, 1998	0.47	15%
Rimek, 2002	0.38	7%
Shah, 1998	0.22	-

Index test

Commercial nucleic acid amplification tests

Study	Index test
Baek, 2000	Amplicor
Bemer-Melchior, 1998	Amplicor
Ehlers, 1996	Amplified M. Tuberculosis Direct test - standard
Gamboa, 1997	Amplified M. Tuberculosis Direct test - standard
Gamboa, 1998	Amplified M. Tuberculosis Direct test - enhanced
	Amplified M. Tuberculosis Direct test - standard
Rimek, 2002	Cobas Amplicor
Shah, 1998	Amplicor

<table>
<tr><th>Bibliographic reference</th><th>Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Reference standard</td><td>Reference standards for tests for detecting active tuberculosis can be defined as follows:
A: culture and/or microscopy smear test
B: very high clinical suspicion of TB, with or without a response to treatment
C: clinical suspicion of TB, but it is not certain one way or the other
Studies may use one or more of these reference tests either alone or in combination with each other as a reference strategy
Strategy A alone, although previously considered good practice is now recognised as an inadequate reference standard, especially in smear-negative patients; although culture specificity is high, sensitivity is much poorer
Clinical diagnosis, although improving sensitivity, has a relatively low specificity for tuberculosis diagnosis
<table>
<tr><td>Study</td><td>Reference standard</td></tr>
<tr><td>Baek, 2000</td><td>histology plus response to treatment</td></tr>
<tr><td>Bemer-Melchior, 1998</td><td>culture alone</td></tr>
<tr><td>Ehlers, 1996</td><td>culture alone</td></tr>
<tr><td>Gamboa, 1997</td><td>culture alone</td></tr>
<tr><td>Gamboa, 1998</td><td>culture plus x-ray</td></tr>
<tr><td>Rimek, 2002</td><td>culture alone</td></tr>
<tr><td>Shah, 1998</td><td>culture alone</td></tr>
</table></td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td>Study</td><td>Index test</td><td>Sensitivity (95% CI)</td><td>Specificity (95% CI)</td></tr>
<tr><td>Baek, 2000</td><td>Amplicor</td><td>76% (50 to 93%)</td><td>100% (74 to 100%)</td></tr>
<tr><td>Bemer-Melchior, 1998</td><td>Amplicor</td><td>73% (39 to 94%)</td><td>82% (60 to 95%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, Drobniewski F and Lalvani A (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3)**

Ehlers, 1996	Amplified M. TB Direct test - standard	93% (66 to 100%)	100% (78 to 100%)
Gamboa, 1997	Amplified M. TB Direct test - standard	82% (57 to 96%)	64% (31 to 89%)
Gamboa, 1998	Amplified M. TB Direct test - enhanced	78% (52 to 94%)	100% (83 to 100%)
	Amplified M. TB Direct test - standard	89% (65 to 99%)	100% (83 to 100%)
Rimek, 2002	Cobas Amplicor	40% (16 to 68%)	92% (73 to 99%)
Shah, 1998	Amplicor	90% (55 to 100%)	100% (90 to 100%)

Source of funding	NIHR Health Technology Assessment Programme
Comments	Data for LCx, which is not available in the UK, was not extracted Other diagnostics for lymph node tuberculosis evaluated by the review were in-house and therefore not relevant

a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.3.5.2 Denkinger, 2014

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**

Is there concern that the included patients do not match the review question? no

Is there concern that the index test, its conduct, or interpretation differ from the review question? no

Is there concern that the target condition as defined by the reference standard does not match the review question? no

Study	Blinding	Selection	Prospective enrolment?
Al-Ateah, 2012	yes	consecutive	yes
Armand, 2011	yes	convenience	no
Causse, 2011	yes	consecutive	yes
Hanif, 2011	no	consecutive	yes
Hillemann, 2011	yes	consecutive	yes
Moure, 2012	yes	convenience	no
Safianowska, 2012	no	consecutive	yes
Tortoli, 2012	yes	convenience	no
Vadwai, 2011	yes	consecutive	yes
Zeka, 2011	yes	consecutive	no

Number of patients

Study	n
Al-Ateah, 2012	8
Armand, 2011	18
Causse, 2011	87

<table>
<tr><th>Bibliographic reference</th><th>Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. European Respiratory Journal 44(2): 435-46</th></tr>
<tr><td></td><td>
<table>
<tr><td>Hanif, 2011</td><td>9</td></tr>
<tr><td>Hillemann, 2011</td><td>65</td></tr>
<tr><td>Moure, 2012</td><td>38</td></tr>
<tr><td>Safianowska, 2012</td><td>4</td></tr>
<tr><td>Tortoli, 2012</td><td>118</td></tr>
<tr><td>Vadwai, 2011</td><td>178</td></tr>
<tr><td>Zeka, 2011</td><td>26</td></tr>
</table>
</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with suspected tuberculosis
Characteristics of included participants</td></tr>
<tr><td>Index test</td><td>Xpert MTB/RIF</td></tr>
<tr><td>Reference standard</td><td>Culture-based</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><th>Study</th><th>True positives</th><th>False positives</th><th>False negatives</th><th>True negatives</th></tr>
<tr><td>Al-Ateah, 2012</td><td>5</td><td>0</td><td>1</td><td>2</td></tr>
<tr><td>Armand, 2011</td><td>8</td><td>0</td><td>8</td><td>2</td></tr>
<tr><td>Causse, 2011</td><td>16</td><td>0</td><td>1</td><td>70</td></tr>
<tr><td>Hanif, 2011</td><td>6</td><td>0</td><td>0</td><td>3</td></tr>
<tr><td>Hillemann, 2011</td><td>6</td><td>3</td><td>4</td><td>52</td></tr>
<tr><td>Moure, 2012</td><td>24</td><td>0</td><td>10</td><td>4</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
	Safianowska, 2012 — 2 — 0 — 0 — 2 Tortoli, 2012 — 24 — 4 — 5 — 85 Vadwai, 2011 — 32 — 17 — 2 — 127 Zeka, 2011 — 11 — 2 — 3 — 10
Source of funding	No details provided
Comments	Data not extracted for duplicate studies
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.3 Fanny, 2012

Bibliographic reference	**Fanny ML, Beyam N, Gody JC, Zandanga G, Yango F, Manirakiza A, Rigouts L, Pierre-Audigier C, Gicquel B and Bobossi G (2012) Fine-needle aspiration for diagnosis of tuberculous lymphadenitis in children in Bangui, Central African Republic. BMC Pediatrics 12: 191**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	**Fanny ML, Beyam N, Gody JC, Zandanga G, Yango F, Manirakiza A, Rigouts L, Pierre-Audigier C, Gicquel B and Bobossi G (2012) Fine-needle aspiration for diagnosis of tuberculous lymphadenitis in children in Bangui, Central African Republic. BMC Pediatrics 12: 191**
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no *Domain 4: Flow and timing* Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? *yes* • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no; 2 samples were contaminated
Number of patients	131 participants
Patient characteristics	Inclusion Children aged 0 to 17 years with suspected, persistent tuberculous lymphadenitis, defined as a painless firm or soft swelling in a group of superficial lymph nodes Characteristics of included participants

<table>
<tr><th>Bibliographic reference</th><th>Fanny ML, Beyam N, Gody JC, Zandanga G, Yango F, Manirakiza A, Rigouts L, Pierre-Audigier C, Gicquel B and Bobossi G (2012) Fine-needle aspiration for diagnosis of tuberculous lymphadenitis in children in Bangui, Central African Republic. BMC Pediatrics 12: 191</th></tr>
<tr><td></td><td>
<table>
<tr><th>Demographics</th><th>n (%)</th></tr>
<tr><td>Age, years</td><td></td></tr>
<tr><td>0-5</td><td>60 (45.8)</td></tr>
<tr><td>6-10</td><td>36 (27.5)</td></tr>
<tr><td>11-14</td><td>24 (18.3)</td></tr>
<tr><td>15-17</td><td>11 (8.4)</td></tr>
<tr><td>Sex</td><td></td></tr>
<tr><td>Male</td><td>68 (52)</td></tr>
<tr><td>Female</td><td>63 (48)</td></tr>
<tr><td>HIV status</td><td></td></tr>
<tr><td>Positive</td><td>36 (35%)</td></tr>
<tr><td>Negative</td><td>63 (61%)</td></tr>
<tr><td>Unknown</td><td>4 (4%)</td></tr>
<tr><td>Site of lymph nodes</td><td></td></tr>
<tr><td>Cervical</td><td>99/131(76%)</td></tr>
<tr><td>Axillary</td><td>66/131 (50%)</td></tr>
<tr><td>Other</td><td>102/131 (78%)</td></tr>
<tr><td>Contact with family TB</td><td>66/131 (53%)</td></tr>
</table>
</td></tr>
<tr><td>Index test</td><td>Ziehl-Neelsen microscopy
Fine needle aspirate</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen culture
Fine needle aspirate</td></tr>
<tr><td>Location</td><td>Bangui, Central African Republic</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td></td><td colspan="2">Reference standard</td></tr>
<tr><td></td><td>Positive</td><td>Negative</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Fanny ML, Beyam N, Gody JC, Zandanga G, Yango F, Manirakiza A, Rigouts L, Pierre-Audigier C, Gicquel B and Bobossi G (2012) Fine-needle aspiration for diagnosis of tuberculous lymphadenitis in children in Bangui, Central African Republic. BMC Pediatrics 12: 191**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 39</td><td>FP 17</td></tr><tr><td>Negative</td><td>FN 49</td><td>TN 24</td></tr></table> No nontuberculous mycobacteria were identified Sensitivity of index test (95% CI)a = 44.3% (33.9 to 54.7%) Specificity of index test (95% CI)a = 58.5% (43.5 to 73.6%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.4 Gamboa, 1997a

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. *International Journal of Tuberculosis and Lung Disease* 1(6): 542-55**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. *International Journal of Tuberculosis and Lung Disease* 1(6): 542-55**
	Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	35 specimens

<table>
<tr><th>Bibliographic reference</th><th>Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55</th></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients suspected of having tuberculosis
Patients who had received antituberculosis therapy</td></tr>
<tr><td>Index test</td><td>Fluorescence microscopy with Ziehl-Neelsen confirmation
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td>Reference standard</td><td>Culture (Löwenstein-Jensen, Colestos and BACTEC 12B and 13A)
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide
Incubated for 8 weeks
A BACTEC Growth Index of >100 was considered positive</td></tr>
<tr><td>Location</td><td>Barcelona, Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
5</td><td>FP
3</td></tr>
<tr><td>Negative</td><td>FN
12</td><td>TN
15</td></tr>
</table>
Sensitivity of index test (95% CI)a = 29.4% (7.8 to 51.1%)
Specificity of index test (95% CI)a = 83.3% (66.1 to 100%)</td></tr>
<tr><td>Source of funding</td><td>No details provided</td></tr>
<tr><td>Comments</td><td>Data for the Amplified M. Tuberculosis Direct test is included in the Dinnes et al (2007) systematic review</td></tr>
<tr><td colspan="2">a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.5.5 Gamboa, 1997b

Bibliographic reference	Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, though details provided were limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? yes Domain 4: Flow and timing

<table>
<tr><th>Bibliographic reference</th><th>Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10</th></tr>
<tr><td></td><td>Could the patient flow have introduced bias? low risk of bias
• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? yes</td></tr>
<tr><td>Number of patients</td><td>28 specimens</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with clinical signs or symptoms of tuberculosis</td></tr>
<tr><td>Index test</td><td>Fluorescence microscopy with Ziehl-Neelsen confirmation
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td></td><td>Amplified M. Tuberculosis Direct test
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td>Reference standard</td><td>Culture (Löwenstein-Jensen, Colestos and BACTEC 12B)
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide
Incubated for 8 weeks</td></tr>
<tr><td>Location</td><td>Barcelona, Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td>Index test</td><td>Positive</td><td>TP
5</td><td>FP
3</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10**
	<table><tr><td></td><td>Negative</td><td>FN 12</td><td>TN 8</td></tr></table> Sensitivity of index test (95% CI)a = 29.4% (7.8 to 51.1%) Specificity of index test (95% CI)a = 72.7% (46.4 to 99.1%)
	Diagnostic test accuracy – Amplified M. Tuberculosis Direct test <table><tr><td></td><td></td><td>Reference standard</td><td></td></tr><tr><td></td><td></td><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 14</td><td>FP 4</td></tr><tr><td>Negative</td><td>FN 3</td><td>TN 7</td></tr></table> Sensitivity of index test (95% CI)a = 82.4% (64.2 to 100%) Specificity of index test (95% CI)a = 63.6% (35.2 to 92.1%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.6 Kerleguer, 2004

Bibliographic reference	**Kerleguer A, Fabre M, Bernatas JJ, Gerome P, Nicand E, Herve V and Koeck JL (2004) Clinical evaluation of the gen-probe amplified mycobacterium tuberculosis direct test for rapid diagnosis of tuberculosis lymphadenitis. Journal of Clinical Microbiology 42(12): 5921-2**
Study type	Cross-sectional

Bibliographic reference	**Kerleguer A, Fabre M, Bernatas JJ, Gerome P, Nicand E, Herve V and Koeck JL (2004) Clinical evaluation of the gen-probe amplified mycobacterium tuberculosis direct test for rapid diagnosis of tuberculosis lymphadenitis. Journal of Clinical Microbiology 42(12): 5921-2**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? • If a threshold was used, was it pre-specified? microscopy, unclear; Amplified M. Tuberculosis Direct test, yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

<table>
<tr><th>Bibliographic reference</th><th>Kerleguer A, Fabre M, Bernatas JJ, Gerome P, Nicand E, Herve V and Koeck JL (2004) Clinical evaluation of the gen-probe amplified mycobacterium tuberculosis direct test for rapid diagnosis of tuberculosis lymphadenitis. Journal of Clinical Microbiology 42(12): 5921-2</th></tr>
<tr><td></td><td>• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? yes</td></tr>
<tr><td>Number of patients</td><td>197 specimens sampled from 153 patients</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients attending the study clinic (a centre specialising in tuberculosis diagnosis and treatment) presenting with a lymph node with a diameter of >10 mm
Characteristics of included participants
Cervical specimens, 98; submaxillar specimens, 42; axillar specimens, 21; supraclavicular specimens, 19; inguinal specimens, 10; other specimens, 7</td></tr>
<tr><td>Index test</td><td>Microscopy
Fine needle aspirate
Decontamination using the N-acetyl-l-cysteine-sodium hydroxide procedure</td></tr>
<tr><td></td><td>Amplified Mycobacterium Tuberculosis Direct test
Fine needle aspirate
Decontamination using the N-acetyl-l-cysteine-sodium hydroxide procedure
Threshold for positivity: 1,000,000 RLU; the run was validated when the negative-control value was <20,000 RLU and the positive-control value was >500,000 RLU</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen, Coletsos and MGIT 960 culture
Fine needle aspirate
Decontamination using the N-acetyl-l-cysteine-sodium hydroxide procedure</td></tr>
<tr><td>Location</td><td>Djibouti, Republic of Djibouti</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td></td><td colspan="2">Reference standard</td></tr>
<tr><td></td><td>Positive</td><td>Negative</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Kerleguer A, Fabre M, Bernatas JJ, Gerome P, Nicand E, Herve V and Koeck JL (2004) Clinical evaluation of the gen-probe amplified mycobacterium tuberculosis direct test for rapid diagnosis of tuberculosis lymphadenitis. Journal of Clinical Microbiology 42(12): 5921-2**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 30</td><td>FP 0</td></tr><tr><td>Negative</td><td>FN 78</td><td>TN 89</td></tr></table> Sensitivity of index test (95% CI)a = 27.8% (19.3 to 36.2%) Specificity of index test (95% CI)a = 99.4% (97.9 to 100%)
	Diagnostic test accuracy – Amplified Mycobacterium Tuberculosis Direct test <table><tr><td colspan="2"></td><td>Reference standard</td><td></td></tr><tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 100</td><td>FP 15</td></tr><tr><td>Negative</td><td>FN 8</td><td>TN 74</td></tr></table> Sensitivity of index test (95% CI)a = 92.6% (87.7 to 97.5%) Specificity of index test (95% CI)a = 83.2% (75.4 to 90.9%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.7 Ligthelm, 2011

Bibliographic reference	Ligthelm LJ, Nicol MP, Hoek KG, Jacobson R, van Helden PD, Marais BJ, Warren RM and Wright CA (2011) Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. Journal of Clinical Microbiology 49(11): 3967-70
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no *Domain 4: Flow and timing*

Bibliographic reference	**Ligthelm LJ, Nicol MP, Hoek KG, Jacobson R, van Helden PD, Marais BJ, Warren RM and Wright CA (2011) Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. Journal of Clinical Microbiology 49(11): 3967-70**
	Could the patient flow have introduced bias? *low risk of bias* • Was there an appropriate interval between index test(s) and reference standard? *yes* • Did all patients receive a reference standard? *yes* • Did patients receive the same reference standard? *yes* • Were all patients included in the analysis? *no, 2 cases did not have adequate smears for diagnosis*
Number of patients	50 participants; data available for 48
Patient characteristics	*Inclusion* Patients with suspected tuberculous lymphadenitis based on cytological screening (cytomorphology of lymph node consistent with an inflammatory process) *Characteristics of included participants*

Bibliographic reference	**Ligthelm LJ, Nicol MP, Hoek KG, Jacobson R, van Helden PD, Marais BJ, Warren RM and Wright CA (2011) Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. Journal of Clinical Microbiology 49(11): 3967-70**
	Characteristic / No. of patients (n = 48) / % of patients Age <5 yrs: 2 / 4.2 5–20 yrs: 6 / 12.5 >20 yrs: 40 / 83.3 Gender Male: 20 / 41.7 Female: 28 / 58.3 On TB treatment: 2 / 4.2 HIV infection status Positive: 9 / 18.8 Negative: 3 / 6.6 Unknown: 36 / 75 Culture positive/HIV positive: 4/9 / 44.4 Cytological features Reactive lymph node: 10 / 20.8 Features consistent with TB: 32 / 66.7 Acute bacterial infection: 1 / 2.1 Malignancy or suggestive of malignancy: 4 / 8.3 Epithelial inclusion cyst: 1 / 2.1
Index test	Ziehl-Neelsen and Papanicolaou stain-induced fluorescence microscopy Fine needle aspirate
	Xpert MTB/RIF Fine needle aspirate
Reference standard	MGIT 960 culture Fine needle aspirate
Location	South Africa
Outcomes measures and effect size	*Diagnostic test accuracy – Xpert MTB/RIF* Reference standard: Positive / Negative

Bibliographic reference	**Ligthelm LJ, Nicol MP, Hoek KG, Jacobson R, van Helden PD, Marais BJ, Warren RM and Wright CA (2011) Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. Journal of Clinical Microbiology 49(11): 3967-70**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 29</td><td>FP 2</td></tr><tr><td>Negative</td><td>FN 1</td><td>TN 16</td></tr></table> Sensitivity of index test (95% CI)a = 96.7% (90.2 to 100%) Specificity of index test (95% CI)a = 88.9% (74.4 to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.8 Malbruny, 2011

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. *International Journal of Tuberculosis and Lung Disease* 15(4): 553-5**
Study type	Cross-sectional
Study quality	*Domain 1: Patient selection* Could the selection of patients have introduced bias? *unclear risk of bias* • Was a consecutive or random sample of patients enrolled? *unclear* • Was a case-control design avoided? *yes* • Did the study avoid inappropriate exclusions? *no, although details provided are limited* Is there concern that the included patients do not match the review question? *no*

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. *International Journal of Tuberculosis and Lung Disease* 15(4): 553-5**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? *unclear risk of bias* • Were the index test results interpreted without knowledge of the results of the reference standard? *unclear* • If a threshold was used, was it pre-specified? *unclear* Is there concern that the index test, its conduct, or interpretation differ from the review question? *no* *Domain 3: Reference standard* Could the reference standard, its conduct, or its interpretation have introduced bias? *unclear risk of bias* • Is the reference standard likely to correctly classify the target condition? *yes* • Were the reference standard results interpreted without knowledge of the results of the index test? *unclear* Is there concern that the target condition as defined by the reference standard does not match the review question? *yes* *Domain 4: Flow and timing* Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	23 specimens
Patient characteristics	Inclusion Clinically suspected tuberculosis
Index test	Fluorescence microscopy

<table>
<tr><th>Bibliographic reference</th><th>Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease 15(4): 553-5</th></tr>
<tr><td></td><td>Pleural fluid specimen</td></tr>
<tr><td></td><td>Xpert MTB/RIF
Pleural fluid specimen</td></tr>
<tr><td>Reference standard</td><td>BACTEC MGIT 960 and Colestos culture
Pleural fluid specimen
Inoculation for 6 to 12 weeks
Confirmation using TB Ag MPT64 Rapid</td></tr>
<tr><td>Location</td><td>Caen, France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
3</td><td>FP
0</td></tr>
<tr><td>Negative</td><td>FN
3</td><td>TN
17</td></tr>
</table>
Diagnostic test accuracy – Xpert MTB/RIF
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td>Index test</td><td>Positive</td><td>TP
6</td><td>FP
0</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. *International Journal of Tuberculosis and Lung Disease* 15(4): 553-5**
	<table><tr><td></td><td>Negative</td><td>FN 0</td><td>TN 17</td></tr></table>
Source of funding	No details provided
Comments	
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.9 Nataraj, 2002

Bibliographic reference	**Nataraj G, Kurup S, Pandit A and Mehta P (2002) Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. Journal of Postgraduate Medicine 48(2): 113-6**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes

Bibliographic reference	Nataraj G, Kurup S, Pandit A and Mehta P (2002) Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. Journal of Postgraduate Medicine 48(2): 113-6
	Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	250 patients
Patient characteristics	Inclusion Patients with clinical suspicion of tuberculous lymphadenitis based on enlarged cervical and/or axillary lymph node(s) and a history suggestive of tuberculosis Characteristics of included participants The age of the patients ranged from 12 to 55 years, the majority being in the 21-30 age group (42.7%) The male to female ratio was 1:1.3 The majority of the aspirations were from cervical lymph nodes (58%) followed by axillary lymph nodes (42%)
Index test	Cytology Fine needle aspirate Two independent observers recorded the cytological findings for the presence or absence of granulomas, Langerhan's giant

<table>
<tr><th>Bibliographic reference</th><th>Nataraj G, Kurup S, Pandit A and Mehta P (2002) Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. Journal of Postgraduate Medicine 48(2): 113-6</th></tr>
<tr><td></td><td>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</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen culture
Fine needle aspirate
Incubation for at least 8 weeks</td></tr>
<tr><td>Location</td><td>Mumbai, India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
129</td><td>FP
61</td></tr>
<tr><td>Negative</td><td>FN
1</td><td>TN
59</td></tr>
</table>
Sensitivity of index test (95% CI)a = 99.2% (97.7 to 100%)
Specificity of index test (95% CI)a = 49.2% (40.2 to 58.1%)</td></tr>
<tr><td>Source of funding</td><td>No details provided</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.5.10 Osores, 2006

Bibliographic reference	**Osores F, Nolasco O, Verdonck K, Arévalo J, Ferrufino JC, Agapito J, Huayanay L, Gotuzzo E and Maguiña C (2006) Clinical evaluation of a 16S ribosomal RNA polymerase chain reaction test for the diagnosis of lymph node tuberculosis. Clinical Infectious Disease 43(7): 855-9**
Study type	Cross-sectional

Bibliographic reference	**Osores F, Nolasco O, Verdonck K, Arévalo J, Ferrufino JC, Agapito J, Huayanay L, Gotuzzo E and Maguiña C (2006) Clinical evaluation of a 16S ribosomal RNA polymerase chain reaction test for the diagnosis of lymph node tuberculosis. Clinical Infectious Disease 43(7): 855-9**
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? low risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although 11 of the total cases of tuberculosis were diagnosed by histopathology (i.e. were culture-negative) • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias

<table>
<tr><th>Bibliographic reference</th><th>Osores F, Nolasco O, Verdonck K, Arévalo J, Ferrufino JC, Agapito J, Huayanay L, Gotuzzo E and Maguiña C (2006) Clinical evaluation of a 16S ribosomal RNA polymerase chain reaction test for the diagnosis of lymph node tuberculosis. Clinical Infectious Disease 43(7): 855-9</th></tr>
<tr><td></td><td>• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? no, 12 excluded from the analysis due to quality of the biopsy specimen</td></tr>
<tr><td>Number of patients</td><td>166 participants; data available on 154</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with superficial lymphadenopathy in whom the attending physician suspected tuberculosis
Characteristics of included participants
Median age was 29 years (interquartile range, 21 to 40 years)
97 patients (62.9%) were men</td></tr>
<tr><td>Index test</td><td>Amplicor
Fine needle aspirate and biopsy samples from an enlarged lymph node</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen culture and/or histopathology
Fine needle aspirate and biopsy samples from an enlarged lymph node</td></tr>
<tr><td>Location</td><td>Lima, Peru</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – aspirate
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
26</td><td>FP
4</td></tr>
<tr><td>Negative</td><td>FN
29</td><td>TN
95</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Osores F, Nolasco O, Verdonck K, Arévalo J, Ferrufino JC, Agapito J, Huayanay L, Gotuzzo E and Maguiña C (2006) Clinical evaluation of a 16S ribosomal RNA polymerase chain reaction test for the diagnosis of lymph node tuberculosis. Clinical Infectious Disease 43(7): 855-9**
	Sensitivity of index test (95% CI)a = 47.3% (34.1 to 60.5%) Specificity of index test (95% CI)a = 96.0% (92.1 to 99.8%)
	Diagnostic test accuracy – biopsy <table><tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr><tr><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 29</td><td>FP 3</td></tr><tr><td>Negative</td><td>FN 26</td><td>TN 96</td></tr></table> Sensitivity of index test (95% CI)a = 52.7% (39.5 to 65.9%) Specificity of index test (95% CI)a = 97.0% (93.6 to 100%)
Source of funding	Partly funded by the Peruvian Foundation 'Instituto Hipolito Unanue' and by the Directorate-General for Development Cooperation of the Belgian Government Roche donated the Amplicor kits
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.11 Pfyffer, 1996

Bibliographic reference	**Pfyffer GE, Kissling P, Jahn EM, Welscher HM, Salfinger M and Weber R (1996) Diagnostic performance of amplified Mycobacterium tuberculosis direct test with cerebrospinal fluid, other nonrespiratory, and respiratory specimens. Journal of Clinical Microbiology 34(4): 834-41**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias

Bibliographic reference	Pfyffer GE, Kissling P, Jahn EM, Welscher HM, Salfinger M and Weber R (1996) Diagnostic performance of amplified Mycobacterium tuberculosis direct test with cerebrospinal fluid, other nonrespiratory, and respiratory specimens. Journal of Clinical Microbiology 34(4): 834-41
	• Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes

<table>
<tr><th>Bibliographic reference</th><th>Pfyffer GE, Kissling P, Jahn EM, Welscher HM, Salfinger M and Weber R (1996) Diagnostic performance of amplified Mycobacterium tuberculosis direct test with cerebrospinal fluid, other nonrespiratory, and respiratory specimens. Journal of Clinical Microbiology 34(4): 834-41</th></tr>
<tr><td></td><td>• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? yes</td></tr>
<tr><td>Number of patients</td><td>46 specimens</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with a high suspicion of tuberculosis based on clinical and radiological findings; or
Immunosuppression, due to HIV, immunosuppressive therapy, transplant etc; or
High prevalence in a particular population – for example, prisoner, drug abuser, homeless etc</td></tr>
<tr><td>Index test</td><td>Amplified Mycobacterium tuberculosis Direct test</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen, BACTEC 12 B and Middlebrook 7H10 and selective 7H11 culture</td></tr>
<tr><td>Location</td><td>Zurich, Switzerland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td></td><td></td><td>Reference standard</td><td></td></tr>
<tr><td></td><td></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
12</td><td>FP
3</td></tr>
<tr><td>Negative</td><td>FN
0</td><td>TN
31</td></tr>
</table>
Sensitivity of index test (95% CI)a = 96.0% (85.1 to 100%)
Specificity of index test (95% CI)a = 91.2% (81.6 to 100%)</td></tr>
<tr><td>Source of funding</td><td>Supported by the Swiss Federal Office of Public Health and the Zurcher Lungenliga
Gen-Probe provided the Amplified Mycobacterium tuberculosis Direct test kits</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.5.12 Rimek, 2002

Bibliographic reference	Rimek D, Tyagi S and Kappe R (2002) Performance of an IS6110-based PCR assay and the COBAS AMPLICOR MTB PCR system for detection of Mycobacterium tuberculosis complex DNA in human lymph node samples. Journal of Clinical Microbiology 40(8): 3089-92
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

<table>
<tr><th>Bibliographic reference</th><th>Rimek D, Tyagi S and Kappe R (2002) Performance of an IS6110-based PCR assay and the COBAS AMPLICOR MTB PCR system for detection of Mycobacterium tuberculosis complex DNA in human lymph node samples. Journal of Clinical Microbiology 40(8): 3089-92</th></tr>
<tr><td></td><td>Could the patient flow have introduced bias? low risk of bias
• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? unclear</td></tr>
<tr><td>Number of patients</td><td>43 human lymph node samples from 40 patients</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with possible lymph node tuberculosis
Characteristics of included participants
18 females and 22 males
Median age of 25 years (range, 1 to 91 years)</td></tr>
<tr><td>Index test</td><td>Fluorescence microscopy with Kinyoun confirmation
Biopsy samples</td></tr>
<tr><td>Reference standard</td><td>Löwenstein-Jensen and MGIT 960 culture
Biopsy samples</td></tr>
<tr><td>Location</td><td>Unclear</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td>Index test</td><td>Positive</td><td>TP
3</td><td>FP
1</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Rimek D, Tyagi S and Kappe R (2002) Performance of an IS6110-based PCR assay and the COBAS AMPLICOR MTB PCR system for detection of Mycobacterium tuberculosis complex DNA in human lymph node samples. Journal of Clinical Microbiology 40(8): 3089-92**
	<table><tr><td></td><td>Negative</td><td>FN 15</td><td>TN 24</td></tr></table> Sensitivity of index test (95% CI)a = Specificity of index test (95% CI)a =
Source of funding	Supported by the International Association for Exchange of Students for Technical Experience of the German Academic Exchange Service, and by the Gemeinnutzige Gesellschaft zur Forderung von wissenschaftlichen Nachwuchskraften m.b.H., Heidelberg, Germany
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.5.13 Van Rie, 2013

Bibliographic reference	**Van Rie A, Page-Shipp L, Mellet K, Scott L, Mkhwnazi M, Jong E, Omar T, Beylis N, Stevens W, Sanne I and Menezes CN (2013) Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(11): 1409-15**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias

Bibliographic reference	Van Rie A, Page-Shipp L, Mellet K, Scott L, Mkhwnazi M, Jong E, Omar T, Beylis N, Stevens W, Sanne I and Menezes CN (2013) Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(11): 1409-15
	• Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? no, patients for whom the culture results went missing (n = 12), were contaminated (n = 6), yielded nontuberculous mycobacteria (n = 4), or was not interpretablea (n = 2), or patients with an invalid Xpert result were excluded
Number of patients	373 patients
Patient characteristics	Inclusion Clinical suspicion of lymph node tuberculosis HIV positivity Adults (18 years or above)

Bibliographic reference	**Van Rie A, Page-Shipp L, Mellet K, Scott L, Mkhwnazi M, Jong E, Omar T, Beylis N, Stevens W, Sanne I and Menezes CN (2013) Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(11): 1409-15**
	Not in receipt of treatment for active or latent tuberculosis Characteristics of included participants
Index test	Ziehl–Neelsen microscopy Fine needle aspirate specimens
	Xpert MTB/RIF Fine needle aspirate specimens
Reference standard	MGIT 960 culture

		n	%
Gender	Male	170	51
	Female	164	49
Age	<36 years	184	53
	≥36 years	160	47
Inpatient	Yes	162	47
	No	182	53
CD4[a]	<100	115	39
	100–249	97	32
	≥250	87	29
On ART	Yes	59	17
	No	285	83
Cough present	Yes	235	68
	No	109	32
Sputum microscopy[b]	AFB-positive	12	4
	No AFB	121	35
	Not done	211	61
Sputum culture	Positive	49	14
	Negative	38	11
	Missing[c]	257	75

[a] CD4 count in cells/mm^3 missing for 45 participants

[b] Acid-fast bacilli (AFB) detected by auramine and/or Ziehl–Neelsen stain

[c] Includes 250 cultures not done and eight contaminated cultures

<table>
<tr><th>Bibliographic reference</th><th>Van Rie A, Page-Shipp L, Mellet K, Scott L, Mkhwnazi M, Jong E, Omar T, Beylis N, Stevens W, Sanne I and Menezes CN (2013) Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(11): 1409-15</th></tr>
<tr><td></td><td>Fine needle aspirate specimens</td></tr>
<tr><td>Location</td><td>Johannesburg, South Africa</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
76</td><td>FP
8</td></tr>
<tr><td>Negative</td><td>FN
73</td><td>TN
187</td></tr>
</table>
Sensitivity of index test (95% CI)b = 51.0% (43.0 to 59.0%)
Specificity of index test (95% CI)b = 95.9% (93.1 to 98.7%)
Diagnostic test accuracy – Xpert MTB/RIF
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
139</td><td>FP
10</td></tr>
<tr><td>Negative</td><td>FN
23</td><td>TN
172</td></tr>
</table>
Sensitivity of index test (95% CI)b = 85.8% (80.4 to 91.2%)
Specificity of index test (95% CI)b = 94.5% (91.2 to 97.8%)</td></tr>
<tr><td>Source of funding</td><td>Supported by the United States Agency for International Development and the National Institutes for Health</td></tr>
</table>

Bibliographic reference	**Van Rie A, Page-Shipp L, Mellet K, Scott L, Mkhwnazi M, Jong E, Omar T, Beylis N, Stevens W, Sanne I and Menezes CN (2013) Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases 32(11): 1409-15**
	The Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland, provided access to the Xpert MTB/RIF instrument and cartridges at preferential pricing
Comments	
a Defined as acid-fast bacilli-positive but no species identification possible b Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.6 Diagnosis of active pericardial tuberculosis

1.3.6.1 Lee, 2002

Bibliographic reference	**Lee JH, Lee CW, Lee SG, Yang HS, Hong MK, Kim JJ, Park SW, Chi HS and Park SJ (2002) Comparison of polymerase chain reaction with adenosine deaminase activity in pericardial fluid for the diagnosis of tuberculous pericarditis. American Journal of Medicine 113(6): 519-21**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? low risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? yes

Bibliographic reference	Lee JH, Lee CW, Lee SG, Yang HS, Hong MK, Kim JJ, Park SW, Chi HS and Park SJ (2002) Comparison of polymerase chain reaction with adenosine deaminase activity in pericardial fluid for the diagnosis of tuberculous pericarditis. American Journal of Medicine 113(6): 519-21
	• If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? where culture-confirmed, yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? yes
Number of patients	67 participants
Patient characteristics	Inclusion Patients with large pericardial effusions (defined as a sum of echo-free pericardial spaces in diastole exceeding 20mm) who had received invasive diagnostic procedures Exclusion Patients with pericardial effusions due to acute myocardial infarction, heart failure, end-stage renal disease, hypothyroidism, or trauma Characteristics of included participants Age (mean±SD) = 55±18 years

Bibliographic reference	**Lee JH, Lee CW, Lee SG, Yang HS, Hong MK, Kim JJ, Park SW, Chi HS and Park SJ (2002) Comparison of polymerase chain reaction with adenosine deaminase activity in pericardial fluid for the diagnosis of tuberculous pericarditis. American Journal of Medicine 113(6): 519-21**
	37 men, 30 women
Index test	Cobas Amplicor Pericardial fluid specimens obtained by pericardiostomy
Reference standard	A diagnosis of tuberculous pericarditis was defined as a positive Löwenstein-Jenson culture on pericardial tissue specimens (obtained by pericardiostomy and incubated for 8 weeks) for M. tuberculosis, or typical caseating granuloma formation in biopsy tissue, supported by a clinical response to antituberculosis therapy during the follow-up and the absence of an alternate diagnosis
Location	Seoul, South Korea
Outcomes measures and effect size	Diagnostic test accuracy – Cobas Amplicor Reference standard Positive Negative Index test Positive: TP 9, FP 0 Index test Negative: FN 3, TN 55 Sensitivity of index test (95% CI)a = 75.0% (50.5 to 99.5%) Specificity of index test (95% CI)a = 99.1% (96.6 to 100%)
Source of funding	No details provided
Comments	Data for adenosine deanimase activity was included in the Tuon (2006) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; SD, standard deviation; TN, true negative; TP, true positive	

1.3.6.2 Reuter, 2006

Bibliographic reference	**Reuter H, Burgess L, van Vuuren W and Doubell A (2006) Diagnosing tuberculous pericarditis. QJM 99(12): 827-39**
Study type	Cross-sectional

Bibliographic reference	Reuter H, Burgess L, van Vuuren W and Doubell A (2006) Diagnosing tuberculous pericarditis. QJM 99(12): 827-39
Study quality	*Domain 1: Patient selection* Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, although details provided were limited Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes, where culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes

Bibliographic reference	Reuter H, Burgess L, van Vuuren W and Doubell A (2006) Diagnosing tuberculous pericarditis. QJM 99(12): 827-39
	• Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? yes
Number of patients	Amplicor: 48 participants Tuberculin skin test: 52 participants
Patient characteristics	Inclusion Patients presenting with pericardial effusions
Index test	Amplicor Pericardial fluid specimens
	Tuberculin skin test Threshold for positivity: 10 mm or 15 mm induration
Reference standard	Definite tuberculous pericarditis was diagnosed by one or more of the following criteria: i) isolation of M. tuberculosis from the drained pericardial effusion or pericardial biopsy specimen (positive Ziehl-Neelsen stain and/or positive BACTEC MGIT 960 culture); and/or ii) demonstration of granulomatous inflammation on histological examination of the pericardial biopsy sample; and/or iii) isolation of M. tuberculosis from sputum or non-pericardial exudates in the presence of clinical and/or radiological evidence of tuberculosis, associated with a positive response to anti-tuberculous therapy, and in the absence of any other obvious cause for pericardial effusions Probable tuberculous pericarditis was diagnosed in patients who presented with compatible clinical features (at least three of the following five symptoms: cough, weight loss, fever, night sweats, anorexia) in the absence of an alternative diagnosis, and associated with a sustained response to anti-tuberculous chemotherapy Non-tuberculous pericardial effusion was diagnosed in patients who were effusion/sputum smear- and culture-negative, for whom an alternative diagnosis was established, and in whom no evidence of tuberculosis was detected for 6 months after initial presentation
Location	South Africa
Outcomes measures and effect size	Diagnostic test accuracy – Amplicor Reference standard Positive Negative

Bibliographic reference	Reuter H, Burgess L, van Vuuren W and Doubell A (2006) Diagnosing tuberculous pericarditis. QJM 99(12): 827-39
	Index test – Positive: TP 10, FP 0; Negative: FN 23, TN 15 Sensitivity of index test (95% CI)a = 30.3% (14.6 to 46.0%) Specificity of index test (95% CI)a = 96.8% (88.0 to 100%)
	Diagnostic test accuracy – tuberculin skin test, 10 mm induration Reference standard: Positive / Negative Index test – Positive: TP 32, FP 7; Negative: FN 4, TN 9 Sensitivity of index test (95% CI)a = 88.9% (78.6 to 99.2%) Specificity of index test (95% CI)a = 56.3% (31.9 to 80.6%)
	Diagnostic test accuracy – tuberculin skin test, 15 mm induration Reference standard: Positive / Negative Index test – Positive: TP 16, FP 1

Bibliographic reference	Reuter H, Burgess L, van Vuuren W and Doubell A (2006) Diagnosing tuberculous pericarditis. QJM 99(12): 827-39
	Negative: FN 20, TN 15 Sensitivity of index test (95% CI)a = 44.4% (28.2 to 60.7%) Specificity of index test (95% CI)a = 93.8% (81.9 to 100%)
Source of funding	No details provided
Comments	Data for adenosine deanimase activity was included in the Tuon (2006) systematic review
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.6.3 Tuon, 2006

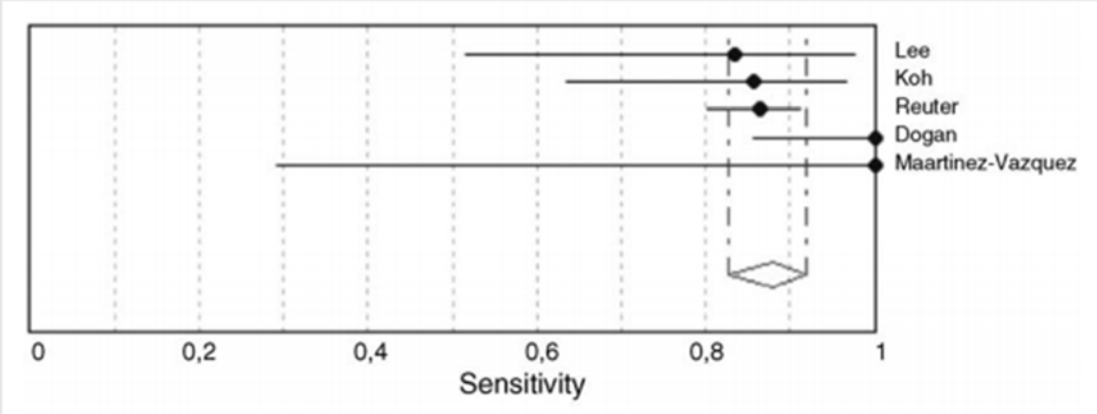
Bibliographic reference	Tuon FF, Litvoc MN and Lopes MI (2006) Adenosine deaminase and tuberculous pericarditis – a systematic review with meta-analysis. Acta Tropica 99(1): 67-74
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? no Is there concern that the index test, its conduct, or interpretation differ from the review question? no Is there concern that the target condition as defined by the reference standard does not match the review question? not all were culture-based reference standards

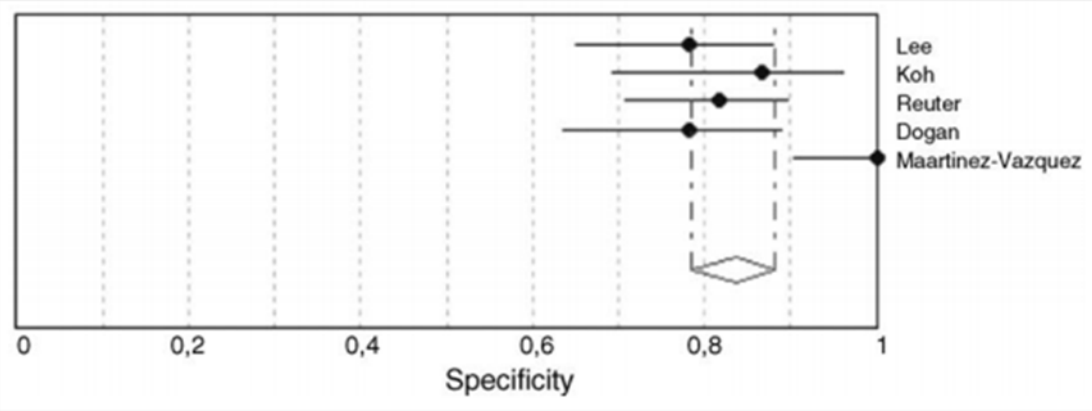
Study	Consecutive or	Case-control?	Prospective?	Overall quality

Bibliographic reference	**Tuon FF, Litvoc MN and Lopes MI (2006) Adenosine deaminase and tuberculous pericarditis – a systematic review with meta-analysis. Acta Tropica 99(1): 67-74**

	random sample?			
Lee, 2002	yes	no	yes	high
Koh, 1997	yes	no	yes	high
Reuter, 2005	yes	no	yes	high
Dogan, 1999	yes	no	yes	high
Martinez-Vazquez, 1986	yes	no	yes	moderate

Number of patients	5 studies
Study characteristics	Inclusion The selected articles had to be written in English Data on adenosine deanimase activity in pericardial effusion from tuberculous pericarditis patients and control groups were necessary to calculate the sensitivity and specificity The method used for adenosine deanimase activity had to be the same in all the studies, avoiding the measurement bias The cut-off value for adenosine deanimase activity of 40 U/l was selected because this was the value used on the majority of the studies and seems to offer the best diagnostic threshold; when different cut-off values were used, the respective authors were contacted to acquire data regarding a cutoff value of 40 U/l Only prospective studies were considered To exclude repeated casuistics, authors were contacted when articles were from the same medical service with overlapping time intervals otherwise the publication with the largest casuistic was considered
Index test	Adenosine deanimase activity Measured by Giusti's method Threshold for positivity: 40 U/l
Reference standard	The cases included patients with at least one diagnostic criterion for tuberculous pericarditis: 1) Mycobacterium tuberculosis positive in pericardial effusion or tissue culture (gold standard) 2) histopathological exam of pericardial with granulomas containing alcohol-acid resistant bacilli 3) granulomas in pericardial tissue associated with active tuberculosis in another site Patients with clinical and/or laboratory evidence of tuberculous pericarditis that had clinical improvement after empirical treatment for tuberculosis were also included as tuberculous pericarditis cases even if they lack the diagnostic criteria

<table>
<tr><th>Bibliographic reference</th><th>Tuon FF, Litvoc MN and Lopes MI (2006) Adenosine deaminase and tuberculous pericarditis – a systematic review with meta-analysis. Acta Tropica 99(1): 67-74</th></tr>
<tr><td></td><td>described above because there are no significant difference in the adenosine deanimase activity level between the pericardial fluid in group of confirmed tuberculous pericarditis and the group of strongly suspected pericardial tuberculosis
The control groups of each article included in this meta-analysis were composed by patients with other pericardial diseases with moderate to large pericardial effusion, excluding those whose effusion were cardiac surgery related (e.g. after revascularization surgery)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td>Study</td><td>Sensitivity (95% CI)</td><td>Specificity (95% CI)</td></tr>
<tr><td>Lee, 2002</td><td>83% (50 to 97%)</td><td>78% (64 to 87%)</td></tr>
<tr><td>Koh, 1997</td><td>85% (62% to 96%)</td><td>86% (68 to 95%)</td></tr>
<tr><td>Reuter, 2005</td><td>86% (79 to 91%)</td><td>81% (70 to 89%)</td></tr>
<tr><td>Dogan, 1999</td><td>100% (82 to 100%)</td><td>78% (63 to 88%)</td></tr>
<tr><td>Martinez-Vazquez, 1986</td><td>100% (31 to 100%)</td><td>100% (88 to 100%)</td></tr>
</table>

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

Bibliographic reference	**Tuon FF, Litvoc MN and Lopes MI (2006) Adenosine deaminase and tuberculous pericarditis – a systematic review with meta-analysis. Acta Tropica 99(1): 67-74**
	 Pooled sensitivity of index test (95% CI) = 88% (82 to 91%) Pooled specificity of index test (95% CI) = 83% (78 to 88%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7 Diagnosis of active pleural tuberculosis

1.3.7.1 Denkinger, 2014

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**

Is the literature search sufficiently rigorous to identify all the relevant studies? yes

Is study quality assessed and reported? yes

Is an adequate description of methodology included, and the methods used appropriate to the question? yes

Additional criteria

Is there concern that the included patients do not match the review question? no

Is there concern that the index test, its conduct, or interpretation differ from the review question? no

Is there concern that the target condition as defined by the reference standard does not match the review question? no

Study	Blinding	Selection	Prospective enrolment?
Al-Ateah, 2012	yes	consecutive	yes
Armand, 2011	yes	convenience	no
Causse, 2011	yes	consecutive	yes
Christopher, 2013	yes	consecutive	yes
Friedrich, 2011	yes	consecutive	yes
Hanif, 2011	no	consecutive	yes
Hillemann, 2011	yes	consecutive	yes
Moure, 2012	yes	convenience	no
Porcel, 2013	no	consecutive	yes
Safianowska, 2012	no	consecutive	yes

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**

Tortoli, 2012	yes	convenience	no
Vadwai, 2011	yes	consecutive	yes
Zeka, 2011	yes	consecutive	no

Number of patients

Study	n
Al-Ateah, 2012	13
Armand, 2011	8
Causse, 2011	34
Christopher, 2013	87
Friedrich, 2011	24
Hanif, 2011	11
Hillemann, 2011	105
Moure, 2012	34
Porcel, 2013	66
Safianowska, 2012	32
Tortoli, 2012	330
Vadwai, 2011	29
Zeka, 2011	56

Patient characteristics

Inclusion

<table>
<tr><th>Bibliographic reference</th><td>Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. European Respiratory Journal 44(2): 435-46</td></tr>
<tr><td></td><td>Patients with suspected tuberculosis
Characteristics of included participants</td></tr>
<tr><td>Index test</td><td>Xpert MTB/RIF</td></tr>
<tr><td>Reference standard</td><td>Culture-based</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><th>Study</th><th>True positives</th><th>False positives</th><th>False negatives</th><th>True negatives</th></tr>
<tr><td>Al-Ateah, 2012</td><td>3</td><td>0</td><td>0</td><td>10</td></tr>
<tr><td>Armand, 2011</td><td>3</td><td>0</td><td>4</td><td>1</td></tr>
<tr><td>Causse, 2011</td><td>4</td><td>0</td><td>0</td><td>30</td></tr>
<tr><td>Christopher, 2013</td><td>0</td><td>4</td><td>0</td><td>83</td></tr>
<tr><td>Friedrich, 2011</td><td>5</td><td>0</td><td>4</td><td>15</td></tr>
<tr><td>Hanif, 2011</td><td>3</td><td>0</td><td>0</td><td>8</td></tr>
<tr><td>Hillemann, 2011</td><td>0</td><td>2</td><td>0</td><td>103</td></tr>
<tr><td>Moure, 2012</td><td>9</td><td>0</td><td>19</td><td>6</td></tr>
<tr><td>Porcel, 2013</td><td>2</td><td>3</td><td>3</td><td>58</td></tr>
<tr><td>Safianowska, 2012</td><td>0</td><td>0</td><td>2</td><td>30</td></tr>
<tr><td>Tortoli, 2012</td><td>5</td><td>3</td><td>10</td><td>312</td></tr>
<tr><td>Vadwai, 2011</td><td>5</td><td>0</td><td>5</td><td>19</td></tr>
<tr><td>Zeka, 2011</td><td>0</td><td>0</td><td>4</td><td>52</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>No details provided</td></tr>
</table>

Bibliographic reference	**Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M and Steingart KR (2014) Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal* 44(2): 435-46**
Comments	Data not extracted for duplicate studies
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.2 Baba, 2008

Bibliographic reference	**Baba K, Sørnes S, Hoosen AA, Lekabe JM, Mpe MJ, Langeland N, Dyrhol-Riise AM (2008) Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. BMC Infectious Diseases 8: 35**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although less reliably in those

Bibliographic reference	**Baba K, Sørnes S, Hoosen AA, Lekabe JM, Mpe MJ, Langeland N, Dyrhol-Riise AM (2008) Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. BMC Infectious Diseases 8: 35**
	diagnosed by smear only • Were the reference standard results interpreted without knowledge of the results of the index test? yes Is there concern that the target condition as defined by the reference standard does not match the review question? if cases defined by smear only, there may be some nontuberculous mycobacteria included Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no, some smear, some culture • Were all patients included in the analysis? no
Number of patients	34 participants Data available: • diagnostic test accuracy – blood specimens = 29 • diagnostic test accuracy – pleural fluid specimens = 32
Patient characteristics	Inclusion Patients presenting with pleural effusion and clinically suspected pleural tuberculosis Characteristics of included participants All adults

Bibliographic reference	**Baba K, Sørnes S, Hoosen AA, Lekabe JM, Mpe MJ, Langeland N, Dyrhol-Riise AM (2008) Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. BMC Infectious Diseases 8: 35**
	Characteristics / **Number** Gender Females: 12 Males: 22 Age: median (range): 39 (20–70) Clinical symptoms: n (%) Chest pain: 34 (100%) Productive cough: 10 (29%) Fever: 16 (47%) Shortness of breath: 16 (47%) Night sweat: 29 (85%) Loss of weight: 31 (91%) Lymphadenopathy: 27 (79%) Oral thrush: 25 (74%) Chest x-ray infiltrates: n (%): 2 (6%) Culture positive TB: n (%): 12 (35%) Total TB cases: n (%): 28 (82%) Non-TB cases: n (%): 6 (18%) HIV positive patients: n (%): 25 (74%) CD4 cell count HIV positive: median (range)[a]: 80 (7–328) CD4 cell count > 200 cells/microL: 2 (8%) CD4 cell count 100–200 cells/microL: 7 (28%) CD4 cell count < 100 cells/microL: 13 (52%) CD4 cell count HIV negative: median (range): 457 (241–927) [a] CD4 cell count was not available for three of the patients.
Index test	Interferon-gamma release assay QuantiFERON TB®-Gold in pleural fluid (pleural fluid mononuclear cells) and blood specimens Test was positive if the tuberculosis antigen minus the nil value was ≥0.35 IU/ml
Reference standard	Microscopy or culture (BacT-alert for up to 4 weeks) of pleural fluid
Location	Pretoria, South Africa
Outcomes measures and	Diagnostic test accuracy – blood specimens

Bibliographic reference	**Baba K, Sørnes S, Hoosen AA, Lekabe JM, Mpe MJ, Langeland N, Dyrhol-Riise AM (2008) Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. BMC Infectious Diseases 8: 35**
effect size	<table><tr><td colspan="2"></td><td>Reference standard</td></tr><tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 7</td><td>FP 10</td></tr><tr><td>Negative</td><td>FN 1</td><td>TN 5</td></tr></table>Sensitivity of index test (95% CI)a = 87.5% (64.6 to 100%) Specificity of index test (95% CI)a = 33.3% (9.5 to 57.2%) Indeterminate results = 6/29 Diagnostic test accuracy – pleural fluid specimens<table><tr><td colspan="2"></td><td>Reference standard</td></tr><tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 3</td><td>FP 9</td></tr><tr><td>Negative</td><td>FN 0</td><td>TN 4</td></tr></table>Sensitivity of index test (95% CI)a = 100% (100 to 100%) Specificity of index test (95% CI)a = 30.8% (5.7 to 55.9%) Indeterminate results =16/32
Source of funding	Funded by grants from Haukeland University Hospital and the University of Bergen
Comments	

Bibliographic reference	Baba K, Sørnes S, Hoosen AA, Lekabe JM, Mpe MJ, Langeland N, Dyrhol-Riise AM (2008) Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. BMC Infectious Diseases 8: 35
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.3 Burgess, 1996

Bibliographic reference	Burgess LJ, Maritz FJ, Le Roux I and Taljaard JJ (1996) Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. *Chest* 109(2): 414-9
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? some risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? thresholds were used, but a range were used and the most effective reported Is there concern that the index test, its conduct, or interpretation differ from the review question? not standardised Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? some risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although less reliably in those not

Bibliographic reference	**Burgess LJ, Maritz FJ, Le Roux I and Taljaard JJ (1996) Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. *Chest* 109(2): 414-9**
	culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? some risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? no • Were all patients included in the analysis? no
Number of patients	472 specimens from 472 participants included Data available for 303 127 patients were excluded due to diagnoses of hemothorax (5), grossly turbid empyemas (14), or transudative effusions (108); an additional 42 patients were excluded as no differential cell counts were available
Patient characteristics	Inclusion Exudative pleural fluid specimens from patients admitted to medical, surgical, gynaecologic, and paediatric wards *Exclusion* Transudative effusions Patients having haemathoraces or empyemas too turbid for analysis Characteristics of included studies 176 were men (58%) and 127 were women (42%) Average age of the patient population was 49 (SD 20.72) years (range, 6 months to 98 years)
Index test	ADA activity plus lymphocyte:neutrophil ratio in exudative pleural fluid specimens ADA: • determined on all exudative pleural fluid specimens according to the method described by Giust; adenosine is deaminated by ADA and the free ammonia is estimated by Berthelot's reaction • one unit of ADA is defined as the amount of enzyme required to release 1 µmol of ammonia per minute from adenosine at

<table>
<tr><th>Bibliographic reference</th><th>Burgess LJ, Maritz FJ, Le Roux I and Taljaard JJ (1996) Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. Chest 109(2): 414-9</th></tr>
<tr><td></td><td>standard assay conditions
• threshold for positivity = ≥50 U/l
Lymphocyte:neutrophil ratio:
• threshold for positivity = ≥0.75</td></tr>
<tr><td>Reference standard</td><td>Tuberculous pleuritis was classified into three diagnostic subclasses:
• identification of the bacillus in pleural fluid or biopsy specimen by stain or by culture, or by the presence of granulomas in pleural biopsy tissue
• positive sputum culture in the presence of clinical and radiologic evidence for tuberculosis and in the absence of any other obvious cause associated with pleural effusions
• clinical and radiologic evidence for tuberculosis in the absence of any other obvious cause associated with pleural effusions and associated with a positive response to antituberculosis therapy</td></tr>
<tr><td>Location</td><td>South Africa</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td colspan="2" rowspan="2"></td><td>Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
126</td><td>FP
8</td></tr>
<tr><td>Negative</td><td>FN
17</td><td>TN
152</td></tr>
</table>
Sensitivity of index test (95% CI)a = 88.1% (82.8 to 93.4%)
Specificity of index test (95% CI)a = 95.0% (91.6 to 98.4%)</td></tr>
<tr><td>Source of funding</td><td>No details provided</td></tr>
<tr><td>Comments</td><td>Data for ADA alone is included in the meta-analysis by Liang et al (2008)</td></tr>
<tr><td colspan="2">a Calculated by reviewer
Abbreviations: ADA, adenosine deanimase; CI, confidence interval; FN, false negative; FP, false positive; SD, standard deviation; TN, true negative; TP, true positive</td></tr>
</table>

1.3.7.4 Caballero, 1999

Bibliographic reference	Caballero M, Ruiz R, Márquez de Prado M, Seco M, Borque L and Escanero JF (1999) Development of a microparticle-enhanced nephelometric immunoassay for quantitation of human lysozyme in pleural effusion and plasma. Journal of Clinical Laboratory Analysis 13(6): 301-7
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? participants did not have specific suspicion of tuberculosis *Domain 2: Index test(s)* Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes, although less reliably in those not culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no

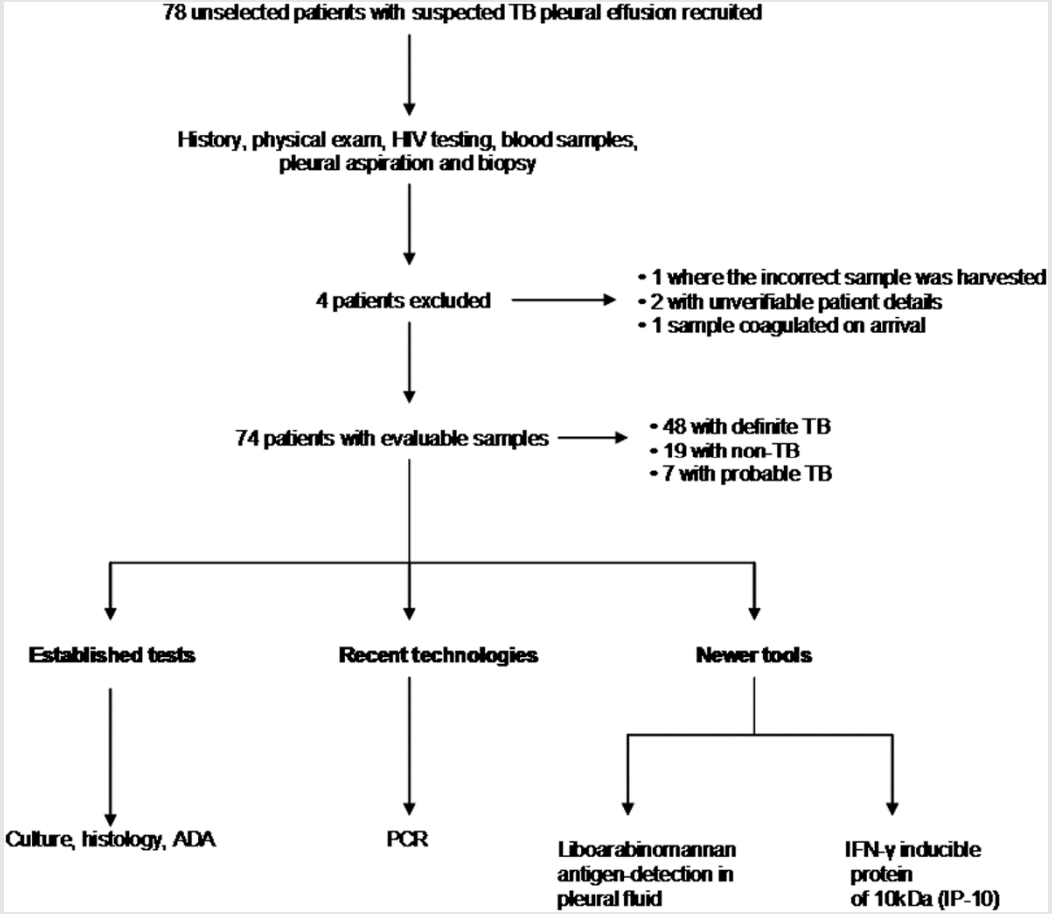
<table>
<tr><th>Bibliographic reference</th><th>Caballero M, Ruiz R, Márquez de Prado M, Seco M, Borque L and Escanero JF (1999) Development of a microparticle-enhanced nephelometric immunoassay for quantitation of human lysozyme in pleural effusion and plasma. Journal of Clinical Laboratory Analysis 13(6): 301-7</th></tr>
<tr><td></td><td>Domain 4: Flow and timing
Could the patient flow have introduced bias? some risk of bias
• Was there an appropriate interval between index test(s) and reference standard? unclear
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? no
• Were all patients included in the analysis? yes</td></tr>
<tr><td>Number of patients</td><td>92 participants</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Pleural fluid specimens from patients with undiagnosed pleural effusion</td></tr>
<tr><td>Index test</td><td>ADA activity in pleural fluid</td></tr>
<tr><td>Reference standard</td><td>The diagnosis was determined by culture of pleural fluid or biopsy, or by the presence of granulomas with necrosis in pleural biopsy specimens accompanied by compatible clinical and therapeutic evolution</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
5</td><td>FP
11</td></tr>
<tr><td>Negative</td><td>FN
1</td><td>TN
75</td></tr>
</table>
Sensitivity of index test (95% CI)a = 83.3% (53.5 to 100%)
Specificity of index test (95% CI)a = 87.2% (80.2 to 94.3%)</td></tr>
</table>

Bibliographic reference	Caballero M, Ruiz R, Márquez de Prado M, Seco M, Borque L and Escanero JF (1999) Development of a microparticle-enhanced nephelometric immunoassay for quantitation of human lysozyme in pleural effusion and plasma. Journal of Clinical Laboratory Analysis 13(6): 301-7
Source of funding	No details provided
Comments	Lysozyme data included in the Dinnes et al (2007) meta-analysis
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.5 Dheda, 2009

Bibliographic reference	Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

Bibliographic reference	Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689
	• Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? *** risk of bias • Was there an appropriate interval between index test(s) and reference standard? unclear • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? some culture, some histology plus treatment response • Were all patients included in the analysis? no
Number of patients	78 participants; data available for 74

Bibliographic reference	Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689
	
Patient characteristics	Inclusion Patients with suspected tuberculosis pleural effusion (persistent fever, night sweats or cough, chest pain, loss of weight, previous or recent tuberculosis contact, or any patient in whom, due to suggestive symptoms or signs, tuberculosis was part of the differential diagnosis) Exclusion Those under 18 years of age Pregnancy

<table>
<tr><th>Bibliographic reference</th><th>Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689</th></tr>
<tr><td></td><td>Characteristics of included participants
Of those tested, 20/51 (49%) were HIV positive</td></tr>
<tr><td>Index test</td><td>Amplified M. Tuberculosis Direct test conducted on pleural fluid</td></tr>
<tr><td></td><td>LAM antigen concentration in the pleural fluid
Measured using Clearview® TB ELISA
Thresholds: >30 g/l; >60 g/l</td></tr>
<tr><td></td><td>ADA activity in pleural fluid
Derived using colorimetric methods
Thresholds: >30 IU/l; >47 IU/l; >13 IU/l</td></tr>
<tr><td>Reference standard</td><td>Culture and/or histology in keeping with tuberculosis (caseous necrosis or acid fast bacilli with or without granuloma formation)
Definite tuberculosis:
• MGIT 960 culture (sputum, pleural fluid or tissue) and/ or histology and a clinicoradiological picture consistent with tuberculosis with a response to antituberculosis treatment
Non-tuberculosis:
• alternative diagnosis made on histology or pleural fluid aspiration, not treated for tuberculosis, and on 3 to 6 month follow-up there were no features to suggest tuberculosis</td></tr>
<tr><td>Location</td><td>Cape Town, South Africa</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – Amplified M. Tuberculosis Direct test
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
3</td><td>FP
2</td></tr>
<tr><td>Negative</td><td>FN
45</td><td>TN
24</td></tr>
</table>
Sensitivity of index test (95% CI)a = 6.3% (0.0 to 13.1%)
Specificity of index test (95% CI)a = 92.3% (82.1 to 100%)</td></tr>
</table>

Bibliographic reference	**Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689**

Diagnostic test accuracy – LAM (cut-off: >30 g/l)

		Reference standard	
		Positive	Negative
Index test	Positive	TP 45	FP 23
	Negative	FN 3	TN 3

Sensitivity of index test (95% CI)a = 93.8% (86.9 to 100%)
Specificity of index test (95% CI)a = 11.5% (0.0 to 23.8%)

Diagnostic test accuracy – LAM (cut-off: >60 g/l)

		Reference standard	
		Positive	Negative
Index test	Positive	TP 22	FP 2
	Negative	FN 2	TN 24

Sensitivity of index test (95% CI)a = 91.7% (80.6 to 100%)
Specificity of index test (95% CI)a = 92.3% (82.1 to 100%)

Diagnostic test accuracy – ADA (cut-off: >13 IU/l)

		Reference standard	
		Positive	Negative

Bibliographic reference	Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689

Index test	Positive	TP 48	FP 16
	Negative	FN 0	TN 10

Sensitivity of index test (95% CI)a = 100% (100 to 100%)
Specificity of index test (95% CI)a = 38.5% (19.8 to 57.2%)
Diagnostic test accuracy – ADA (cut-off: >30 IU/l)

		Reference standard	
		Positive	Negative
Index test	Positive	TP 46	FP 8
	Negative	FN 2	TN 18

Sensitivity of index test (95% CI)a = 95.8% (90.2 to 100%)
Specificity of index test (95% CI)a = 69.2% (51.5 to 87.0%)
Diagnostic test accuracy – ADA (cut-off: >47 IU/l)

		Reference standard	
		Positive	Negative
Index test	Positive	TP 44	FP 2

Bibliographic reference	**Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, et al (2009) Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting. PLoS ONE 4(3): e4689**
	<table><tr><td></td><td>Negative</td><td>FN 4</td><td>TN 24</td></tr></table> Sensitivity of index test (95% CI)a = 91.7% (83.9 to 99.5%) Specificity of index test (95% CI)a = 92.3% (82.1 to 100%)
Source of funding	Supported by the South African National Research Foundation (SARChI), the South African Medical Research Council and the UCL-UCT Collaboration Initiative The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Comments	
a Calculated by reviewer Abbreviations: ADA, adenosine deanimase; CI, confidence interval; FN, false negative; FP, false positive; LAM, lipoarabinomannan; TN, true negative; TP, true positive	

1.3.7.6 Gamboa, 1997a

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes Is there concern that the included patients do not match the review question? no Domain 2: Index test(s)

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
	Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	49 pleural exudate specimens
Patient characteristics	Inclusion Patients suspected of having tuberculosis Patients who had received antituberculosis therapy

<table>
<tr><th>Bibliographic reference</th><th>Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55</th></tr>
<tr><td>Index test</td><td>Fluorescence microscopy with Ziehl-Neelsen confirmation
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td>Reference standard</td><td>Amplified M. Tuberculosis Direct test
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td></td><td>Culture (Löwenstein-Jensen, Colestos and BACTEC 12B and 13A)
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide
Incubated for 8 weeks
A BACTEC Growth Index of >100 was considered positive</td></tr>
<tr><td>Location</td><td>Barcelona, Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
1</td><td>FP
1</td></tr>
<tr><td>Negative</td><td>FN
13</td><td>TN
34</td></tr>
</table>
Sensitivity of index test (95% CI)a = 7.1% (0.0 to 20.6%)
Specificity of index test (95% CI)a = 97.1% (91.6 to 100%)
Diagnostic test accuracy – Amplified M. Tuberculosis Direct test
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Gamboa F, Manterola JM, Lonca J, Viñado B, Matas L, Giménez M, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Dominguez J and Ausina V (1997) Rapid detection of Mycobacterium tuberculosis in respiratory specimens, blood and other non-respiratory specimens by amplification of rRNA. International Journal of Tuberculosis and Lung Disease 1(6): 542-55**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 14</td><td>FP 0</td></tr><tr><td>Negative</td><td>FN 0</td><td>TN 35</td></tr></table> Sensitivity of index test (95% CI)a = 100% (100 to 100%) Specificity of index test (95% CI)a = 100% (100 to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.7 Gamboa, 1997b

Bibliographic reference	**Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? low risk of bias • Was a consecutive or random sample of patients enrolled? yes • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, though details provided were limited

Bibliographic reference	**Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10**
	Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? *unclear* Is there concern that the target condition as defined by the reference standard does not match the review question? *yes* *Domain 4: Flow and timing* Could the patient flow have introduced bias? *low risk of bias* • Was there an appropriate interval between index test(s) and reference standard? *yes* • Did all patients receive a reference standard? *yes* • Did patients receive the same reference standard? *yes* • Were all patients included in the analysis? *yes*
Number of patients	41 pleural exudate specimens

<table>
<tr><th>Bibliographic reference</th><th>Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10</th></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with clinical signs or symptoms of tuberculosis</td></tr>
<tr><td>Index test</td><td>Fluorescence microscopy with Ziehl-Neelsen confirmation
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td></td><td>Amplified M. Tuberculosis Direct test
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide</td></tr>
<tr><td>Reference standard</td><td>Culture (Löwenstein-Jensen, Colestos and BACTEC 12B)
Specimen digested and decontaminated with sodium dodecyl (lauryl) sulphate-sodium hydroxide
Incubated for 8 weeks</td></tr>
<tr><td>Location</td><td>Barcelona, Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
1</td><td>FP
1</td></tr>
<tr><td>Negative</td><td>FN
12</td><td>TN
27</td></tr>
</table>
Sensitivity of index test (95% CI)a =
Specificity of index test (95% CI)a =
Diagnostic test accuracy – Amplified M. Tuberculosis Direct test
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Gamboa F, Manterola JM, Viñado B, Matas L, Giménez M, Lonca J, Manzano JR, Rodrigo C, Cardona PJ, Padilla E, Domínguez J and Ausina V (1997) Direct detection of Mycobacterium tuberculosis complex in nonrespiratory specimens by Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test. Journal of Clinical Microbiology 35(1): 307-10**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 13</td><td>FP 0</td></tr><tr><td>Negative</td><td>FN 0</td><td>TN 28</td></tr></table> Sensitivity of index test (95% CI)a = 100% (100 to 100%) Specificity of index test (95% CI)a = 100% (100 to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.8 Hasaneen, 2003

Bibliographic reference	**Hasaneen NA, Zaki ME, Shalaby HM and El-Morsi AS (2003) Polymerase chain reaction of pleural biopsy is a rapid and sensitive method for the diagnosis of tuberculous pleural effusion. *Chest* 124(6): 2105-11**
Study type	Cross-sectional
Study quality	*Domain 1: Patient selection* Could the selection of patients have introduced bias? *unclear risk of bias* • Was a consecutive or random sample of patients enrolled? *unclear* • Was a case-control design avoided? *yes* • Did the study avoid inappropriate exclusions? *yes, although details provided were limited* Is there concern that the included patients do not match the review question? *no*

Bibliographic reference	**Hasaneen NA, Zaki ME, Shalaby HM and El-Morsi AS (2003) Polymerase chain reaction of pleural biopsy is a rapid and sensitive method for the diagnosis of tuberculous pleural effusion. *Chest* 124(6): 2105-11**
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? *unclear risk of bias* • Were the index test results interpreted without knowledge of the results of the reference standard? *yes* • If a threshold was used, was it pre-specified? *unclear* Is there concern that the index test, its conduct, or interpretation differ from the review question? *no* *Domain 3: Reference standard* Could the reference standard, its conduct, or its interpretation have introduced bias? *low risk of bias* • Is the reference standard likely to correctly classify the target condition? *yes* • Were the reference standard results interpreted without knowledge of the results of the index test? *unclear* Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	45 participants
Patient characteristics	Inclusion Patients with pleural effusion Characteristics of included participants 27 men and 18 women

<table>
<tr><th>Bibliographic reference</th><th>Hasaneen NA, Zaki ME, Shalaby HM and El-Morsi AS (2003) Polymerase chain reaction of pleural biopsy is a rapid and sensitive method for the diagnosis of tuberculous pleural effusion. Chest 124(6): 2105-11</th></tr>
<tr><td></td><td>Mean (± SD) age of 46 ± 2.30 years
None of the patients were tested for HIV</td></tr>
<tr><td>Index test</td><td>Ziehl-Neelsen microscopy of pleural fluid and biopsy specimens</td></tr>
<tr><td></td><td>Histopathologic examination of pleural biopsy specimen fixed in formalin for caseating granuloma</td></tr>
<tr><td>Reference standard</td><td>Culture and and histopathologic examination for caseating granuloma
Culture:
• Löwenstein-Jensen or BACTEC 12B liquid culture of pleural fluid and biopsy specimens
• incubation for 8 weeks
• a growth index of ≥10 was considered positive
Histopathology
• examination for caseating granuloma</td></tr>
<tr><td>Location</td><td>Egypt</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy (pleural fluid)
<table>
<tr><td colspan="2"></td><td>Reference standard</td><td></td></tr>
<tr><td colspan="2"></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
0</td><td>FP
0</td></tr>
<tr><td>Negative</td><td>FN
26</td><td>TN
19</td></tr>
</table>
Sensitivity of index test (95% CI)a = 0% (0 to 0%)
Specificity of index test (95% CI)a = 100% (100 to 100%)
Diagnostic test accuracy – microscopy (pleural biopsy)
<table>
<tr><td></td><td>Reference standard</td></tr>
<tr><td></td><td>Positive</td><td>Negative</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Hasaneen NA, Zaki ME, Shalaby HM and El-Morsi AS (2003) Polymerase chain reaction of pleural biopsy is a rapid and sensitive method for the diagnosis of tuberculous pleural effusion. *Chest* 124(6): 2105-11**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 1</td><td>FP 0</td></tr><tr><td>Negative</td><td>FN 25</td><td>TN 19</td></tr></table> Sensitivity of index test (95% CI)a = 3.9% (0.0 to 11.2%) Specificity of index test (95% CI)a = 100% (100 to 100%)
	Diagnostic test accuracy – histopathology (pleural biopsy) <table><tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr><tr><td>Positive</td><td>Negative</td></tr><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 14</td><td>FP 0</td></tr><tr><td>Negative</td><td>FN 12</td><td>TN 19</td></tr></table> Sensitivity of index test (95% CI)a = 53.9% (34.7 to 73.0%) Specificity of index test (95% CI)a = 100% (100 to 100%)
Source of funding	No details provided
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.9 Lee, 2009

Bibliographic reference	Lee LN, Chou CH, Wang JY, Hsu HL, Tsai TH, Jan IS, Hsueh PR and Yang PC (2009) Enzyme-linked immunospot assay for interferon-gamma in the diagnosis of tuberculous pleurisy. Clinical Microbiology and Infection 15(2): 173-9
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? yes, though details provided Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes, though not all culture-confirmed • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing

<table>
<tr><th>Bibliographic reference</th><th>Lee LN, Chou CH, Wang JY, Hsu HL, Tsai TH, Jan IS, Hsueh PR and Yang PC (2009) Enzyme-linked immunospot assay for interferon-gamma in the diagnosis of tuberculous pleurisy. Clinical Microbiology and Infection 15(2): 173-9</th></tr>
<tr><td></td><td>Could the patient flow have introduced bias? low risk of bias
• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? no
• Were all patients included in the analysis? 1 participants missing for the data collected from peripheral blood specimens</td></tr>
<tr><td>Number of patients</td><td>40 participants</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients presenting with pleural effusion of undetermined aetiology
Patients aged ≥18 years
Characteristics of included participants
All had received <2 weeks of antituberculosis chemotherapy or were not treated at the time of study
HIV tests performed in 8 participants, all were negative</td></tr>
<tr><td>Index test</td><td>T-SPOT.TB on pleural fluid or peripheral blood</td></tr>
<tr><td>Reference standard</td><td>Tuberculous pleurisy was classified as confirmed if any of the following criteria were met: (i) culture of pleural fluid, pleural biopsy material or sputum yielded M. tuberculosis; (ii) the histology of pleural biopsy material showed granulomatous inflammation with positive acid-fast bacilli; and (iii) the histology of pleural biopsy material showed granulomatous inflammation without acid-fast bacilli, but there was obvious clinical improvement after antituberculous chemotherapy
Clinical improvement was defined as defervescence and disappearance of pleural effusions after antituberculous chemotherapy, without the concomitant use of other antimicrobials or corticosteroids.</td></tr>
<tr><td>Location</td><td>Taiwan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – pleural fluid
<table>
<tr><td rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Lee LN, Chou CH, Wang JY, Hsu HL, Tsai TH, Jan IS, Hsueh PR and Yang PC (2009) Enzyme-linked immunospot assay for interferon-gamma in the diagnosis of tuberculous pleurisy. Clinical Microbiology and Infection 15(2): 173-9**

Index test	Positive	TP 14	FP 1
	Negative	FN 7	TN 18

Sensitivity of index test (95% CI)a = 66.7% (46.5 to 86.8%)
Specificity of index test (95% CI)a = 94.7% (84.7 to 100%)
Diagnostic test accuracy – peripheral blood

		Reference standard	
		Positive	Negative
Index test	Positive	TP 11	FP 3
	Negative	FN 5	TN 20

Sensitivity of index test (95% CI)a = 68.8% (46.0 to 91.5%)
Specificity of index test (95% CI)a =87.0% (73.2 to 100%)

Source of funding	This work was supported, in part, by Institute for Biotechnology and Medicine Industry, Taiwan
Comments	

a Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

1.3.7.10 Liang, 2008

Bibliographic reference	**Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube**

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review ques Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes, using both STARD (maximum score: 25) and QUADAS (m Is an adequate description of methodology included, and the methods used appropriate to the question? Additional criteria Is there concern that the included patients do not match the review question? details of included particip those with suspected tuberculosis Is there concern that the index test, its conduct, or interpretation differ from the review question? no Is there concern that the target condition as defined by the reference standard does not match the revie reference standards

Study	Quality score	
	STARD	QUADAS
Piras	5	4
Blake	9	9
Maritz	9	9
Pettersson	8	9
Niwa	9	9
Raj	9	9
Sinha	11	10

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube

Strankinga	11	9
Teo	11	9
Fontan Bueso	9	7
Kim	10	9
Ocana	8	9
Gilhotra	8	9
Hsu	10	9
Moriwaki	10	9
Segura	10	9
Baganha	8	9
Gupta	9	9
Banales	12	10
Maartens	11	9
Shimokata	6	5
Kaur	11	7
Muranishi	11	9
Nagaraja	12	9
Prasad	10	9
Valdes	8	5

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube

Aoki	12	10
Chiang	10	9
DeOliveira	12	11
Burgess	13	10
Querol	12	10
Orphanidou	10	9
Shibagaki	9	9
Valdes	13	10
Villena	14	12
Kim	12	9
Ogawa	9	5
Ghelani	11	9
Perez-Rodriguez	11	9
Riantawan	14	12
Villegas	12	9
Gorguner	11	9
Lim	10	9
Nagesh	16	13
Reechaipichitkul	16	12

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube

Sharma	14	12
Yamada	12	10
Andreasyan	10	9
Aoe	11	9
Lima	10	9
Porcel	13	10
Tahhan	8	5
Chen	13	10
Neves	8	9
Poyraz	13	8
El-Ansary	10	9
Gaga	12	10
Moon	13	9
Okamato	10	9
Sharma	12	10
Tozkoparan	11	9
Celik	11	9
Morimoto	11	9

Number of patients	8036 participants from 63 studies

<table>
<tr><th>Bibliographic reference</th><th>Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube</th></tr>
<tr><td>Patient characteristics</td><td>Details not provided</td></tr>
<tr><td>Index test</td><td>ADA activity
<table>
<tr><th>Study</th><th>Method</th><th>Cut-off (IU/l)</th></tr>
<tr><td>Piras</td><td>Giusti</td><td>30</td></tr>
<tr><td>Blake</td><td>Non-Giusti</td><td>30</td></tr>
<tr><td>Maritz</td><td>Giusti</td><td>40</td></tr>
<tr><td>Pettersson</td><td>Giusti</td><td>30</td></tr>
<tr><td>Niwa</td><td>Unknown</td><td>30</td></tr>
<tr><td>Raj</td><td>Giusti</td><td>40</td></tr>
<tr><td>Sinha</td><td>Giusti</td><td>30</td></tr>
<tr><td>Strankinga</td><td>Giusti</td><td>53</td></tr>
<tr><td>Teo</td><td>Giusti</td><td>50</td></tr>
<tr><td>Fontan Bueso</td><td>Giusti</td><td>33</td></tr>
<tr><td>Kim</td><td>Giusti</td><td>41</td></tr>
<tr><td>Ocana</td><td>Giusti</td><td>43</td></tr>
<tr><td>Gilhotra</td><td>Giusti</td><td>40</td></tr>
<tr><td>Hsu</td><td>Giusti</td><td>50</td></tr>
<tr><td>Moriwaki</td><td>Non-Giusti</td><td>33</td></tr>
<tr><td>Segura</td><td>Giusti</td><td>71</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube

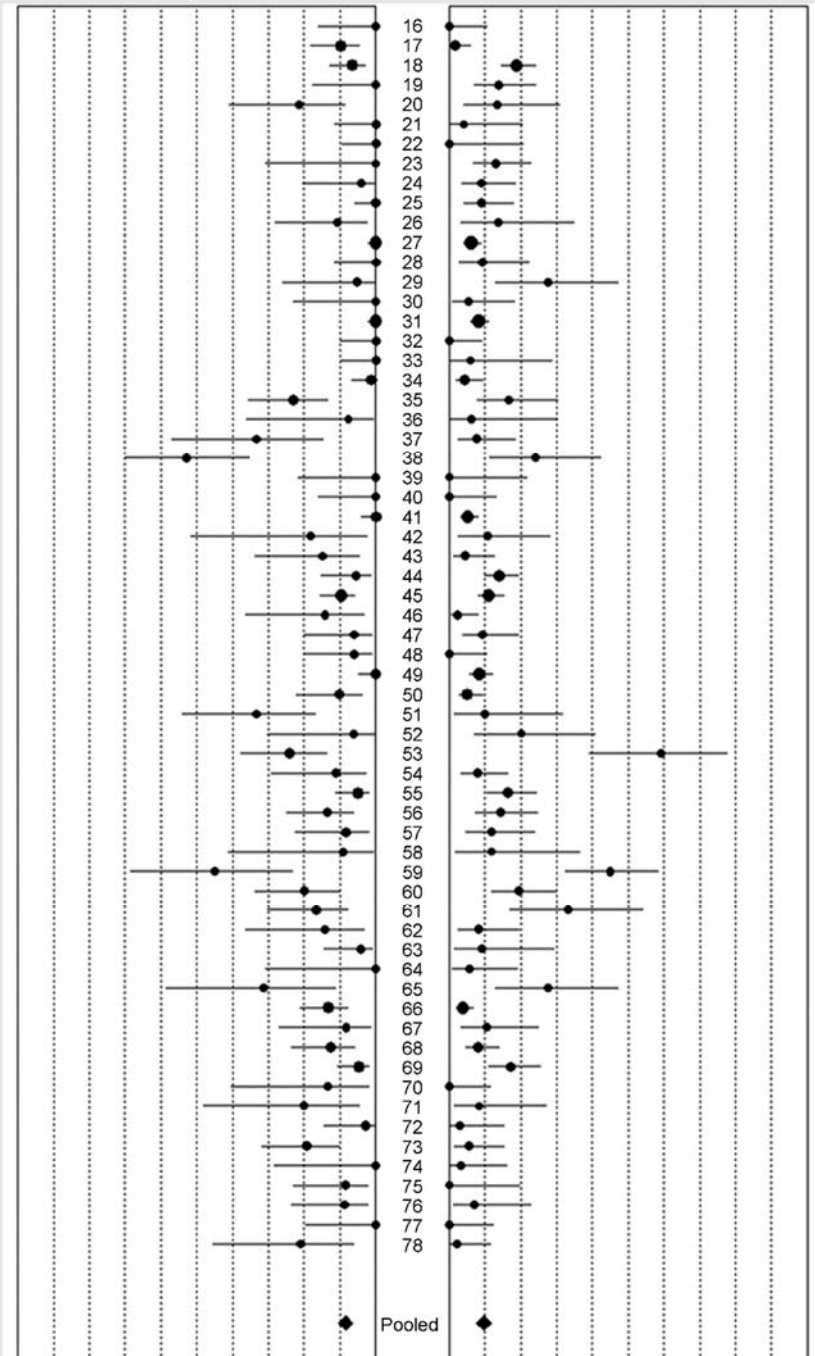
Baganha	Giusti	40
Gupta	Giusti	50.8
Banales	Giusti	70
Maartens	Giusti	45
Shimokata	Non-Giusti	30
Kaur	Giusti	30
Muranishi	Giusti	50
Nagaraja	Giusti	50
Prasad	Unknown	30
Valdes	Giusti	47
Aoki	Non-Giusti	45
Chiang	Giusti	45
DeOliveira	Giusti	40
Burgess	Giusti	50
Querol	Non-Giusti	45
Orphanidou	Giusti	40
Shibagaki	Non-Giusti	30
Valdes	Giusti	47
Villena	Non-Giusti	33
Kim	Non-Giusti	32

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube

Ogawa	Unknown	33
Ghelani	Giusti	40
Perez-Rodriguez	Non-Giusti	40
Riantawan	Giusti	60
Villegas	Giusti	45.5
Gorguner	Giusti	50
Lim	Non-Giusti	40
Nagesh	Giusti	50
Reechaipichitkul	Giusti	48
Sharma	Giusti	35
Yamada	Non-Giusti	45
Andreasyan	Non-Giusti	20
Aoe	Non-Giusti	40
Lima	Giusti	40
Porcel	Non-Giusti	40
Tahhan	Giusti	40
Chen	Non-Giusti	55.8
Neves	Giusti	39
Poyraz	Giusti	45

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube
	El-Ansary, Giusti, 35 Gaga, Giusti, 50 Moon, Giusti, 45 Okamato, Non-Giusti, 32 Sharma, Giusti, 33 Tozkoparan, Unknown, 50 Celik, Giusti, 35.6 Morimoto, Non-Giusti, 57
Reference standard	In all 63 studies included, the study by Piras16 did not mention the diagnosis standard for TPE; in 28 studies, the c standard); in the remaining 34 studies, some TPE patients were diagnosed based on “gold standard”, and some pa pleural fluid analysis, radiology and the responsiveness to anti-tuberculous chemotherapy
Outcomes measures and effect size	Diagnostic test accuracy

Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube



Bibliographic reference	Liang QL, Shi HZ, Wang K, Qin SM and Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tube
Source of funding	None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript
Comments	
a Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.11 Liao, 2009

Bibliographic reference	Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? yes Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias

<table>
<tr><th>Bibliographic reference</th><th>Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8</th></tr>
<tr><td></td><td>• Is the reference standard likely to correctly classify the target condition? yes
• Were the reference standard results interpreted without knowledge of the results of the index test? unclear
Is there concern that the target condition as defined by the reference standard does not match the review question? no
Domain 4: Flow and timing
Could the patient flow have introduced bias? low risk of bias
• Was there an appropriate interval between index test(s) and reference standard? yes
• Did all patients receive a reference standard? yes
• Did patients receive the same reference standard? yes
• Were all patients included in the analysis? yes</td></tr>
<tr><td>Number of patients</td><td>32 participants</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Patients with suspected tuberculosis
Adults</td></tr>
<tr><td>Index test</td><td>T.SPOT-TB using peripheral blood and pleural effusion
Threshold: ≥10 pots per test well when the background control had a count of <5, or at least twice the value found in the background control wells, when the background control had a count of ≥5</td></tr>
<tr><td>Reference standard</td><td>‘Recovery’ of M. tuberculosis from a clinical specimen – i.e. fluorescence microscopy or culture (Middlebrook 7H11 selective agar, or BACTEC MGIT 960)</td></tr>
<tr><td>Location</td><td>Taiwan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Liao CH, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL and Hsueh PR (2009) Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. Journal of Infection 59(6): 402-8**
	<table><tr><td rowspan="2">Index test</td><td>Positive</td><td>TP 8</td><td>FP 8</td></tr><tr><td>Negative</td><td>FN 3</td><td>TN 13</td></tr></table> Sensitivity of index test (95% CI)a = 72.7% (46.4 to 99.1%) Specificity of index test (95% CI)a = 61.9% (41.1 to 82.7%)
Source of funding	Supported by the Institute for Biotechnology and Medicine Industry, Taiwan
Comments	
[a] Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.12 Malbruny, 2011

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? no, although details provided are limited Is there concern that the included patients do not match the review question? no

Bibliographic reference	Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease
	Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear • If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? yes Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	12 specimens
Patient characteristics	Inclusion Clinically suspected tuberculosis
Index test	Fluorescence microscopy

<table>
<tr><th>Bibliographic reference</th><th>Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease</th></tr>
<tr><td></td><td>Pleural fluid specimen</td></tr>
<tr><td></td><td>Gene Xpert MTB/RIF
Pleural fluid specimen</td></tr>
<tr><td>Reference standard</td><td>BACTEC MGIT 960 and Colestos culture
Pleural fluid specimen
Inoculation for 6 to 12 weeks
Confirmation using TB Ag MPT64 Rapid</td></tr>
<tr><td>Location</td><td>Caen, France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy – microscopy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
0</td><td>FP
0</td></tr>
<tr><td>Negative</td><td>FN
2</td><td>TN
10</td></tr>
</table>
Diagnostic test accuracy – Xpert MTB/RIF
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td>Index test</td><td>Positive</td><td>TP
0</td><td>FP
0</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Malbruny B, Le Marrec G, Courageux K, Leclercq R and Cattoir V (2011) Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. International Journal of Tuberculosis and Lung Disease**
	<table><tr><td></td><td>Negative</td><td>FN 2</td><td>TN 10</td></tr></table>
Source of funding	No details provided
Comments	
[a] Calculated by reviewer Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive	

1.3.7.13 Maurya, 2011

Bibliographic reference	**Maurya AK, Kant S, Kushwaha RA, Nag VL, Kumar M and Dhole TN (2011) The advantage of using IS6110-PCR vs. BACTEC culture for rapid detection of Mycobacterium tuberculosis from pleural fluid in northern India. Bioscience Trends 5(4): 159-64**
Study type	Cross-sectional
Study quality	Domain 1: Patient selection Could the selection of patients have introduced bias? unclear risk of bias • Was a consecutive or random sample of patients enrolled? unclear • Was a case-control design avoided? yes • Did the study avoid inappropriate exclusions? unclear Is there concern that the included patients do not match the review question? no Domain 2: Index test(s) Could the conduct or interpretation of the index test have introduced bias? unclear risk of bias • Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic reference	Maurya AK, Kant S, Kushwaha RA, Nag VL, Kumar M and Dhole TN (2011) The advantage of using IS6110-PCR vs. BACTEC culture for rapid detection of Mycobacterium tuberculosis from pleural fluid in northern India. Bioscience Trends 5(4): 159-64
	• If a threshold was used, was it pre-specified? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3: Reference standard Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk of bias • Is the reference standard likely to correctly classify the target condition? yes • Were the reference standard results interpreted without knowledge of the results of the index test? unclear Is there concern that the target condition as defined by the reference standard does not match the review question? no Domain 4: Flow and timing Could the patient flow have introduced bias? low risk of bias • Was there an appropriate interval between index test(s) and reference standard? yes • Did all patients receive a reference standard? yes • Did patients receive the same reference standard? yes • Were all patients included in the analysis? yes
Number of patients	102 participants
Patient characteristics	Inclusion Clinically suspected cases of pleural tuberculosis Characteristics of included participants 77 (75%) patients were males and 25 (25%) were females The mean age of all patients was 30.4 ± 13.2 years Patients 25-44 years of age accounted for 42.2% of the total cases Among all cases, 70 were newly detected cases (68.6%), 25 were previous treated cases (24.5%), 5 were on treatment (4.9%) and 2 were unknown (1.9%)

<table>
<tr><th>Bibliographic reference</th><th>Maurya AK, Kant S, Kushwaha RA, Nag VL, Kumar M and Dhole TN (2011) The advantage of using IS6110-PCR vs. BACTEC culture for rapid detection of Mycobacterium tuberculosis from pleural fluid in northern India. Bioscience Trends 5(4): 159-64</th></tr>
<tr><td></td><td>The history of contact with tuberculosis patients was determined in 20 cases (19.6%)
19(18.2%) had a history of diabetic mellitus
2 cases were HIV positive (2.5%) and they had an antiretroviral
100 were HIV negative (97.5%).
17 patients had haempotosis (16.6%), 62 cough (60.7%), 75 fever (75.9%), 71 anorexia and/or weight loss (70%), 53 chest pain (51.9%), 58 night sweat and or chills (56.5%) and 21 dyspnoea (20.5%)</td></tr>
<tr><td>Index test</td><td>Ziehl-Neelsen microscopy
Pleural aspirate</td></tr>
<tr><td>Reference standard</td><td>BACTEC 460 culture
Pleural aspirate</td></tr>
<tr><td>Location</td><td>Lucknow, India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnostic test accuracy
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference standard</td></tr>
<tr><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Index test</td><td>Positive</td><td>TP
15</td><td>FP
2</td></tr>
<tr><td>Negative</td><td>FN
33</td><td>TN
52</td></tr>
</table>
Sensitivity of index test (95% CI)[a] = 31.3% (18.1 to 44.4%)
Specificity of index test (95% CI)[a] = 96.3% (91.3 to 100%)</td></tr>
<tr><td>Source of funding</td><td>Supported by a grant from Indian Council of Medical Research, New Delhi</td></tr>
<tr><td>Comments</td><td></td></tr>
<tr><td colspan="2">[a] Calculated by reviewer
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive</td></tr>
</table>

1.3.7.14 Pai, 2004

Bibliographic reference	**Pai M, Flores LL, Hubbard A, Riley LW and Colford JM Jr (2004) Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infectious Diseases 4: 6**
Study type	Systematic review
Study quality	Does the review address an appropriate and clearly focused question that is relevant to the review question? yes Does the review collect the type of studies considered relevant to the review question? yes Is the literature search sufficiently rigorous to identify all the relevant studies? yes Is study quality assessed and reported? yes Is an adequate description of methodology included, and the methods used appropriate to the question? yes Additional criteria Is there concern that the included patients do not match the review question? unclear Is there concern that the index test, its conduct, or interpretation differ from the review question? review included LCx, which is no longer available in the UK; reviewer did not extract this data Is there concern that the target condition as defined by the reference standard does not match the review question? no

Study	Double or single blind	Consecutive or random sample	Reference standard	Study quality
D'Amato, 1996	unknown	unknown	culture	low
Mitarai, 2000	no	yes	culture/biopsy	medium
Reischl, 1998	yes	yes	culture	high
Shah, 1998	unknown	yes	culture	medium
Artiles, 2001	no	yes	culture/clinical	medium
Ehlers, 1996	yes	no	culture/clinical	medium
Gamboa, 1997	yes	no	culture	high

<table>
<tr><th>Bibliographic reference</th><th>Pai M, Flores LL, Hubbard A, Riley LW and Colford JM Jr (2004) Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infectious Diseases 4: 6</th></tr>
<tr><td></td><td>
<table>
<tr><td>Gamboa, 1997</td><td>yes</td><td>no</td><td>culture</td><td>high</td></tr>
<tr><td>Pfyffer, 1996</td><td>unknown</td><td>unknown</td><td>culture</td><td>low</td></tr>
<tr><td>Vlaspolder, 1995</td><td>unknown</td><td>yes</td><td>culture</td><td>medium</td></tr>
</table>
</td></tr>
<tr><td>Number of patients</td><td>963 participants from 10 evaluations</td></tr>
<tr><td>Study characteristics</td><td>All published studies on nucleic acid amplification tests for the direct detection of M. tuberculosis in pleural fluid specimens
For inclusion, a study had to:
1. report a comparison of an nucleic acid amplification test against a reference standard, and provide data necessary for the computation of both sensitivity and specificity;
2. include at least 10 pleural fluid specimens (since studies with very few specimens are vulnerable to selection bias)
Studies on use of nucleic acid amplification tests on pleural biopsy and/or cytology specimens were excluded</td></tr>
<tr><td>Index test</td><td>4 evaluations of Amplicor, 6 evaluations of the Amplified M. Tuberculosis Direct test
<table>
<tr><td>Study</td><td>Index test</td></tr>
<tr><td>D'Amato, 1996</td><td>Amplicor</td></tr>
<tr><td>Mitarai, 2000</td><td>Amplicor</td></tr>
<tr><td>Reischl, 1998</td><td>Amplicor</td></tr>
<tr><td>Shah, 1998</td><td>Amplicor</td></tr>
<tr><td>Artiles, 2001</td><td>Amplified M. Tuberculosis Direct test</td></tr>
<tr><td>Ehlers, 1996</td><td>Amplified M. Tuberculosis Direct test</td></tr>
<tr><td>Gamboa, 1997</td><td>Amplified M. Tuberculosis Direct test</td></tr>
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<tr><td>Pfyffer, 1996</td><td>Amplified M. Tuberculosis Direct test</td></tr>
<tr><td>Vlaspolder, 1995</td><td>Amplified M. Tuberculosis Direct test</td></tr>
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<tr><td>Reference standard</td><td>
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<tr><td>Study</td><td>Reference standard</td></tr>
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Bibliographic reference	**Pai M, Flores LL, Hubbard A, Riley LW and Colford JM Jr (2004) Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infectious Diseases 4: 6**

D'Amato, 1996	culture
Mitarai, 2000	culture/biopsy
Reischl, 1998	culture
Shah, 1998	culture
Artiles, 2001	culture/clinical
Ehlers, 1996	culture/clinical
Gamboa, 1997	culture
Gamboa, 1997	culture
Pfyffer, 1996	culture
Vlaspolder, 1995	culture

Outcomes measures and effect size

Diagnostic test accuracy

Study	No. in study	No. of pleural specimens or subjects with TB/no. without TB	Sensitivity (95% CI)	Specificity (95% CI)
D'Amato, 1996	92	3/89	0.67 (0.13, 0.98)	1.00 (0.96, 1.00)
Mitarai, 2000	75	33/42	0.27 (0.14, 0.46)	0.98 (0.86, 1.00)
Reischl, 1998	69	3/66	0.67 (0.13, 0.98)	0.98 (0.91, 1.00)
Shah, 1998	375	8/367	0.50 (0.18, 0.82)	1.00 (0.98, 1.00)
Artiles, 2001	101	5/96	0.20 (0.01, 0.70)	0.98 (0.92, 1.00)
Ehlers, 1996	35	3/32	1.00 (0.29, 1.00)	1.00 (0.89, 1.00)
Gamboa, 1997	49	13/36	1.00 (0.75, 1.00)	1.00 (0.90, 1.00)

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	Gamboa, 1997	41	13/28	1.00 (0.75, 1.00)	1.00 (0.88, 1.00)
	Pfyffer, 1996	65	4/61	0.50 (0.09, 0.91)	0.95 (0.85, 0.99)
	Vlaspolder, 1995	61	5/56	0.20 (0.01, 0.70)	0.96 (0.87, 0.99)
Source of funding	Support by the National Institutes of Health, Fogarty AIDS International Training Program				
Comments					
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive					