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Appendices

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A systematic review of rapid diagnostic tests for the detection of tuberculosis infection

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Appendix 1

Literature search details

Literature was identified from several sources, including electronic databases and other sources, including:

1. General health and biomedical databases: MEDLINE; PubMED (current year); EMBASE; Science Citation Index; BIOSIS.
2. Specialist electronic databases: DARE; MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers); the Cochrane Library and relevant specialist registers of the Cochrane Collaboration, particularly the Infectious Diseases group; Microbiology Abstracts; EconLit.
3. Grey literature and conference proceedings: NLM (National Library of Medicine) Gateway Databases; Index to Scientific and Technical Proceedings; Conference Proceedings Index; PapersFirst; HMIC (Health Management Information Consortium); Index to Theses; Dissertation Abstracts; SIGLE; WorldCat; British Library Public Catalogue; COPAC.
4. Research in Progress: National Research Register (NRR); Current Controlled Trials; Clinical Trials.gov.
5. Handsearching of selected meeting abstracts and conference proceedings.
6. Checking of reference lists.
7. A Science Citation Index search to identify articles which have cited key papers in the field.
8. Contact with individual experts and those with an interest in this field (e.g. Public Health Laboratory Service, SCIEH) to uncover grey and unpublished literature.
9. Contact with manufacturers of tests.

Sample search strategy used

Database: MEDLINE (1996 to August Week 2 2003)

Search strategy

1. Gene Amplification/ (3426)
2. ligase chain reaction.ti,ab. (294)
3. lcr.ti,ab. (545)
4. polymerase chain reaction.ti,ab. (46724)
5. Polymerase Chain Reaction/ (70001)
6. pcr.ti,ab. (73663)
7. nucleic acid sequenc$.ti,ab. (611)
8. nucleic acid amplification.ti,ab. (371)
9. Nucleic Acid Amplification Techniques/ (870)
10. naa.ti,ab. (995)
11. direct amplification.ti,ab. (70)
12. strand displacement amplification.ti,ab. (41)
13. signal amplification.ti,ab,hw. (540)
14. sequence amplification.ti,ab,hw. (60)
15. nucleic acid probe$.ti,ab,hw. (232)
16. rna probe$.ti,ab,hw. (1459)
17. dna amplification$.ti,ab. (929)
18. dna probe$.ti,ab,hw. (6675)
19. dot blot$.ti,ab,hw. (1971)
20. insite.ti,ab. (2)
21. insertion site typ$.ti,ab. (2)
22. mtd.ti,ab. (1032)
23. amtd$.ti,ab,hw. (27)
24. mycobacteri$ tuberculosis direct.ti,ab. (68)
25. amplicor.ti,ab. (630)
26. gen?probe.ti,ab. (7)
27. gen probe.ti,ab. (152)
28. probe?tec.ti,ab. (3)
29. probe tec.ti,ab. (1)
30. bdprobetec.ti,ab. (13)
31. lcx.ti,ab. (348)
32. pra.ti,ab. (1021)
33. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (139207)
34. immunochromatograph$.ti,ab. (259)
35. hplc.ti,ab. (20624)
36. high performance liquid chromatog$.ti,ab. (14671)
37. mycolic acid$.ti,ab. (269)
38. tuberculostearic acid.ti,ab,hw. (30)
39. ict tuberculosis.ti,ab. (5)
40. ict tb.ti,ab. (4)
41. MYCOBACTERIOPHAGES/ (57)
42. bacteriophage$.ti,ab. (3639)
43. BACTERIOPHAGES/ (1862)
44. ((phenotyp$ or phage$) adj (assay$ or test$)).ti,ab. (453)
45. spoligotyp$.ti,ab. (159)
46. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (34938)
47. (rapid adj2 diagnos$).ti,ab. (2321)
48. (rapid adj2 assay$).ti,ab. (1633)
49. rapid test$.ti,ab. (505)
50. rapid culture.ti,ab. (36)

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51. radiometric culture$.ti,ab. (24)
52. middlebrook.ti,ab. (96)
53. line probe assay$.ti,ab. (171)
54. In Situ Hybridization, Fluorescence/ (12060)
55. (fluoresc$ adj3 hybrid$).ti,ab. (8957)
56. bact.ti,ab. (148)
57. bact?alert.ti,ab. (2)
58. bact alert.ti,ab. (90)
59. bactec.ti,ab. (451)
60. septi?che?k.ti,ab. (1)
61. septi che?k.ti,ab. (26)
62. myco.ti,ab. (63)
63. mycobacteri$ growth indicator tube.ti,ab. (71)
64. mgit.ti,ab. (109)
65. accu?probe.ti,ab. (61)
66. accu probe.ti,ab. (1)
67. inno.ti,ab. (133)
68. lipa.ti,ab. (235)
69. imx.ti,ab. (210)
70. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (19796)
71. Serologic Tests/ (2685)
72. ((serolog$ or antibod$ or antigen$) adj test$).ti,ab. (5560)
73. ((antibod$ or antigen$) adj diagnos$).ti,ab. (570)
74. (antigen$ adj mycobacteri$).ti,ab. (189)
75. enzyme immunoassay$.ti,ab. (4788)
76. enzyme linked immunosorbent assay$.ti,ab. (13192)
77. eia.ti,ab. (2091)
78. elisa.ti,ab. (23468)
79. elispot.ti,ab. (675)
80. enzyme linked immunospot.ti,ab. (328)
81. IMMUNOASSAY/ (3455)
82. immunozym.ti,ab. (5)
83. pathozyme$.ti,ab. (6)
84. quanti?feron.ti,ab. (8)
85. ((ifn or interferon or tnf) adj (assay$ or test$)).ti,ab. (70)
86. Adenosine Deaminase/ (972)
87. adenosine de?aminase.ti,ab. (1090)
88. 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 (47423)
89. 33 or 46 or 70 or 88 (224957)
90. exp TUBERCULOSIS/ (17012)
91. tubercul$.ti,ab,hw. (24109)
92. 90 or 91 (24271)
93. 89 and 92 (3510)
94. roc.ti,ab. (2954)
95. sroc.ti,ab. (12)
96. accuracy.ti,ab. (35524)
97. false negativ$.ti,ab. (5134)
98. false positiv$.ti,ab. (8023)
99. predictive value$.ti,ab. (13983)
100. specificit$.ti,ab. (68110)
101. sensitivit$.ti,ab. (99495)
102. receiver operat$ characteristic$.ti,ab. (4120)
103. (receiver operat$ adj2 curve).ti,ab. (1278)
104. roc curve$.ti,ab. (1863)
105. exp "Sensitivity and Specificity"/ (102101)
106. di.fs. (348693)
107. diagnos$.ti,ab,hw. (344534)
108. 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 (695971)
109. 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 107 (531299)
110. 93 and 108 (2133)
111. 93 and 109 (1956)
112. limit 111 to yr=2002-2003 (364)
113. limit 110 to yr=2002-2003 (386)
114. from 112 keep 1-200 (200)
115. from 114 keep 1 (1)

Appendix 2

Checklist for study inclusion in the TB review

Study author: _____ Year: _____ RefID: _____

Test evaluated:#

	Include	**Exclude**
Population	Active tuberculosis ☐ Latent tuberculosis ☐ 'Per patient data' ☐	Other myco infection ☐ Other disease ☐ 'Per specimen' data only ☐ 'Spiked' specimens only ☐
Index test	Fully automated liquid culture ☐ Direct detection in clinical specimen ☐ Serological tests ☐ Cell-mediated immune response tests ☐	Microscopy ☐ Traditional culture ☐ Detection in culture ☐
Reference test*	Culture ± smear ☐ High clin susp ± tment response ☐ Clinical suspicion ☐ Other reference test ☐	No reference test ☐
Study design*	Cohort ☐ Case-control ☐	'Design-free' ☐
Outcomes*	Accuracy ☐ Diagnostic thinking, pt mgmt or outcomes ☐ Other relevant ☐	Technical efficacy ☐
Data*	Sufficient for 2 × 2 table ☐	Insufficient data ☐
Other reason for exclusion:		

If paper does not evaluate a test but provides useful background information or economics data then write 'Background' or 'Economics' here.

* Relevant for active TB only. All studies evaluating the clinical application of a test to detect latent TB infection should be included.

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Appendix 3

Quality assessment criteria used

QUADAS tool (Whiting and colleagues, 2004[51])

Item	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice?			
2. Were selection criteria clearly described?			
3. Is the reference standard likely to classify the target condition correctly?			
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?			
5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?			
6. Did patients receive the same reference standard regardless of the index test result?			
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
8a. Was the execution of the index test described in sufficient detail to permit replication of the test?			
8b. Was the execution of the reference standard described in sufficient detail to permit its replication?			
9a. Were the index test results interpreted without knowledge of the results of the reference standard?			
9b. Were the reference standard results interpreted without knowledge of the results of the index test?			
10. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
11. Were uninterpretable/intermediate test results reported?			
12. Were withdrawals from the study explained?			

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Appendix 4

Data extraction form

TB Database Study

StudyId: 93 Study Ref: Author: Year: DataDoubleCheck

Journal: Volume: Page:

GENERAL

TB Active/Latent:

If TB Active:

TB Active Note:

Geographical Setting:

Institute Type:

Pop Description:

PARTICIPANTS

Adults/Children:

Inpatient/Outpatient:

HIV Status:

TB Suspicion:

Pop Group Note

TB Suspect Why?

Were patient characteristics reported:

Basic Characteristics

Age Mean: % Male: % Ethnic Groups:

Age Median: % Inpatient:

Age Range: % BCG:

Age Other: % Foreign: % HIV Positive:

Other Characteristics - Comorbidities

1:

2:

3:

Other Characteristics - Symptom

1:

2:

3:

Notes:

Sub Group Characteristics:

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TB Database Study

StudyId: 93 Study Ref: Author: Year: ☐ DataDoubleCheck

Journal: Volume: Page:

DESIGN

Cohort/Case Control:

Sample Size:

No Patient Excluded:

Reasons for exclusion of any participants:

Recruitment:

Recruitment Note:

Prospective/ Retro:

Data Collection Note:

☐ Case Control Same Pop

Case Control Note:

Design Note:

Details of Clinical Sample Collection

☐ BAL	☐ Joint Aspirate	☐ Pleural Fluid
☐ Blood	☐ Lymph Biopsy	☐ Sputum
☐ CSF	☐ Paraffin	☐ Urine
☐ Gastric Aspirate	☐ Peritoneal Fluid	

Other sample:

Sample CollectionNote:

Number of Eligible Tests:

TB Database Study

StudyId: 93 Study Ref: Author: Year: ☐ DataDoubleCheck

Journal: Volume: Page:

REFERENCE TEST

☐ Smear ☐ Other Rapid Culture Post-hoc Categorisation:

☐ Culture ☐ Histology

☐ Clinical ☐ Response to Anti-TB Therapy

☐ Microbiology+Clinical Anti-TB F'up Period:

Other Ref Test:

☐ Were all patients followed up to determine final diagnosis?

Follow-up Note:

Notes on Ref Test:

Discrepant Results Reanalysis:

Further Details:

How were Indeterminate Results handled:

Further Details.

No Observers: Observer Kappa:

Disagreement Resolution:

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TB Database Study

StudyId: 93 Study Ref: Author: Year: ☐ DataDoubleCheck
Journal: Volume: Page:

INDEX TESTS

Test Group: Molecular amplification In-house/Other Test Name:
Test Name:
Serodiagnostic Antigen:
Cutoff Values Evaluated:
Cutoff Values Used:
Controls Used:
No Patients:
No of Samples Tested:
Notes on Test:

Test Group: Molecular amplification In-house/Other Test Name:
Test Name:
Serodiagnostic Antigen:
Cutoff Values Evaluated:
Cutoff Values Used:
Controls Used:
No Patients:
No of Samples Tested:
Notes on Test:

TB Database Study

StudyId: 93 Study Ref: Author: Year: ☐ DataDoubleCheck
Journal: Volume: Page:

COMPARISIONS

Test 1: Reference-Reference
Test 2: Molecular amplification-

Description of Patients: Enter "All patients" if all

No Discrepant Results: ☐ Results estimated from accuracy data

Pre-discrepant Analysis	**TEST 1**			**Post-discrepant Analysis**	**TEST 2**		
	Positive	Indeterminate	Negative		Positive	Indeterminate	Negative
TEST 2 Positive				**TEST 2** Positive			
Indeterminate				Indeterminate			
Negative				Negative			

Pre-Discrepant Notes: Post-Discrepant Notes:

Notes on Test Comparison:

%TB Prevalence: ☐ Sub-groups Defined

TB Database Study

StudyId: 93 Study Ref: Author: Year: ☐ DataDoubleCheck
Journal: Volume: Page:

QUALITY ASSESSMENT

Quality Assessment

1. Representative:
2. Selection Criteria:
3 Ref Test Appropriate:
4. Ref/Index Test Time Short:
5 Verification:
6. Verification with same Ref Test:
7. Ref/Index Tests Independent:
Note:
8a. Index Test Reproducible:
8b. Ref Test Reproducible:
9a. Index Test Blind:
9b. Ref Test Blind:
10. Data Same As In Practice:
11. All Test Results Reported:
12. Withdraw Explained:

Other relevant comments on the study

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Appendix 5

Moses and colleagues' method[187] for summary ROC analysis

Heterogeneity in DORs at different thresholds arises when the diseased and non-diseased groups differ in both the average value of the underlying diagnostic marker and also in the variance of the values. For example, diseased patients may have higher values of a diagnostic marker than non-diseased patients, but also the values of diseased people may be more variable than the values of non-diseased people. Where this is the case, dichotomising the diagnostic marker scale at different points will yield different DORs. The ORs at higher cut-points will be higher than those at lower cut-points. When the points are plotted as a ROC curve, the curve will not be symmetrical about the sensitivity = specificity line. The values of sensitivity at high values of specificity will be higher than the values of specificity at correspondingly high values of sensitivity.

In the equations and figures which follow, the logarithm of the DOR is denoted by D and the logarithm of the measure of threshold by S. D and S can be calculated using any of the equivalent equations:

$$S = \ln\left[\frac{TPR}{(1-TPR)} \times \frac{FPR}{(1-FPR)}\right] = \text{logit}(TPR) + \text{logit}(FPR)$$

$$D = \ln(\text{DOR}) = \ln\left[\frac{TPR}{(1-TPR)} \times \frac{(1-FPR)}{FPR}\right] = \ln\left(\frac{\text{LR +ve}}{\text{LR –ve}}\right) = \text{logit}(TPR) - \text{logit}(FPR)$$

where the logit indicates the logarithm of the odds, as used in logistic regression.

Moses and colleagues' method[187] first considers a plot of the logarithm of the DOR (D) against the measure of threshold (S) calculated for each of the studies. They then propose computing the best-fitting straight line through the points on the graph. If the equation of the fitted line is given by

$$D = a + bS$$

testing the significance of the estimate of the slope parameter b tests whether there is significant variation in diagnostic performance with threshold. If the line can be assumed horizontal (i.e. $b = 0$), the DOR does not change with threshold, and the method yields symmetrical ROC curves, similar to those obtained from directly pooling ORs as explained above. However, if there is a significant trend in the DOR with diagnostic threshold (i.e. $b \neq 0$), then the ROC curves are asymmetric, the summary ROC curve being calculated as

$$\text{sensitivity} = \frac{1}{1 + \dfrac{1}{e^{a/(1-b)} \times \left(\dfrac{1-\text{specificity}}{\text{specificity}}\right)^{(1+b)/(1-b)}}}$$

We obtained estimates of the parameters a and b from ordinary least-squares regression (i.e. weighting each study equally). Although it is possible to weight by inverse variance as it combines studies according to the precision of their estimates of the OR, this method is problematic when sensitivity or specificity (and hence ORs) is high, as the equation for the approximate variance of a log(DOR) ratio becomes biased when any of the counts of true positives, true negatives, false positives or false negatives is close to zero.[286]

Since the SROC curve and associated DOR can be difficult to interpret, the point of maximum sensitivity and specificity (Q^*) is often presented. Q^* is the value on the curve at which sensitivity is equal to specificity, and is the point where the threshold parameter, S, is equal to zero.[187] It is estimated using the intercept value a estimated from the regression equation [this is the log(DOR) when the threshold parameter is zero] and inserting it into the equation

$$Q^* = \sqrt{e^a}/(1 + \sqrt{e^a})$$

However, the value of Q^* may not be particularly useful when the range of estimates of sensitivity and specificity from the studies does not include values near the Q^* point. An alternative is to find

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the point on the curve which corresponds with the mean value of S.

The specificity at this point is obtained as:

$$\text{specificity} = 1 - \text{FPR} = \frac{1 - \exp\left(\frac{\text{mean } S - \text{mean } D}{2}\right)}{1 + \exp\left(\frac{\text{mean } S - \text{mean } D}{2}\right)}$$

and the sensitivity as

$$\text{sensitivity} = \frac{\exp\left[\text{mean } D\left(\frac{1 - \text{specificity}}{\text{specificity}}\right)\right]}{1 + \exp\left[\text{mean } D\left(\frac{1 - \text{specificity}}{\text{specificity}}\right)\right]}$$

Investigating heterogeneity in DOR with thresholds and other factors

If it is important to allow for variation of the DOR with threshold at the same time as investigating other sources of heterogeneity, then Moses and colleagues' model can be extended to allow for covariates.[287,288] A covariate, X, can be added to the regression equation for each potential effect modifier:

$$D = a + bS + c_1X_1$$

The exponential of each of these terms estimates multiplicative increases in DORs (relative ORs) for each factor. An underlying assumption of these models is that the shape of the summary ROC curves is not affected by covariates.

Appendix 6

Summary of previous systematic reviews of tests for detecting active tuberculosis infection

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Study	Inclusion criteria	Search strategy	Method of analysis	Results	Heterogeneity investigation
Sarmiento, 2003[188] PCR Pulmonary TB	*Participants/specimens* Smear-negative respiratory specimens *Tests* PCR *Reference test* Any *Study design* All designs ≥ 10 participants *Outcomes* Sensitivity and specificity could be estimated	MEDLINE BIOSIS English or Spanish Searched to July 2002	Sensitivity and specificity pooled using random effects methods; heterogeneity tested using Cochran's *Q* SROC analysis (referenced to Irwig, 1994)[244] used to produce DOR Heterogeneity investigated by pooling in strata and by adding covariates to regression model to produce RDORs that quantify the relative diagnostic accuracy of each stratum	50 data sets from 45 papers were included: • 16 per patient data in respiratory specimens • 5 per patient data in respiratory specimens • 29 per specimen data None of the studies met all 28 quality assessment criteria; fewer than 40% reported results by no. of patients, reported clinical characteristics of patients or used as a reference standard of combined culture and clinical criteria. Sensitivity and specificity ranged from 9 to 100% and from 25 to 100%, respectively Respiratory specimens ($n = 16$) Pooled: Se 72%; Sp 96%; DOR 51.1 (95% CI: 27.6 to 94.8) Gastric specimens ($n = 5$) Pooled: Se 50%; Sp 86% DOR: not reported	Studies of respiratory specimens that included bronchial specimens showed higher accuracy than studies that evaluated only sputum specimens (RDOR 2.46, $p = 0.04$), as did studies that did not report that tests were applied blindly (RDOR 8.81, $p < 0.01$). None of the other variables investigated showed a significant effect, including prospective/retrospective design, region, reference standard, smear staining method, purification method, target sequence, use of negative extraction controls, or controls to monitor inhibition, use of dUTP-UNG or detection method Relative to studies of gastric aspirates, studies of sputum only had higher accuracy (RDOR 3.7, $p = 0.07$), as did those with bronchial/sputum specimens (RDOR 7.1, $p = 0.01$) Authors concluded that PCR is not consistently accurate enough to be routinely recommended for the diagnosis of SPT
Pai, 2004[59] NAATs Pleural TB	*Participants/specimens* Pleural fluid specimens *Tests* NAAT *Reference test* Any *Study design* All designs ≥ 10 specimens *Outcomes* Sensitivity and specificity could be estimated	PubMED EMBASE Web of Science BIOSIS Cochrane Library LILACS Handsearching Reference lists Manufacturer and expert contacts English or Spanish Searched to January 2003	Sensitivity, specificity, LRs and DORs pooled using random effects methods; heterogeneity tested using χ^2 and Fisher's exact tests SROC analysis (Moses method) (1993)[187] Heterogeneity investigated by pooling in strata	40 studies included Commercial tests ($n = 14$): Se 0.62 (95% CI: 0.43 to 0.77), heterogeneity test $p < 0.01$ Sp 0.98 (95% CI: 0.96 to 0.98), $p = 0.12$ LR+: 25.4 (95% CI: 16.2 to 40.0) , $p = 0.46$ LR–: 0.40 (95% CI: 0.24 to 0.67), $p < 0.01$ SROC curve showed no trade-off between sensitivity and specificity In-house tests ($n = 26$): Both sensitivity and specificity estimates were significantly heterogeneous. Clinically meaningful summary estimates could not be determined for in-house tests	All commercial tests had consistently high specificity estimates; the sensitivity estimates, however, were heterogeneous across studies. Stratification by test reduced the heterogeneity to some degree Stratified analysis of the inhouse tests identified two potential explanatory factors for the heterogeneity: 1. use of case–control design DOR 68.3 (test for heterogeneity $p = 0.39$) compared with 28.7 ($p < 0.01$) for cross-sectional studies 2. target sequence IS6110 DOR 62.4 ($p = 0.42$) compared with 25.5 ($p < 0.01$) for other target sequences

continued

Study	Inclusion criteria	Search strategy	Method of analysis	Results	Heterogeneity investigation
					Authors suggest that commercial NAA tests may have a potential role in confirming (ruling in) tuberculous pleuritis. However, these tests have low and variable sensitivity and, therefore, may not be useful in excluding (ruling out) the disease
Pai, 2003[56] NAATs TB meningitis	*Participants/specimens* CSF specimens *Tests* NAATS *Reference test* Any *Study design* All designs ≥ 10 specimens *Outcomes* Sensitivity and specificity could be estimated	MEDLINE EMBASE Web of Science BIOSIS Cochrane Library LILACS Reference lists Manufacturer and expert contacts English or Spanish Searched to 2002	Sensitivity, specificity, LRs and DORs pooled using random effects methods; heterogeneity tested using the χ^2 test SROC analysis (Moses method) (1993)[187] Heterogeneity investigated by pooling in strata	49 studies were included Commercial tests (n = 14) Pooled: Se 0.56 (95% CI: 0.46 to 0.66) Sp 0.98 (0.97 to 0.99), LR+ 35.1 (19.0 to 64.6), LR– 0.44 (0.33 to 0.60), DOR 96.4 (42.8 to 217.3) In-house tests (n = 35): summary accuracy could not be established with confidence because of wide variability in test accuracy	Commercial tests: No significant heterogeneity identified ($p < 0.05$); exclusion of 2 studies with inadequate reference tests (clinical diagnosis only) made little difference to summary estimates In-house tests: all summary measures significantly heterogeneous, except for DOR (p = 0.28). Stratified analyses indicated that study design and blinded test interpretation had most effect on summary DOR • case–control (n = 19): 86.5 (95% CI: 39.3 to 190.2) • cross-sectional (n = 16): 43.3 (22.5 to 83.3) • blinded (n = 21): 46.9 (24.9 to 88.6) • non-blinded (n = 14): 82.3 (39.8 to 170.2) Authors conclude that commercial NAA tests show a potential role in confirming tuberculous meningitis diagnosis, although their overall low sensitivity precludes the use of these tests to rule out tuberculous meningitis with certainty

continued

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Study	Inclusion criteria	Search strategy	Method of analysis	Results	Heterogeneity investigation
Greco, 2003[86] ADA IFN-γ Pleural TB	*Participants/specimens* Pleural fluid specimens *Tests* ADA IFN-γ *Reference test* Any *Study design* All designs *Outcomes* Sensitivity and specificity could be estimated	MEDLINE Reference lists English language Searched 1978–2000	Cumulative sensitivity and specificity estimated by combining study results into a SROC (referenced Moses, 1993[187]). Four SROC curves constructed for each comparison: one using entire control group and one each for control groups restricted to those with exudative, malignant and parapneumonic pleural effusions, respectively. The *Q*-point (defined as intersection with diagonal line from top-left to bottom-right corner, or point where Se = Sp) used as global measure of test efficacy Heterogeneity of ORs tested using χ^2 test	31 on ADA, including 4738 patients 13 on IFN-γ, including 1189 patients SROC curves yielded a *Q*-point of 93% for ADA, 96% for IFN-γ Only 16/31 ADA studies and 5/13 IFN-γ studies considered to have used rigorous criteria to define TB pleurisy and described them in sufficient detail. Reference standards were not clearly described and limited demographic variables provided	SROC curves when control groups restricted to exudative effusions: 94.5% for ADA; 95.8% for IFN-γ SROC curves when control groups restricted to malignant effusions: 95.2% for ADA; 96% for IFN-γ SROC curves when control groups restricted to parapneumonic effusions: 96% for ADA; 94.2% for IFN-γ Significant heterogeneity amongst ORs found for both ADA and IFN-γ studies ($p < 0.05$). Heterogeneity remained when control groups were restricted and within subgroups identified by methodological analysis Authors conclude with the caveat that limitations in the design of the studies summarised may distort estimates of test performance, ADA and IFN-γ appear to be reasonably accurate at detecting TB pleurisy
Goto, 2003[189] ADA Pleural TB	*Participants/specimens* Pleural fluid specimens *Tests* ADA Criteria for positive test result had to be described *Reference test* Explicitly described *Study design* All designs *Outcomes* Sensitivity and specificity could be estimated	MEDLINE Cochrane Library Reference lists English only Searched 1966–9	SROC analysis (Moses, 1993[187]) unweighted least-squares regression Point of maximum sensitivity and specificity used as measure of test efficacy Multiple regression analysis used to investigate heterogeneity by adding covariates to regression model	40 studies included. The summary test performance: 92.2% Slope of unweighted regression line 0.535 (95% CI: 0.161 to 0.908) Intercept: 4.940 (95% CI: 4.368 to 5.513)	Studies including more pts with transudative effusions (≥20%) showed better test performance (β-coefficient = 1.477, $p = 0.01$), as did studies conducted in Europe (β-coefficient = 1.368, $p = 0.02$). Studies conducted in East Asia had a significantly worse performance compared with those in other regions (β-coefficient = 1.246, $p = 0.045$). Difference for other clinical variables reported not to reach statistical significance (results not given). Variables investigated included publication year, mean age, proportion of men, number of patients, cut-off, type of gold standard, prevalence of TB pleurisy, malignant disease, non-tuberculous infection, transudate and undiagnosed cases, study design, method measuring ADA and presence/absence of HIV-infected patients Authors conclude that test performance of ADA in tuberculous pleural effusion is reasonably good. Measurement of pleural ADA is therefore likely to be a useful diagnostic tool for tuberculous pleurisy

IFN, interferon; LR, likelihood ratio; Se, selectivity; Sp, specificity.

Appendix 7

NAAT evaluations in pulmonary TB – study details

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr.[p]
Commercial tests															
Abe, 1993[289]*	AMTD – Standard	s	100	24	0.24	135	0.91 (0.75 to 0.98) [29/32]	0.95 (0.89 to 0.98) [98/103]	189.47 (42.69 to 840.80)	R	C alone	?	?	?	?
	Smear positive			100	0.88	25	1.00 (0.85 to 1.00) [22/22]	0.67 (0.09 to 0.99) [2/3]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.11	92	0.70 (0.35 to 0.93) [7/10]	0.95 (0.88 to 0.99) [78/82]	45.50 (8.44 to 245.34)						
Abu-Amero, 2002[290]	Amplicor – Cobas	s	100	3	0.1	626	0.80 (0.68 to 0.89) [51/64]	1.00 (0.99 to 1.00) [562/562]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	?
Al Zahrani, 2000[83]*	AMTD – Standard	s	100	2	0.12	383	0.42 (0.29 to 0.56) [20/47]	1.00 (0.99 to 1.00) [336/336]	0.00 (0.00 to 0.00)	P	C + Clin + T + X	Y	P	Y	Y
	Amplicor – Manual	s	100	2	0.12	487	0.43 (0.28 to 0.58) [24/57]	1.00 (0.99 to 1.00) [430/430]	0.00 (0.00 to 0.00)	P	C + Clin + T + X	Y	P	Y	Y
Alcala, 2001[291]	AMTD – Standard	s	100	10	0.17	365	0.87 (0.76 to 0.94) [54/62]	0.88 (0.84 to 0.92) [267/303]	50.06 (22.05 to 113.67)	P	C + Clin	?	?	?	Y
Alonso, 1998[292]	LcX assay	m	65	3	0.07	213	0.87 (0.60 to 0.98) [13/15]	0.94 (0.90 to 0.97) [186/198]	100.75 (20.36 to 498.57)	L	C + Clin	?	?	?	?
Arimura, 1996[293]	Amplicor – Manual	s	100	7	0.34	76	0.73 (0.52 to 0.88) [19/26]	0.96 (0.86 to 1.00) [48/50]	65.14 (12.40 to 342.22)	?	C alone	?	?	?	Y
	Smear positive			100	1	5	1.00 (0.48 to 1.00) [5/5]	– (–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.3	71	0.67 (0.43 to 0.85) [14/21]	0.96 (0.86 to 1.00) [48/50]	48.00 (8.94 to 257.67)						
Bemer-Melchior, 2000[294]	Amplicor – Cobas	r	58	7	0.21	205	0.48 (0.32 to 0.63) [21/44]	1.00 (0.98 to 1.00) [161/161]	0.00 (0.00 to 0.00)	P	C + Clin	?	R	?	N
Bennedson, 1996[295]	Amplicor – Manual	r		8	0.11	3794	0.60 (0.55 to 0.65) [251/419]	0.99 (0.98 to 0.99) [3333/3375]	118.56 (82.58 to 170.22)	L	C alone	Y	?	?	?
Bergmann, 1996[296]	Amplicor – Manual	r	85	5	0.06	502	0.71 (0.52 to 0.86) [22/31]	0.99 (0.97 to 1.00) [465/471]	189.44 (61.93 to 579.48)	L	C alone	?	?	?	?
	Smear positive			100	0.68	25	0.94 (0.71 to 1.00) [16/17]	0.88 (0.47 to 1.00) [7/8]	112.00 (6.10 to 2,057.38)						
	Smear negative‡			0	0.03	481	0.43 (0.18 to 0.71) [6/14]	0.99 (0.98 to 1.00) [462/467]	69.30 (17.48 to 274.73)						
Bergmann, 1999[297]	AMTD – Enhanced	r		2	0.05	489	0.80 (0.59 to 0.93) [20/25]	0.99 (0.97 to 1.00) [458/464]	305.33 (85.88 to 1,085.60)	L	C + Clin	?	P	?	?

continued

Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
	Smear positive			100	0.63	16	1.00 (0.69 to 1.00) [10/10]	0.83 (0.36 to 1.00) [5/6]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.03	473	0.67 (0.38 to 0.88) [10/15]	0.99 (0.97 to 1.00) [453/458]	181.20 (45.18 to 726.75)						
Cartuyvels, 1996[298]	Amplicor – Manual	r	57	2	0.02	536	0.69 (0.39 to 0.91) [9/13]	0.97 (0.95 to 0.98) [508/523]	76.20 (21.08 to 275.40)	L	C alone	?	?	?	N
Catanzaro, 2000[299]	AMTD – Enhanced	s	100	19	0.21	338	0.83 (0.73 to 0.91) [60/72]	0.97 (0.95 to 0.99) [259/266]	185.00 (69.88 to 489.75)	P	C + Clin	Y	P	N	Y
	Low suspicion of TB				0.05	224	0.83 (0.52 to 0.98) [10/12]	0.97 (0.93 to 0.99) [205/212]	146.43 (26.89 to 797.42)						
	Intermediate suspicion of TB				0.29	68	0.75 (0.51 to 0.91) [15/20]	1.00 (0.93 to 1.00) [48/48]	0.00 (0.00 to 0.00)						
	High suspicion of TB				0.87	46	0.88 (0.73 to 0.96) [35/40]	1.00 (0.54 to 1.00) [6/6]	0.00 (0.00 to 0.00)						
Cavusoglu, 2002[198]	AMTD – Standard	s	100	51	0.52	63	0.91 (0.76 to 0.98) [30/33]	0.93 (0.78 to 0.99) [28/30]	140.00 (21.75 to 901.01)	L	C + Clin + T + X	?	R	?	?
Chedore, 1999[191]	AMTD – Enhanced	r		24	0.31	616	1.00 (0.98 to 1.00) [194/194]	0.98 (0.96 to 0.99) [414/422]	0.00 (0.00 to 0.00)	L	C + Clin	?	P	?	N
	Smear positive‡			100	0.36	517	1.00 (0.98 to 1.00) [188/188]	0.98 (0.96 to 0.99) [323/329]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.06	99	1.00 (0.54 to 1.00) [6/6]	0.98 (0.92 to 1.00) [91/93]	0.00 (0.00 to 0.00)						
Chin, 1995[300]	Amplicor – Manual	r	94	3	0.09	227	0.43 (0.22 to 0.66) [9/21]	0.99 (0.97 to 1.00) [204/206]	76.50 (14.85 to 394.01)	P	C + T + X	?	?	Y	Y
Cohen, 1998[301]*	Amplicor – Manual	s	100	14	0.32	85	0.74 (0.54 to 0.89) [20/27]	0.93 (0.83 to 0.98) [54/58]	38.57 (10.19 to 146.03)	P	C alone	Y	P	Y	N
	Smear positive			100	1.00	12	1.00 (0.74 to 1.00) [12/12]	– (–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.21	73	0.53 (0.27 to 0.79) [8/15]	0.93 (0.83 to 0.98) [54/58]	15.43 (3.67 to 64.82)						
D'Amato, 1995[302]	Amplicor – Manual	r		4	0.08	365	0.61 (0.41 to 0.78) [17/28]	0.99 (0.97 to 1.00) [333/337]	128.66 (37.09 to 446.31)	P	C + Clin + X	?	?	?	Y
Denis, 1998[303]	LcX assay			9	0.08	208	0.82 (0.57 to 0.96) [14/17]	0.98 (0.95 to 1.00) [188/191]	292.44 (53.96 to 1,584.80)	P	C + Clin + T	?	?	?	?

continued

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr.[p]
Devallois, 1996[304]	Amplicor – Manual	r		8	0.05	370	1.00 (0.83 to 1.00) [20/20]	1.00 (0.99 to 1.00) [350/350]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	?
dos Anjos Filho, 2002[305]	Amplicor – Manual‡	m	88	0	0.44	98	0.79 (0.64 to 0.90) [34/43]	0.82 (0.69 to 0.91) [45/55]	17.00 (6.22 to 46.43)	P	C alone	?	?	?	Y
Ehlers, 1996[306]	AMTD – Standard	r	41	7	0.18	261	0.83 (0.69 to 0.92) [39/47]	0.95 (0.91 to 0.97) [203/214]	89.97 (34.00 to 238.05)	L	C alone	?	?	?	Y
	Gastric aspirate only	g			0.19	59	0.73 (0.39 to 0.94) [8/11]	1.00 (0.93 to 1.00) [48/48]	0.00 (0.00 to 0.00)						
Eing, 1998[307]*	Amplicor – Cobas	m	49	2	0.03	833	0.89 (0.72 to 0.98) [25/28]	1.00 (0.99 to 1.00) [801/805]	1,668.75 (354.54 to 7,854.39)	L	C alone	?	?	?	Y
Gleason Beavis, 1995[308]	Amplicor – Manual	s	100	19	0.06	270	0.73 (0.45 to 0.92) [11/15]	0.98 (0.95 to 0.99) [249/255]	114.13 (28.09 to 463.68)	P	C alone	Y	P	?	?
Gomez-Pastrana, 2001[309]	Amplicor – Manual	B/g	0	3	0.28	88	0.44 (0.24 to 0.65) [11/25]	0.94 (0.85 to 0.98) [59/63]	11.59 (3.21 to 41.86)	R	C + Clin + T + X	Y	P	Y	Y
Hoffner, 1996 (a)[310]	AMTD – Standard	s	100	14	0.3	274	0.85 (0.76 to 0.92) [70/82]	0.86 (0.81 to 0.91) [166/192]	37.24 (17.79 to 77.97)	R	C alone	Y	?	Y	Y
Hoffner, 1996 (b)[311]	AMTD – Standard	r	71	12	0.06	309	0.88 (0.64 to 0.99) [15/17]	0.99 (0.98 to 1.00) [290/292]	1,087.50 (143.18 to 8,260.05)	P	C alone	?	P	?	Y
Kambashi, 2001[312]*	AMTD – Standard	s	100	15	0.78	92	0.88 (0.78 to 0.94) [63/72]	0.85 (0.62 to 0.97) [17/20]	39.67 (9.66 to 162.83)	P	C + Clin + T	Y	?	?	Y
Kang, 2002[313]	Amplicor – Manual	la	0		0.38	45	0.65 (0.38 to 0.86) [11/17]	1.00 (0.88 to 1.00) [28/28]	0.00 (0.00 to 0.00)	R	C + Clin + T + H	?	R	?	N
La Rocco, 1994[314]	AMTD – Standard	s	100	21	0.24	246	0.95 (0.86 to 0.99) [56/59]	0.98 (0.95 to 1.00) [184/187]	1,144.89 (224.76 to 5,831.98)	L	C + Clin	?	?	?	?
Lim, 2000[315]	Amplicor – Cobas‡	m	87	0	0.06	441	0.44 (0.24 to 0.65) [11/25]	0.99 (0.97 to 1.00) [411/416]	64.59 (19.77 to 210.98)	P	C + Clin + T + X	Y	P	Y	Y
	Low pretest probability				0.01	334	0.33 (0.01 to 0.91) [1/3]	0.99 (0.97 to 1.00) [328/331]	54.67 (3.84, 778.46)						
	Intermediate pretest probability				0.03	87	0.33 (0.01 to 0.91) [1/3]	0.98 (0.92 to 1.00) [82/84]	20.50 (1.27 to 330.54)						
	High pretest probability				0.95	20	0.47 (0.24 to 0.71) [9/19]	1.00 (0.03 to 1.00) [1/1]	0.00 (0.00 to 0.00)						
Lim, 2002[316]	Amplicor – Cobas	r		6	0.16	128	0.75 (0.51 to 0.91) [15/20]	0.99 (0.95 to 1.00) [107/108]	321.00 (35.07 to 2,937.96)	P	C + Clin + T + X	?	P	?	Y

continued

Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
	Smear positive			100	0.8	10	1.00 (0.63 to 1.00) [8/8]	1.00 (0.16 to 1.00) [2/2]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.1	118	0.58 (0.28 to 0.85) [7/12]	0.99 (0.95 to 1.00) [105/106]	147.00 (15.05 to 1,436.20)						
Lindbrathen, 1997[317]	LcX assay†	m	96	19	0.24	482	0.90 (0.83 to 0.95) [106/118]	0.98 (0.96 to 0.99) [356/364]	393.08 (156.57 to 986.88)	L	C alone	?	?	?	?
	Smear positive			100	0.95	93	0.97 (0.90 to 0.99) [85/88]	0.20 (0.01 to 0.72) [1/5]	7.08 (0.60 to 84.20)						
	Smear negative‡			0	0.08	389	0.70 (0.51 to 0.85) [21/30]	0.99 (0.97 to 1.00) [355/359]	207.08 (58.89 to 728.14)						
Lockman, 2003[193]	Amplicor – Manual	s	100	52	0.66	112	0.68 (0.56 to 0.78) [50/74]	0.92 (0.79 to 0.98) [35/38]	24.31 (6.79 to 87.04)	R	C alone	?	P	?	Y
	Smear positive‡			100	0.79	58	0.83 (0.69 to 0.92) [38/46]	0.83 (0.52 to 0.98) [10/12]	23.75 (4.34 to 129.86)						
	Smear negative‡			0	0.3	53	0.63 (0.35 to 0.85) [10/16]	0.92 (0.78 to 0.98) [34/37]	18.89 (3.99 to 89.44)						
Middleton, 2003[318]	AMTD – Standard	r	56	23	0.12	773				P	C alone	?	?	?	Y
	Cut-off: 71,000						0.83 (0.73 to 0.90) [76/92]	0.91 (0.89 to 0.93) [620/681]	48.28 (26.50 to 87.96)						
	Cut-off: 7,300,000						0.90 (0.82 to 0.95) [83/92]	0.85 (0.82 to 0.88) [579/681]	52.35 (25.50 to 107.48)						
	Cut-off: 30,000						0.93 (0.86 to 0.98) [86/92]	0.66 (0.62 to 0.69) [449/681]	27.74 (11.94 to 64.43)						
Mitarai, 2001 (a)[319]	Amplicor – Manual	g	0	13	0.58	116	0.37 (0.26 to 0.50) [25/67]	0.98 (0.89 to 1.00) [48/49]	28.57 (3.71 to 220.01)	R	C + Clin + T + H + X	?	?	?	Y
Mitarai, 2001 (b)[192]	Amplicor – Manual	s	100	23	0.41	780	0.62 (0.56 to 0.67) [197/319]	0.97 (0.95 to 0.99) [449/461]	60.42 (32.63 to 111.89)	R	C + Clin + T + H + X	?	?	?	Y
	Smear positive‡			100	0.77	179	0.94 (0.89 to 0.97) [130/138]	1.00 (0.91 to 1.00) [41/41]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.3	601	0.37 (0.30 to 0.44) [67/181]	0.97 (0.95 to 0.99) [408/420]	19.98 (10.45 to 38.22)						
Neu, 1999[320]	Amplicor – Manual	g	0	0	0.07	28	1.00 (0.16 to 1.00) [2/2]	0.96 (0.80 to 1.00) [25/26]	0.00 (0.00 to 0.00)	P	C alone	?	P	?	Y

continued

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr.[p]
Osumi, 1995[321]	AMTD – Standard	B	0		0.09	22	0.00 (0.00 to 0.84) [0/2]	0.85 (0.62 to 0.97) [17/20]	0.00 (0.00 to 0.00)	P	C + Clin	Y	?	?	?
Piersimoni, 1998[322]	AMTD – Standard	r	40	6	0.08	219	0.72 (0.47 to 0.90) [13/18]	0.86 (0.80 to 0.90) [172/201]	15.42 (5.11 to 46.51)	P	C + Clin	?	?	?	?
Piersimoni, 2002[203]	AMTD – Enhanced	m	52	19	0.21	402	0.85 (0.75 to 0.92) [72/85]	0.99 (0.98 to 1.00) [315/317]	872.31 (192.59 to 3,951.00)	L	C + Clin	?	R	?	Y
Reischl, 1998[323]	Amplicor – Cobas	m	18	7	0.13	807	0.79 (0.70 to 0.87) [81/102]	0.98 (0.97 to 0.99) [691/705]	190.38 (93.19 to 388.92)	L	C + Clin	?	P	?	Y
Sato, 1998[324]	Amplicor – Manual	s	100	28	0.51	72	0.86 (0.71 to 0.95) [32/37]	0.63 (0.45 to 0.79) [22/35]	10.83 (3.38 to 34.74)	P	C alone	?	?	?	N
	Smear positive			100	0.9	20	0.79 (0.54 to 0.94) [17/18]	1.00 (0.16 to 1.00) [2/2]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.37	52	0.84 (0.68 to 0.94) [15/19]	0.67 (0.48 to 0.82) [22/33]	7.50 (2.01 to 28.05)						
	AMTD – Standard	s	100	28	0.51	72	0.94 (0.73 to 1.00) [31/37]	0.71 (0.54 to 0.85) [25/35]	12.92 (4.13 to 40.43)						
	Smear positive			100	0.9	20	0.94 (0.73 to 1.00) [17/18]	1.00 (0.16 to 1.00) [2/2]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.37	52	0.74 (0.49 to 0.91) [14/19]	0.76 (0.58 to 0.89) [25/33]	8.75 (2.40 to 31.94)						
SeThoe, 1997[325]*	Amplicor – Manual†	m	85	12	0.17	179	0.84 (0.66 to 0.95) [26/31]	0.96 (0.91 to 0.98) [142/148]	123.07 (34.97 to 433.14)	P	C alone	Y	?	Y	Y
Shim, 2002[326]	Amplicor – Cobas	B	0	4	0.16	331	0.50 (0.36 to 0.64) [26/52]	0.99 (0.97 to 1.00) [276/279]	92.00 (26.07 to 324.64)	R	C + Clin + T + H + X	?	P	Y	?
Smith, 1999[327]	AMTD – Enhanced	r	84	8	0.06	151	1.00 (0.66 to 1.00) [9/9]	0.98 (0.94 to 1.00) [139/142]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	Y
	AMTD – Standard	r	84	8	0.06	151	1.00 (0.66 to 1.00) [9/9]	1.00 (0.97 to 1.00) [142/142]	0.00 (0.00 to 0.00)						
Viinanen, 2000[328]	LcX assay	s	100	19	0.26	53	0.93 (0.66 to 1.00) [13/14]	0.95 (0.83 to 0.99) [37/39]	240.50 (20.09 to 2,878.44)	P	C + Clin	Y	P	N	Y
Vuorinen, 1995[329]	Amplicor – Manual	m	52	9	0.1	256	0.85 (0.65 to 0.96) [22/26]	0.99 (0.97 to 1.00) [228/230]	627.00 (108.64 to 3,618.62)	P	C alone	?	?	?	?
	AMTD – Standard	m	52	9	0.1	256	0.85 (0.65 to 0.96) [22/26]	0.99 (0.96 to 1.00) [227/230]	416.17 (87.48 to 1,979.75)						

continued

Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
Wang, 1999[330]	Amplicor – Cobas	r	97	29	0.31	230	0.96 (0.88 to 0.99) [69/72]	0.96 (0.92 to 0.99) [152/158]	582.67 (141.57 to 2,398.14)	L	C alone	?	?	?	?
	Smear positive			100	1	66	0.83 (0.36 to 1.00) [64/66]	– (–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.04	162	0.99 (0.93 to 1.00) [5/6]	1.00 (0.98 to 1.00) [156/156]	0.00 (0.00 to 0.00)						
	AMTD – Standard	r	97	29	0.31	230	0.97 (0.89 to 1.00) [71/72]	0.99 (0.96 to 1.00) [156/158]	5,538.00 (494.00 to 62,083.29)	L	C alone	?	?	?	?
	Smear positive			29	1	66	1.00 (0.95 to 1.00) [66/66]	– (–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative			29	0.04	162	0.83 (0.36 to 1.00) [5/6]	0.99 (0.96 to 1.00) [155/156]	775.00 (42.16 to 14,246.58)						
	LcX assay	r	97	29	0.31	230	1.00 (0.95 to 1.00) [72/72]	0.96 (0.91 to 0.98) [151/158]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	?
	Smear positive			100	1	66	1.00 (0.95 to 1.00) [66/66]	– (–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.04	162	1.00 (0.54 to 1.00) [6/6]	0.99 (0.96 to 1.00) [155/156]	0.00 (0.00 to 0.00)						
Yam, 1998[331]*	Amplicor – Cobas	r		5	0.11	385	0.86 (0.73 to 0.95) [38/44]	1.00 (0.99 to 1.00) [341/341]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Yee, 2002[332]	Amplicor – Cobas	r		9	0.18	85	0.80 (0.52 to 0.96) [12/15]	0.99 (0.92 to 1.00) [69/70]	276.00 (26.46 to 2,878.92)	R	C alone	?	R	?	Y
	Smear negative			9	0.09	77	0.71 (0.29 to 0.96) [5/7]	0.99 (0.92 to 1.00) [69/70]	172.50 (13.25 to 2,245.75)						
Zambardi, 1995[333]	Amplicis Myco B	r	79		0.35	206	0.92 (0.83 to 0.97) [66/72]	0.85 (0.78 to 0.91) [114/134]	62.70 (23.97 to 163.98)	P	C + Clin	Y	?	Y	?
	Sputum only	s	100		0.43	162	0.91 (0.82 to 0.97) [63/69]	0.90 (0.82 to 0.95) [84/93]	98.00 (33.17 to 289.57)						
In-house tests															
Abe, 1993[289]*	IS986	s	100	24	0.24	135	0.81 (0.64 to 0.93) [26/32]	0.94 (0.88 to 0.98) [97/103]	70.06 (20.86 to 235.30)	R	C alone	?	?	?	?
	Smear positive			100	0.88	25	0.95 (0.77 to 1.00) [21/22]	0.67 (0.09 to 0.99) [2/3]	42.00 (1.84 to 959.18)						
	Smear negative‡			0	0.11	92	0.50 (0.19 to 0.81) [5/10]	0.94 (0.86 to 0.98) [77/82]	15.40 (3.32 to 71.44)						

continued

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
Afghani, 1996[334]	IS6110	m	57	18	0.24	82				P	C alone	?	?	?	N
	Chemical DNA extraction						0.60 (0.36 to 0.81) [12/20]	0.92 (0.82 to 0.97) [57/62]	17.10 (4.76 to 61.45)						
	Simple boiling						0.85 (0.62 to 0.97) [17/20]	0.98 (0.91 to 1.00) [61/62]	345.67 (33.76 to 3,539.18)						
Albay, 2003[335]	IS6110	s	100	19	0.33	192	0.84 (0.73 to 0.92) [54/64]	0.98 (0.94 to 1.00) [126/128]	340.20 (72.11 to 1,604.96)	P	C alone	?	?	?	Y
	Smear negative			0	0.17	155	0.59 (0.39 to 0.78) [16/27]	0.98 (0.93 to 1.00) [125/128]	60.61 (15.27 to 240.57)						
Alfonso, 2002[336]	MTP40 and α-antigen	m	21	45	0.34	113	0.74 (0.57 to 0.87) [28/38]	1.00 (0.95 to 1.00) [75/75]	0.00 (0.00 to 0.00)	P	C + Clin + T	?	R	?	Y
Al Ghamdi, 1998[337]	IS6110	B	0	0	0.43	14	1.00 (0.54 to 1.00) [6/6]	0.88 (0.47 to 1.00) [7/8]	0.00 (0.00 to 0.00)	R	Clin + T	Y	P	Y	Y
Amer, 2000[190]	IS6110	r	73	34	0.65	80	0.98 (0.90 to 1.00) [51/52]	0.86 (0.67 to 0.96) [24/28]	306.00 (32.43 to 2,887.07)	P	C alone	?	?	?	Y
	Smear positive			100	0.96	27	0.96 (0.80 to 1.00) [25/26]	0.00 (0.00 to 0.97) [0/1]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.49	53	1.00 (0.87 to 1.00) [26/26]	0.89 (0.71 to 0.98) [24/27]	0.00 (0.00 to 0.00)						
Bahrmand, 1996[338]	MPB70	r	68	35	0.61	271	0.98 (0.94 to 0.99) [160/164]	0.50 (0.40 to 0.59) [53/107]	39.26 (13.57 to 113.55)	R	C alone	?	?	?	Y
	Smear positive			100	0.91	94	0.99 (0.94 to 1.00) [85/86]	0.13 (0.00 to 0.53) [1/8]	12.14 (0.68 to 215.67)						
	Smear negative‡			0	0.44	177	0.96 (0.89 to 0.99) [75/78]	0.53 (0.42 to 0.63) [52/99]	27.66 (8.17 to 93.65)						
Beige, 1995[339]	2.4-kb DNA	s	100	27	0.48	103	0.84 (0.70 to 0.93) [41/49]	0.91 (0.80 to 0.97) [49/54]	50.23 (15.25 to 165.41)	P	C + Clin + H + T	?	P	Y	Y
	65-kDa	s	100	27	0.48	103	0.76 (0.61 to 0.87) [37/49]	0.76 (0.62 to 0.87) [41/54]	9.72 (3.95 to 23.96)						
	MPB64	s	100	27	0.48	103	0.80 (0.66 to 0.90) [39/49]	0.74 (0.60 to 0.85) [40/54]	11.14 (4.42 to 28.06)						
	2.4-kb DNA and MBP64	s	100	27	0.48	103	0.98 (0.89 to 1.00) [48/49]	0.70 (0.56 to 0.82) [38/54]	114.00 (14.46 to 898.62)						
	2.4-kb DNA, MBP64 and 65-kDa	s	100	27	0.48	103	0.98 (0.89 to 1.00) [48/49]	0.70 (0.56 to 0.82) [38/54]	114.00 (14.46 to 898.62)						

continued

Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
Brisson-Noel, 1989[219]	65-kDa	r	49	29	0.37	35	1.00 (0.75 to 1.00) [13/13]	0.91 (0.71 to 0.99) [20/22]	0.00 (0.00 to 0.00)	?	C + Clin + T	?	?	?	Y
	Gastric aspirate only	g	0		0.23	13	1.00 (0.29 to 1.00) [3/3]	0.80 (0.44 to 0.97) [8/10]	0.00 (0.00 to 0.00)						
	Sputum only	s	100		0.35	17	1.00 (0.54 to 1.00) [6/6]	1.00 (0.72 to 1.00) [11/11]	0.00 (0.00 to 0.00)						
Ceyhan, 1996[222]	IS6110	s	100		0.64	22	0.21 (0.05 to 0.51) [3/14]	1.00 (0.63 to 1.00) [8/8]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	Y
Choi, 1996[340]	MTB10 and MTB11	s	100	7	0.08	217	0.94 (0.71 to 1.00) [16/17]	0.94 (0.90 to 0.97) [189/200]	274.91 (33.34 to 2,267.07)	P	C alone	Y	?	?	Y
Cohen, 1998[301]*	IS6110	s	100	14	0.32	85	0.85 (0.66 to 0.96) [23/27]	0.88 (0.77 to 0.95) [51/58]	41.89 (11.15 to 157.37)	P	C alone	Y	P	Y	N
	Smear positive			100	1.00	12	1.00 (0.74 to 1.00) [12/12]	–(–) [0/0]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.21	73	0.73 (0.45 to 0.92) [11/15]	0.88 (0.77 to 0.95) [51/58]	20.04 (4.99 to 80.49)						
Condos, 1996[175]	IS6110	sr		16	0.47	88	0.95 (0.83 to 0.99) [39/41]	0.89 (0.77 to 0.96) [42/47]	163.80 (30.02 to 893.76)	P	C + Clin + T	Y	P	Y	Y
Delacourt, 1995[341]	IS6110	m		2	0.35	68	0.83 (0.63 to 0.95) [20/24]	0.61 (0.45 to 0.76) [27/44]	7.94 (2.31 to 27.26)	P	C + Clin + T	Y	?	Y	Y
Eing, 1998[307]*	IS6110	m	49	2	0.03	833	1.00 (0.88 to 1.00) [28/28]	1.00 (0.99 to 1.00) [803/805]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Eisenach, 1991[342]	IS6110	s	100	50	0.58	162	0.55 (0.45 to 0.66) [52/94]	0.99 (0.92 to 1.00) [67/68]	82.95 (11.05 to 622.83)	L	C + Clin + T	Y	R	Y	N
Fauville-Dufaux, 1992[343]	Ag85	m	49	28	0.4	206	0.90 (0.82 to 0.96) [74/82]	0.94 (0.89 to 0.98) [117/124]	154.61 (53.81 to 444.18)	L	C alone	Y	?	Y	?
Ginesu, 1998[344]	IS6110	m	95	19	0.28	125	0.91 (0.77 to 0.98) [32/35]	0.88 (0.79 to 0.94) [79/90]	76.61 (20.04 to 292.87)	P	C + Clin	?	?	?	Y
Gomez-Pastrana, 1999[345]	65-kDa	B/g	0	4	0.32	117	0.57 (0.39 to 0.73) [21/37]	0.94 (0.86 to 0.98) [75/80]	19.69 (6.46 to 60.02)	R	C + Clin + T	Y	P	Y	Y
Gori, 1996[346]	MTP40	r		28	0.27	124	0.97 (0.84 to 1.00) [32/33]	0.86 (0.77 to 0.92) [78/91]	192.00 (24.10 to 1,529.48)	P	C alone	?	?	?	Y
Herrera, 1996[347]	IS6110	m	77	42	0.57	162	0.87 (0.78 to 0.93) [80/92]	0.93 (0.84 to 0.98) [65/70]	86.67 (29.04 to 258.65)	P	C + Clin + T	?	?	?	?

continued

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr.[p]
	MTP40	m	77	42	0.57	162	0.83 (0.73 to 0.90) [76/92]	1.00 (0.95 to 1.00) [70/70]	0.00 (0.00 to 0.00)						
Kambashi, 2001[312*]	IS6110	s	100	15	0.78	92	0.71 (0.59 to 0.81) [51/72]	0.90 (0.68 to 0.99) [18/20]	21.86 (4.65 to 102.65)	P	Clin + T	Y	?	?	Y
Kocagoz, 1993[348]	IS6110	s	100	33	0.49	78	0.87 (0.72 to 0.96) [33/38]	0.93 (0.80 to 0.98) [37/40]	81.40 (18.05 to 367.13)	R	C + Clin + T	?	?	?	N
Kolk, 1992[349]	IS986	r		51	0.53	53	1.00 (0.88 to 1.00) [28/28]	0.96 (0.80 to 1.00) [24/25]	0.00 (0.00 to 0.00)	L	C alone	Y	?	Y	Y
	Sputum only	s	100	0	0.58	48	1.00 (0.88 to 1.00) [28/28]	0.95 (0.75 to 1.00) [19/20]	0.00 (0.00 to 0.00)						
	Smear positive			100	0.1	21	1.00 (0.16 to 1.00) [2/2]	1.00 (0.82 to 1.00) [19/19]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.96	27	1.00 (0.87 to 1.00) [26/26]	0.00 (0.00 to 0.97) [0/1]	0.00 (0.00 to 0.00)						
Kox, 1994[350]	IS6110	s	100	52	0.6	139	0.90 (0.82 to 0.96) [75/83]	0.71 (0.58 to 0.83) [40/56]	23.44 (9.23 to 59.49)	L	C alone	?	?	?	N
	Smear positive			100	0.96	72	0.88 (0.78 to 0.95) [61/69]	0.00 (0.00 to 0.71) [0/3]	0.00 (0.00 to 0.00)						
	Smear negative‡			0	0.21	67	1.00 (0.77 to 1.00) [14/14]	0.75 (0.62 to 0.86) [40/53]	0.00 (0.00 to 0.00)						
Li, 2000[351]	IS6110	t		0	0.78	68	0.72 (0.58 to 0.83) [38/53]	0.73 (0.45 to 0.92) [11/15]	6.97 (1.92 to 25.34)	L	C + Clin + H	N	R	?	?
Montenegro, 2003[352]	IS6110	r	17	25	0.6	222	0.54 (0.45 to 0.63) [72/133]	0.97 (0.90 to 0.99) [86/89]	33.84 (10.18 to 112.41)	R	C + Clin	?	P	?	Y
Nastasi, 1997[353]	IS6110	m	11	31	0.4	97	0.87 (0.73 to 0.96) [34/39]	0.91 (0.81 to 0.97) [53/58]	72.08 (19.40 to 267.75)	P	Clin + T	?	?	?	N
Pao, 1990[354]	65-kDa	r	83		0.17	284	1.00 (0.93 to 1.00) [49/49]	0.71 (0.64 to 0.76) [166/235]	0.00 (0.00 to 0.00)	?	C alone	?	?	?	?
	Sputum only	s	100		0.16	236	1.00 (0.91 to 1.00) [38/38]	0.69 (0.62 to 0.76) [137/198]	0.00 (0.00 to 0.00)						
Rolfs, 1995[194]	2.4-kb DNA	sr		28	0.53	162	0.26 (0.17 to 0.36) [22/86]	0.97 (0.91 to 1.00) [74/76]	12.72 (2.88 to 56.19)	L	C + Clin + T	Y	P	Y	Y
	IS6110	sr		28	0.53	162	0.33 (0.23 to 0.44) [28/86]	0.95 (0.87 to 0.99) [72/76]	8.69 (2.88 to 26.19)						

continued

Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
	MPB64	sr		28	0.53	162	0.33 (0.23 to 0.44) [28/86]	0.95 (0.87 to 0.99) [72/76]	8.69 (2.88 to 26.19)						
Schluger, 1994[355]	IS6110	r	50	77	0.35	65	1.00 (0.85 to 1.00) [23/23]	0.67 (0.50 to 0.80) [28/42]	0.00 (0.00 to 0.00)	R	C + Clin + H	Y	?	?	?
Se Thoe, 1997[325]*	IS6110†	m	85	12	0.16	187	0.83 (0.65 to 0.94) [25/30]	0.96 (0.91 to 0.98) [142/148]	118.33 (33.54 to 417.46)	P	C alone	Y	?	Y	Y
Shim, 1998[356]	65-kDa	la	0	0	0.24	33	0.88 (0.47 to 1.00) [7/8]	0.96 (0.80 to 1.00) [24/25]	168.00 (9.27 to 3,043.83)	P	C + T	?	?	?	?
Tan, 1997[357]	IS6110	m	59	38	0.31	288	1.00 (0.96 to 1.00) [88/88]	0.91 (0.86 to 0.94) [181/200]	0.00 (0.00 to 0.00)	P	C + Clin + T	?	P	?	Y
Tan, 1999[358]	IS6110	B	0	4	0.17	52	0.67 (0.30 to 0.93) [6/9]	0.93 (0.81 to 0.99) [40/43]	26.67 (4.34 to 163.90)	P	C + Clin + T	?	?	?	?
	Bronchiestasis only		0	4	0	21	– (–) [0/0]	0.86 (0.64 to 0.97) [18/21]	0.00 (0.00 to 0.00)						
	Upper lobe infiltrates		0	4	0.29	31	0.67 (0.30 to 0.93) [6/9]	1.00 (0.85 to 1.00) [22/22]	0.00 (0.00 to 0.00)						
Tansuphasiri, 2002[359]	IS6110 – agarose gel electrophoresis	s	100	42	0.42	190	0.90 (0.81 to 0.96) [71/79]	1.00 (0.97 to 1.00) [111/111]	0.00 (0.00 to 0.00)	R	C alone	?	?	?	Y
	Smear positive			100	0.99	79	0.90 (0.81 to 0.95) [70/78]	1.00 (0.03 to 1.00) [1/1]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.01	111	1.00 (0.03 to 1.00) [1/1]	1.00 (0.97 to 1.00) [110/110]	0.00 (0.00 to 0.00)						
	IS6110 – dot blot hybridisation	s	100	42	0.42	190	0.92 (0.84 to 0.97) [73/79]	0.98 (0.94 to 1.00) [109/111]	663.08 (130.24 to 3,376.03)	R	C alone	?	?	?	Y
	Smear positive			100	0.99	79	0.92 (0.84 to 0.97) [72/78]	1.00 (0.03 to 1.00) [1/1]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.01	111	1.00 (0.03 to 1.00) [1/1]	1.00 (0.97 to 1.00) [110/110]	0.00 (0.00 to 0.00)						
	IS6110 – ELISA	s	100	42	0.42	190	0.90 (0.81 to 0.96) [71/79]	1.00 (0.97 to 1.00) [111/111]	0.00 (0.00 to 0.00)	R	C alone	?	?	?	Y
	Smear positive			100	0.99	79	0.90 (0.81 to 0.95) [70/78]	1.00 (0.03 to 1.00) [1/1]	0.00 (0.00 to 0.00)						
	Smear negative			0	0.01	111	1.00 (0.03 to 1.00) [1/1]	0.98 (0.94 to 1.00) [108/110]	0.00 (0.00 to 0.00)						

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Study[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95% CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr.[p]
Wong, 1998[360]	IS6110	B	0	0	0.57	190	0.97 (0.92 to 0.99) [105/108]	0.73 (0.62 to 0.82) [60/82]	95.45 (27.42 to 332.27)	P	C + Clin + H + T	Y	?	Y	Y
Yam, 1998[331]*	IS6110	r		5	0.11	385	0.91 (0.78 to 0.97) [40/44]	1.00 (0.99 to 1.00) [341/341]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Zambardi, 1993[361]	groEL	m	74	21	0.25	196	0.82 (0.68 to 0.91) [40/49]	0.81 (0.74 to 0.87) [119/147]	18.89 (8.22 to 43.41)	P	C alone	Y	?	Y	Y
	IS6110	m	74	21	0.25	196	0.84 (0.70 to 0.93) [41/49]	0.87 (0.81 to 0.92) [128/147]	34.53 (14.07 to 84.74)						
	Pab	m	74	21	0.25	196	0.80 (0.66 to 0.90) [39/49]	0.84 (0.77 to 0.89) [123/147]	19.99 (8.79 to 45.42)						

[a] Study: * indicates study compares in-house and commercial NAAT tests; † indicates per specimen data used as <10% difference.
[b] Test evaluated and any subgroup information; ‡ denotes dataset included in smear-positive and smear-negative subgroup analyses
[c] Sample tested: s, sputum; r, respiratory; m, mixed (respiratory and non-respiratory); B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate (from percutaneous tranthoracic needle aspiration); sr, serum; u, urine; pf, pleural fluid.
[d] Percentage of total samples tested that were sputum.
[e] Percentage of smear-positive samples tested.
[f] Prevalence of TB in sample tested.
[g] Total: number of patients tested with a given test.
[h] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[i] Specificity (95% confidence interval) [number true negative/total number without disease].
[j] Diagnostic odds ratio (95% confidence interval).
[k] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[l] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[m] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[n] Study design: P, prospective; R, retrospective; ?, can't tell.
[o] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[p] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 8

Simultaneous amplification with molecular probe evaluations in pulmonary TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	% sputum[d]	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95%CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
Bergmann, 2000[362]	*	BDProbeTec ET	r	nr	3400	0.07	332	0.83 (0.52 to 0.98) [10/12]	0.98 (0.96 to 0.99) [314/320]	261.6667 (46.86844 to 1460.886)	L	C alone	?	?	?	?
Huang, 2003[363]		BDProbeTec ET	r	91.8	3400	0.44	89	0.74 (0.58 to 0.87) [29/39]	0.98 (0.89 to 1.00) [49/50]	142.1 (17.29125 to 1167.782)	P	C + T + X	?	?	?	Y
	*	1 specimen per pt						0.74 (0.58 to 0.87) [29/39]	0.98 (0.89 to 1.00) [49/50]	142.1 (17.29125 to 1167.782)	P	C + T + X	?	?	?	Y
		2 specimen per pt						0.77 (0.61 to 0.89) [30/39]	0.98 (0.89 to 1.00) [49/50]	163.3333 (19.69565 to 1354.501)	P	C + T + X	?	?	?	Y
		3 specimen per pt						0.77 (0.61 to 0.89) [30/39]	0.96 (0.86 to 1.00) [48/50]	80 (16.17329 to 395.7141)	P	C + T + X	?	?	?	Y
Piersimoni, 2002[203]	*	BDProbeTec ET	m	52	3400	0.21	402	0.94 (0.87 to 0.98) [80/85]	1.00 (0.98 to 1.00) [316/317]	5056 (582.4772 to 43886.92)	L	C + Clin	?	R	?	Y
Thierry, 1992[195]	*	In-house (MTBc)	r	46.7		0.47	30	0.93 (0.66 to 1.00) [13/14]	0.94 (0.70 to 1.00) [15/16]	195 (11.06031 to 3437.97)	L	C alone	?	?	?	N

[a] Primary analysis: * indicates study data set included in main analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: s, sputum; r, respiratory; m, mixed (respiratory and non-respiratory); B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; sr, serum; u, urine; pf, pleural fluid.
[d] Percentage of total samples tested that were sputum.
[e] Percentage of smear-positive samples tested.
[f] Prevalence of TB in sample tested.
[g] Total number of patients tested with a given test.
[h] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[i] Specificity (95% confidence interval) [number true negative/total number without disease].
[j] Diagnostic odds ratio (95% confidence interval).
[k] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[l] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[m] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[n] Study design: P, prospective; R, retrospective; ?, can't tell
[o] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[p] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 9

Phage-based test evaluations in pulmonary TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	% sputum[d]	Cut-off	% Sm+[e]	Prevalence[f]	Total[g]	Sens (95% CI) [tp/dis][h]	Spec (95% CI) [tn/nodis][i]	DOR (95%CI)[j]	Setting[k]	Reference test[l]	Index blinded[m]	Design[n]	Ref blinded[o]	Pt repr[p]
Albert, 2002[196]	*	FASTPlaqueTB	s	100	20	19	0.14	781	0.70 (0.61 to 0.79) [78/111]	0.99 (0.98 to 1.00) [663/670]	223.8701 (95.81183 to 523.0861)	C	C + Clin + T + X	Y	?	Y	Y
		Smear positive				100	0.78	87	0.84 (0.73 to 0.92) [57/68]	0.89 (0.67 to 0.99) [17/19]	44.04546 (8.883157 to 218.391)						
		Smear negative				0	0.06	694	0.49 (0.33 to 0.65) [21/43]	0.99 (0.98 to 1.00) [646/651]	123.3273 (42.56245 to 357.3484)						
Albay, 2003[335]	*	FASTPlaqueTB	s	100	20	11	0.33	192	0.88 (0.77 to 0.94) [56/64]	0.97 (0.92 to 0.99) [124/128]	217 (62.73108 to 750.6484)	P	C alone	?	?	?	Y
Alcaide, 2003[364]	*	PhageTek MB	r	70.5	20	5	0.15	1483	0.65 (0.56 to 0.73) [87/134]	0.99 (0.98 to 0.99) [1332/1349]	145.0363 (79.94769 to 263.1161)	R	C alone	?	?	?	N
Cavusoglu, 2002[198]	*	FASTPlaqueTB	s	100	20	50	0.52	63	0.27 (0.13 to 0.46) [9/33]	0.97 (0.83 to 1.00) [29/30]	10.875 (1.285081 to 92.02972)	L	C + Clin + T + X	?	R	?	?
Muzaffar, 2002[197]	*	FASTPlaqueTB	s	100	Manuf. inst.	37	0.48	514	0.82 (0.76 to 0.86) [200/245]	0.98 (0.95 to 0.99) [263/269]	194.8148 (81.49853 to 465.6871)	P	C alone	?	?	?	Y
		Smear positive				100	0.91	192	0.87 (0.82 to 0.92) [153/175]	0.88 (0.64 to 0.99) [15/17]	52.15909 (11.16368 to 243.6985)						
		Smear negative				0	0.22	322	0.67 (0.55 to 0.78) [47/70]	0.98 (0.96 to 1.00) [248/252]	126.6957 (41.89421 to 383.1505)						

[a] Primary analysis: * indicates study data set included in main analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Percentage of total samples tested that were sputum.
[e] Percentage of smear-positive samples tested.
[f] Prevalence of TB in sample tested.
[g] Total number of patients tested with a given test.
[h] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[i] Specificity (95% confidence interval) [number true negative/total number without disease].
[j] Diagnostic odds ratio (95% confidence interval).
[k] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[l] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[m] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[n] Study design: P, prospective; R, retrospective; ?, can't tell.
[o] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[p] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 10

Serodiagnostic and biochemical test evaluations in pulmonary TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Anti-TB antibody tests – commercial															
Al Zahrani, 2000[83]	*	Detect TB	sr	1	0.11	421	0.44 (0.29 to 0.59) [21/48]	0.77 (0.72 to 0.81) [287/373]	2.6 (1.4 to 4.8)	P	C + Clin + T	Y	P	Y	Y
				1.6			0.33 (0.20 to 0.48) [16/48]	0.87 (0.83 to 0.90) [325/372]	3.4 (1.7 to 6.6)						
Chander, 1996[365]	*	EIA Pathozyme TB complex	sr		0.28	130	0.92 (0.78 to 0.98) [34/37]	0.82 (0.72 to 0.89) [76/93]	50.7 (13.9 to 184.5)	P	Clin	?	?	?	Y
Charpin, 1990[366]	*	Anda TB IgG	r	0.5	0.30	83	0.48 (0.28 to 0.69) [12/25]	0.71 (0.57 to 0.82) [41/58]	2.2 (0.8 to 5.9)	P	C alone	?	P	?	Y
	*	Anda TB IgM		0.43		83	0.76 (0.55 to 0.91) [19/25]	0.98 (0.91 to 1.00) [57/58]	180.5 (20.4 to 1,596.4)						
Luh, 1996[367]	*	Anda TB IgG	sr	200	0.25	593	0.76 (0.68 to 0.83) [112/147]	0.86 (0.83 to 0.89) [385/446]	20.2 (12.7 to 32.2)	P	C + H + Clin + T + X	?	?	?	Y
	*	Anda TB IgM				593	0.10 (0.06 to 0.16) [15/147]	1.00 (0.98 to 1.00) [444/446]	25.2 (5.7 to 111.7)						
McConkey, 2002[368]	*	ICT test – US study	sr		0.22	73	0.25 (0.07 to 0.52) [4/16]	0.79 (0.66 to 0.89) [45/57]	1.3 (0.3 to 4.6)	P/R	C + Clin + X	Y	P	?	?
	*	ICT test - Egypt study	sr		0.53	159	0.87 (0.78 to 0.93) [74/85]	0.82 (0.72 to 0.90) [61/74]	31.6 (13.2 to 75.5)		C alone				
Somi, 1999[369]	*	Mycodot – On site testing	sr		0.45	185	0.16 (0.09 to 0.25) [13/83]	0.84 (0.76 to 0.91) [86/102]	1.0 (0.4 to 2.2)	R	C + Clin + T	?	?	Y	Y
		Smear negative			0.30	146	0.07 (0.01 to 0.19) [3/44]	0.84 (0.76 to 0.91) [86/102]	0.4 (0.1 to 1.4)						
		Smear positive			1.00	39	0.26 (0.13 to 0.42) [10/39]	–(–) [0/0]	0.0 (0.0 to 0.0)						
		HIV negative			0.30	91	0.33 (0.17 to 0.54) [9/27]	0.77 (0.64 to 0.86) [49/64]	1.6 (0.6 to 4.4)						
		HIV positive			0.60	94	0.07 (0.02 to 0.17) [4/56]	0.97 (0.86 to 1.00) [37/38]	2.8 (0.3 to 26.5)						
	*	Mycodot – Repeat testing by manufacturer	sr		0.45	185	0.08 (0.03 to 0.17) [7/83]	0.97 (0.92 to 0.99) [99/102]	3.0 (0.8 to 12.1)						
Anti-TB Antibody tests – in-house															
Chan, 2000[370]	*	LAM	sr		0.13	104	0.85 (0.55 to 0.98) [11/13]	0.89 (0.81 to 0.95) [81/91]	44.6 (8.6 to 230.5)	R	C alone	Y	?	?	N

continued

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Levy, 1988[371]	*	Sonicated MTB	sr	0.25	0.19	54	0.70 (0.35 to 0.93) [7/10]	0.86 (0.73 to 0.95) [38/44]	14.8 (3.0 to 73.4)	P	C + H	?	P	?	?
	*		r	0.254	0.20	56	0.73 (0.39 to 0.94) [8/11]	0.82 (0.68 to 0.92) [37/45]	12.3 (2.7 to 57.0)						
Morris, 1988[372]	*	Sonicated MTB	sr		0.09	138	0.25 (0.05 to 0.57) [3/12]	0.84 (0.77 to 0.90) [106/126]	1.8 (0.4 to 7.1)	P	C + H + Clin	?	P	?	N
Nicholls, 1976[373]	*	H37Ra	sr		0.24	222	0.79 (0.66 to 0.89) [42/53]	0.86 (0.80 to 0.91) [145/169]	23.1 (10.4 to 50.9)	?	C alone	?	?	?	?
Silva, 2003[374]	*	14kDa	sr	0.19	0.15	383	0.28 (0.17 to 0.42) [16/57]	0.42 (0.37 to 0.48) [138/326]	0.3 (0.2 to 0.5)	R	C + X + TST	Y	P	Y	Y
	*	38kDa				383	0.42 (0.29 to 0.56) [24/57]	0.80 (0.76 to 0.85) [262/326]	3.0 (1.6 to 5.4)						
	*	ESAT-6		0.23		383	0.18 (0.09 to 0.30) [10/57]	0.61 (0.55 to 0.66) [198/326]	0.3 (0.2 to 0.7)						
Tessema, 2002[375]	*	LAM	u	0.45	0.20	1000	0.74 (0.67 to 0.80) [148/200]	0.87 (0.84 to 0.89) [695/800]	18.8 (12.9 to 27.5)	R	Clin + X	?	P	?	Y
	*		sr	7107		1000	0.57 (0.50 to 0.64) [114/200]	0.77 (0.73 to 0.79) [612/800]	4.3 (3.1 to 6.0)						
Zeiss, 1984[376]	*	PPD	sr	0.15	0.13	160	0.67 (0.43 to 0.85) [14/21]	0.76 (0.68 to 0.82) [105/139]	6.2 (2.3 to 16.6)	P	C alone	Y	P	?	Y
Adenosine deaminase															
Conde, 2002[200]	*	ADA	sr	14	0.59	110	0.49 (0.37 to 0.62) [32/65]	0.56 (0.40 to 0.70) [25/45]	1.2 (0.6 to 2.6)	R	C + Clin + T	?	P	?	Y
	*	ADA2				110	0.37 (0.25 to 0.50) [24/65]	0.69 (0.53 to 0.82) [31/45]	1.3 (0.6 to 2.9)						
Antigen															
Cho, 1997[201]	*	LAM&H37Rv	r	0.2	0.39	62	0.63 (0.41 to 0.81) [15/24]	0.92 (0.79 to 0.98) [35/38]	19.4 (4.6 to 82.1)	P	C alone	?	?	?	Y
Cytokine															
Amer, 2000[190]	*	IFN-γ	pf	1.54	0.36	14	1.00 (0.48 to 1.00) [5/5]	0.89 (0.52 to 1.00) [8/9]	0.0 (0.0 to 0.0)	P	C alone	?	?	?	Y
	*	IL-1B		33.35		14	0.40 (0.05 to 0.85) [2/5]	0.89 (0.52 to 1.00) [8/9]	5.3 (0.3 to 82.8)						

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Miscellaneous tests															
Chan, 1992[202]	*	TBSA – 3 specimens per patient	r		0.54	39	0.57 (0.34 to 0.77) [13/23]	0.75 (0.48 to 0.93) [12/16]	3.9 (1.0 to 15.8)	P	C + H + T	Y	P	?	Y
Chan, 1992[202]		Bronchial aspirate				39	0.26 (0.10 to 0.48) [6/23]	0.81 (0.54 to 0.96) [13/16]	1.5 (0.3 to 7.3)						
Chan, 1992[202]		BAL				39	0.52 (0.31 to 0.73) [12/23]	0.81 (0.54 to 0.96) [13/16]	4.7 (1.1 to 21.2)						
Chan, 1992[202]		Transbronchial biopsy				39	0.17 (0.05 to 0.39) [4/23]	0.75 (0.48 to 0.93) [12/16]	0.6 (0.1 to 3.0)						

[a] Primary analysis: * indicates data set included in primary analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: s, sputum; r, respiratory; m, mixed (respiratory and non-respiratory); B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; sr, serum; u, urine; pf, pleural fluid.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 11

NAAT tests in miscellaneous extrapulmonary TB samples – summary study details

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Study	Test[a]	% AFB+[b]	Prev[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Commercial tests													
Alcala, 2001[291]	AMTD – Standard	10	0.12	185	0.82 (0.60 to 0.95) [18/22]	0.91 (0.85 to 0.95) [148/163]	44.40 (13.29 to 148.39)	P	C + Clin	?	?	?	Y
Bemer-Melchoir, 1998[377]	Amplicor – Manual	8	0.18	124	0.64 (0.41 to 0.83) [14/22]	0.93 (0.86 to 0.97) [95/102]	23.75 (7.45 to 75.70)	P	C alone	?	R	?	Y
	Smear positive		0.5	10	1.00 (0.48 to 1.00) [5/5]	0.20 (0.01 to 0.72) [1/5]	0.00 (0.00 to 0.00)						
	Smear negative		0.15	114	0.53 (0.28 to 0.77) [9/17]	0.97 (0.91 to 0.99) [94/97]	35.25 (7.92 to 156.85)						
Chedore, 1999[191]	AMTD – Enhanced	24	0.24	207	1.00 (0.93 to 1.00) [49/49]	0.96 (0.91 to 0.98) [151/158]	0.00 (0.00 to 0.00)	L	C + Clin	?	P	?	N
	Smear positive		0.37	110	1.00 (0.91 to 1.00) [41/41]	0.93 (0.84 to 0.98) [64/69]	0.00 (0.00 to 0.00)						
	Smear negative		0.08	97	1.00 (0.63 to 1.00) [8/8]	0.98 (0.92 to 1.00) [87/89]	0.00 (0.00 to 0.00)						
Ehlers, 1996[306]	AMTD – Standard	7	0.16	294	0.81 (0.67 to 0.91) [39/48]	0.96 (0.93 to 0.98) [237/246]	114.11 (42.65 to 305.29)	L	C alone	?	?	?	Y
	Tissue specimens		0.3	90	0.85 (0.66 to 0.96) [23/27]	1.00 (0.94 to 1.00) [63/63]	0.00 (0.00 to 0.00)						
	Body fluids and aspirates		0.15	79	0.92 (0.62 to 1.00) [11/12]	1.00 (0.95 to 1.00) [67/67]	0.00 (0.00 to 0.00)						
	Misc. other specimens		0.19	120	0.83 (0.61 to 0.95) [19/23]	1.00 (0.96 to 1.00) [97/97]	0.00 (0.00 to 0.00)						
Gamboa, 1997[378]	AMTD – Standard	13	0.43	224	0.74 (0.64 to 0.82) [71/96]	0.95 (0.89 to 0.98) [121/128]	49.09 (20.20 to 119.29)	P	C alone	?	?	?	?
Gamboa, 1998[379]	AMTD – Enhanced	4	0.25	272	0.87 (0.76 to 0.94) [59/68]	1.00 (0.98 to 1.00) [204/204]	0.00 (0.00 to 0.00)	P	C + X	?	?	?	Y
	Smear positive		0.88	24	1.00 (0.84 to 1.00) [21/21]	1.00 (0.29 to 1.00) [3/3]	0.00 (0.00 to 0.00)						
	Smear negative		0.19	248	0.81 (0.67 to 0.91) [38/47]	1.00 (0.98 to 1.00) [201/201]	0.00 (0.00 to 0.00)						
	Other non-respir. specimens	0.19		67	0.92 (0.64 to 1.00) [12/13]	1.00 (0.93 to 1.00) [54/54]	0.00 (0.00 to 0.00)						
	Organic fluid samples		0.24	94	0.87 (0.66 to 0.97) [20/23]	1.00 (0.95 to 1.00) [71/71]	0.00 (0.00 to 0.00)						

continued

Study	Test[a]	% AFB+[b]	Prev[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
	AMTD – Standard	4	0.25	272	0.84 (0.73 to 0.92) [57/68]	1.00 (0.98 to 1.00) [204/204]	0.00 (0.00 to 0.00)	P	C+X	?	?	?	Y
	Smear positive			24	1.00 (0.84 to 1.00) [21/21]	1.00 (0.29 to 1.00) [3/3]	0.00 (0.00 to 0.00)						
	Smear negative		0.08	248	0.77 (0.62 to 0.88) [36/47]	1.00 (0.98 to 1.00) [201/201]	0.00 (0.00 to 0.00)						
	Other non-respir specimens		0.19	67	0.92 (0.64 to 1.00) [12/13]	1.00 (0.93 to 1.00) [54/54]	0.00 (0.00 to 0.00)						
	Organic fluid samples		0.24	94	0.87 (0.66 to 0.97) [20/23]	1.00 (0.95 to 1.00) [71/71]	0.00 (0.00 to 0.00)						
Gamboa, 1998[380]	LcX assay		0.25	526	0.78 (0.70 to 0.85) [101/130]	0.99 (0.97 to 1.00) [391/396]	272.35 (102.83 to 721.32)	L	C alone	?	?	?	Y
	Smear positive		0.54	61	1.00 (0.89 to 1.00) [33/33]	0.86 (0.67 to 0.96) [24/28]	0.00 (0.00 to 0.00)						
	Smear negative		0.21	465	0.70 (0.60 to 0.79) [68/97]	1.00 (0.98 to 1.00) [367/368]	860.55 (115.28 to 6,424.06)						
	Other		0.25	51	0.69 (0.39 to 0.91) [9/13]	0.97 (0.86 to 1.00) [37/38]	83.25 (8.27 to 838.07)						
	Organic fluids		0.22	175	0.67 (0.50 to 0.81) [26/39]	1.00 (0.97 to 1.00) [136/136]	0.00 (0.00 to 0.00)						
	Feces		0.23	35	0.88 (0.47 to 1.00) [7/8]	1.00 (0.87 to 1.00) [27/27]	0.00 (0.00 to 0.00)						
	Blood & bone marrow aspirates		0.25	134	0.85 (0.68 to 0.95) [28/33]	1.00 (0.96 to 1.00) [101/101]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Honore-Bouakline, 2003[381]	Amplicor – Cobas		0.27	111				P	C + Clin + T + H + X	?	?	Y	Y
	PK-Roche extraction method				0.13 (0.04 to 0.31) [4/30]	0.97 (0.91 to 0.99) [87/90]	4.46 (0.94 to 21.23)						
	CTAB-Roche extraction				0.47 (0.28 to 0.66) [14/30]	0.80 (0.70 to 0.88) [72/90]	3.50 (1.45 to 8.47)						
Osumi, 1995[321]	AMTD – Standard		0.22	23	0.60 (0.15 to 0.95) [3/5]	0.94 (0.73 to 1.00) [17/18]	25.50 (1.72 to 377.95)	P	C + Clin	Y	?	?	?
Shah, 1998[382]	Amplicor – Manual	1	0.03	1090	0.75 (0.57 to 0.89) [24/32]	1.00 (0.99 to 1.00) [1054/1058]	790.50 (222.75 to 2,805.34)	L	C alone	?	?	?	Y

continued

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Study	Test[a]	% AFB+[b]	Prev[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Zambardi, 1995[333]	Amplicis Myco B (IS6110)		0.06	52	0.33 (0.01 to 0.91) [1/3]	0.80 (0.66 to 0.90) [39/49]	1.95 (0.16 to 23.73)	P	C + Clin	Y	?	Y	?
In-house tests													
Brisson-Noel, 1989[219]	65-kDa		30	0.3	1.00 (0.66 to 1.00) [9/9]	0.90 (0.70 to 0.99) [19/21]	0.00 (0.00 to 0.00)	?	C + Clin + T	?	?	?	Y
Brisson-Noel, 1991[383]	IS6110		308	0.36	0.98 (0.94 to 1.00) [108/110]	0.79 (0.72 to 0.84) [156/198]	200.57 (47.54 to 846.22)	P	C + Clin	?	?	?	N
Ceyhan, 1996[222]	IS6110		104	0.39	0.41 (0.26 to 0.58) [17/41]	0.98 (0.91 to 1.00) [62/63]	43.92 (5.54 to 348.43)	P	C alone	?	?	?	Y
Hardman, 1996[384]	16SrRNA	48	42	0.26	1.00 (0.72 to 1.00) [11/11]	0.10 (0.02 to 0.26) [3/31]	0.00 (0.00 to 0.00)	P	C alone	?	R	?	?
Kaltwasser, 1993[385]	65-kDa		34	0.59	0.90 (0.68 to 0.99) [18/20]	1.00 (0.77 to 1.00) [14/14]	0.00 (0.00 to 0.00)	?	C + H	?	?	?	Y
Kolk, 1992[349]	IS986	6	174	0.1	0.82 (0.57 to 0.96) [14/17]	0.76 (0.68 to 0.82) [119/157]	14.61 (3.99 to 53.59)	L	C alone	Y	?	Y	Y
Kolk, 1998[386]	IS6110	12	156	0.33	0.75 (0.61 to 0.86) [39/52]	0.99 (0.95 to 1.00) [103/104]	309.00 (39.10 to 2,441.68)	L	C + Clin + H + T	Y	?	N	Y
Kox, 1994[350]	IS6110	52	74	0.16	0.67 (0.35 to 0.90) [8/12]	0.92 (0.82 to 0.97) [57/62]	22.80 (5.04 to 103.08)	L	C alone	?	?	?	N
Portillo-Gomez, 2000[387]	IS6110	13	286	0.23	0.94 (0.85 to 0.98) [61/65]	1.00 (0.98 to 1.00) [221/221]	0.00 (0.00 to 0.00)	L	C + Clin + H + T	?	P	?	Y
Salian, 1998[388]	IS6110	25	60	0.32	0.74 (0.49 to 0.91) [14/19]	1.00 (0.91 to 1.00) [39/39]	0.00 (0.00 to 0.00)	L T	C + Clin +	Y	?	Y	?

[a] Test evaluated and any subgroup information.
[b] Percentage of AFB-positive samples tested if reported.
[c] Prevalence of TB in sample tested.
[d] Total number of patients tested with a given test.
[e] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[f] Specificity (95% confidence interval) [number true negative/total number without disease].
[g] Diagnostic odds ratio (95% confidence interval).
[h] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[i] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[j] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[k] Study design: P, prospective; R, retrospective; ?, can't tell.
[l] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 12

Other tests in miscellaneous extrapulmonary TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Molecular probes test															
Marttila, 1999[204]	*	Inno-LiPA	m		0.68	75	0.59 (0.44 to 0.72) [30/51]	1.00 (0.86 to 1.00) [24/24]	(–)	R	C + Clin + H + T + X	Y	?	?	Y
Anti-TB antibody test – commercial															
Luh, 1996[367]	*	Anda TB IgG	sr	200	0.29	314	0.59 (0.48 to 0.69) [53/90]	0.92 (0.88 to 0.96) [207/224]	17.4 (9.1 to 33.4)	P	C + H + Clin + T + X	?	?	?	Y
	*	Anda TB IgM	sr			314	0.11 (0.05 to 0.19) [10/90]	0.99 (0.97 to 1.00) [222/224]	13.9 (3.0 to 64.7)						
McConkey, 2002[368]	*	ICT test – Egypt study (incls. pulmonary TB)	sr		0.73	274	0.72 (0.66 to 0.79) [145/200]	0.82 (0.72 to 0.90) [61/74]	12.4 (6.3 to 24.3)	P/R	C + Clin + X	Y	P	?	?
	*	ICT test – US study	sr		0.08	62	0.40 (0.05 to 0.85) [2/5]	0.79 (0.66 to 0.89) [45/57]	2.5 (0.4 to 16.7)		C alone				
Anti-TB antibody test – in-house															
Goode, 1980[389]	*	H37Rv (TB type not described)	sr		0.34	83	0.86 (0.67 to 0.96) [24/28]	0.47 (0.34 to 0.61) [26/55]	5.4 (1.6 to 17.6)	?	Not reported	?	?	?	Y
Ivanyi, 1983[390]	*	Sonicated MTB (incls. pulmonary TB)	sr	5	0.45	98	0.56 (0.41 to 0.69) [30/54]	0.95 (0.87 to 0.99) [60/63]	25.0 (7.0 to 89.7)	P	C alone	Y	?	Y	?
Adenosine deaminase tests															
Makhlouf, 1992[205]	*	ADA	m	41	0.11	90	1.00 (0.69 to 1.00) [10/10]	0.85 (0.75 to 0.92) [68/80]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	?
				75			0.80 (0.44 to 0.97) [8/10]	0.93 (0.84 to 0.97) [74/80]	49.3 (8.5 to 286.4)						

[a] Primary analysis: * indicates data set included in primary analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: P, primary hospital; R, referral hospital; L, laboratory; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 13

NAAT evaluations in pleural TB – study details

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Study	Test[a]	% AFB+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Commercial													
Bemer-Melchoir, 1998[377]	Amplicor – Manual	8	0.22	9	0.00 (0.00 to 0.84) [0/2]	1.00 (0.59 to 1.00) [7/7]	0.00 (0.00 to 0.00)	P	C alone	?	R	?	Y
Ehlers, 1996[306]	AMTD – Standard		0.09	35	1.00 (0.29 to 1.00) [3/3]	1.00 (0.89 to 1.00) [32/32]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Gamboa, 1997[378]	AMTD – Standard		0.34	41	0.93 (0.66 to 1.00) [13/14]	1.00 (0.87 to 1.00) [27/27]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	?
Osumi, 1995[321]	AMTD – Standard		0.18	17	0.33 (0.01 to 0.91) [1/3]	0.93 (0.66 to 1.00) [13/14]	6.50 (0.28 to 151.13)	P	C + Clin	Y	?	?	?
Shah, 1998[382]	Amplicor – Manual		0.02	375	0.50 (0.16 to 0.84) [4/8]	1.00 (0.98 to 1.00) [366/367]	366.00 (33.11 to 4,045.33)	L	C alone	?	?	?	Y
Zambardi, 1995[333]	Amplicis Myco B (IS6110)		0.06	17	1.00 (0.03 to 1.00) [1/1]	0.88 (0.62 to 0.98) [14/16]	0.00 (0.00 to 0.00)	P	C + Clin	Y	?	Y	?
In-house													
Ceyhan, 1996[222]	IS6110		0.43	14	0.67 (0.22 to 0.96) [4/6]	1.00 (0.63 to 1.00) [8/8]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	Y
De Wit, 1992[391]	p375 MTB fragment	0	0.63	84	0.81 (0.68 to 0.91) [43/53]	0.77 (0.59 to 0.90) [24/31]	14.74 (4.97 to 43.73)	P	C + Clin + H	Y	P	Y	N
Kolk, 1992[349]	IS986	0	0.06	18	1.00 (0.03 to 1.00) [1/1]	0.88 (0.64 to 0.99) [15/17]	0.00 (0.00 to 0.00)	L	C alone	Y	?	Y	Y
Nagesh, 2001[212]	IS6110?	7	0.33	60	0.70 (0.46 to 0.88) [14/20]	1.00 (0.91 to 1.00) [40/40]	0.00 (0.00 to 0.00)	R	H + T + X	Y	P	Y	?
Pao, 1990[354]	65-kDa		0.23	48	1.00 (0.72 to 1.00) [11/11]	0.78 (0.62 to 0.90) [29/37]	0.00 (0.00 to 0.00)	?	C alone	?	?	?	?
Parandaman, 2000[392]	IS6110, TRC4	6	0.6	50	1.00 (0.88 to 1.00) [30/30]	0.70 (0.46 to 0.88) [14/20]	0.00 (0.00 to 0.00)	R	C + T	?	?	?	N
Portillo-Gomez, 2000[387]	IS6110	14	0.23	73	0.94 (0.71 to 1.00) [16/17]	1.00 (0.94 to 1.00) [56/56]	0.00 (0.00 to 0.00)	L	C + Clin + H + T	?	P	?	Y
Reechaipichitkul, 2000[393]	16SrDNA	15	0.37	98	0.72 (0.55 to 0.86) [26/36]	0.58 (0.45 to 0.70) [36/62]	3.60 (1.48 to 8.74)	P	C + Clin + H + T	Y	?	N	Y
	16SrDNA, 23SrDNA spacer primers				0.50 (0.33 to 0.67) [18/36]	0.61 (0.48 to 0.73) [38/62]	1.58 (0.69 to 3.63)						
Takagi, 1998[394]	IS6110	14	0.68	28	0.89 (0.67 to 0.99) [17/19]	1.00 (0.66 to 1.00) [9/9]	0.00 (0.00 to 0.00)	P	C + Clin + H + T	?	?	?	?

continued

Study	Test[a]	% AFB+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Villegas, 2000[213]	IS6110	0	0.44	140				P	C + Clin + H + T	?	P	?	N
	Agarose gel				0.41 (0.29 to 0.54) [25/61]	0.96 (0.89 to 0.99) [76/79]	17.59 (4.98 to 62.12)						
	Dot blot				0.57 (0.44 to 0.70) [35/61]	0.90 (0.81 to 0.96) [71/79]	11.95 (4.91 to 29.09)						
	Dot blot and agarose gel detection				0.61 (0.47 to 0.73) [37/61]	0.90 (0.81 to 0.96) [71/79]	13.68 (5.60 to 33.43)						
Villena, 1998[395]	IS6110	0	0.25	131	0.42 (0.25 to 0.61) [14/33]	0.99 (0.94 to 1.00) [97/98]	71.47 (8.86 to 576.43)	P	C + Clin + H	?	P	?	?

[a] Test evaluated and any subgroup information.
[b] Percentage of AFB-positive samples tested.
[c] Prevalence of TB in sample tested.
[d] Total number of patients tested with a given test.
[e] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[f] Specificity (95% confidence interval) [number true negative/total number without disease].
[g] Diagnostic odds ratio (95% confidence interval).
[h] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[i] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[j] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[k] Study design: P, prospective; R, retrospective; ?, can't tell.
[l] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 14

Adenosine deaminase evaluations in pleural TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Aoki, 1994[396]	*,†	ADA	pf	45	0.28	39	0.82 (0.48 to 0.98) [9/11]	0.89 (0.72 to 0.98) [25/28]	37.5 (5.4 to 262.2)	P	C+H	?	?	?	?
Banales, 1991[397]	*,†	ADA	pf	70	0.38	218	0.99 (0.93 to 1.00) [81/82]	0.96 (0.91 to 0.98) [130/136]	1,755.0 (207.5 to 14,844.3)	R	C + H	Y	?	?	N
Blake, 1982[398]	*	ADA	pf	30	0.41	202	0.90 (0.82 to 0.96) [74/82)	0.98 (0.94 to 1.00) [118/120]	545.8 (112.8 to 2640.4)	R	C + H + Clin + T + X	?	?	?	?
Burgess, 1996[399]	*,†	ADA	pf	50	0.47	303	0.91 (0.85 to 0.95) [130/143]	0.84 (0.78 to 0.90) [135/160]	54.0 (26.5 to 110.1)	P	C + Clin + T	?	?	?	?
Caballero, 1999[400]	*,†	ADA	pf	40	0.07	92	0.83 (0.36 to 1.00) [5/6]	0.87 (0.78 to 0.93) [75/86]	34.1 (3.6 to 319.7)	P	C + Clin + T	?	?	?	?
Chiang, 1994[210]	*,†	ADA	pf	60	0.29	93	0.85 (0.66 to 0.96) [23/27]	0.95 (0.87 to 0.99) [63/66]	120.8 (25.1 to 581.1)	P	C + H	?	?	?	N
Fontan-Bueso, 1988[401]	*,†	ADA	pf	33	0.44	138	1.00 (0.94 to 1.00) [61/61]	0.91 (0.82 to 0.96) [70/77]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	?	?	?
Ghelani, 1999[206]	*	ADA	pf	40	0.67	81	0.72 (0.58 to 0.83) [38/53]	0.59 (0.39 to 0.78) [16/27]	3.7 (1.4 to 9.7)	P	C + H + T	?	?	?	Y
Goulart de Oliveira, 1994[402]	*,†	ADA	pf	40	0.20	276	0.94 (0.85 to 0.99) [51/54]	0.86 (0.81 to 0.90) [191/222]	104.7 (30.8 to 356.5)	P	C + H + Clin + T	Y	?	?	N
Gupta, 1990[403]	*,†	ADA	pf	50.75	0.67	54	1.00 (0.90 to 1.00) [36/36]	0.94 (0.73 to 1.00) [17/18]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	N
Hsu, 1993[404]	*,†	ADA	pf	80	0.50	60	0.80 (0.61 to 0.92) [24/30]	0.90 (0.73 to 0.98) [27/30]	36.0 (8.1 to 159.9)	P	C + H	?	?	?	N
		Immunocompetent only			0.40	20	1.00 (0.83 to 1.00) [20/20]								
		Immunocompromised only			0.25	10	0.40 (0.12 to 0.74) [4/10]								
	†	ADA	pf	60	0.47	60	0.86 (0.67 to 0.96) [24/28]	0.81 (0.64 to 0.93) [26/32]	26.0 (6.5 to 103.5)						
		Immunocompetent only			0.40	20	1.00 (0.83 to 1.00) [20/20]								
		Immunocompromised only			0.25	10	0.40 (0.12 to 0.74) [4/10]								
		ADA	pf	100	0.38	60	0.96 (0.78 to 1.00) [22/23]	0.78 (0.62 to 0.90) [29/37]	79.8 (9.3 to 685.7)						

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
		Immunocompetent only			0.40	20	0.95 (0.75 to 1.00) [19/20]								
		Immunocompromised only			0.25	10	0.30 (0.07 to 0.65) [3/10]								
Kaur, 1992[225]	*,†	ADA	pf	30	0.38	84	0.50 (0.32 to 0.68) [16/32]	0.92 (0.81 to 0.98) [48/52]	12.0 (3.5 to 41.2)	P	C + H + T	Y	P	Y	N
Kuralay, 1998[405]	*	ADA	pf	30	0.27	95	0.81 (0.61 to 0.93) [21/26]	0.88 (0.78 to 0.95) [60/68]	31.5 (9.3 to 107.0)	P	C + H	?	?	?	?
Maartens, 1991[39]	*,†	ADA	pf	45	0.57	109	0.77 (0.65 to 0.87) [48/62]	0.83 (0.69 to 0.92) [39/47]	16.7 (6.4 to 43.9)	P	C + H + T	?	?	?	?
Maritz, 1982[406]	*	ADA	pf	40	0.29	368	0.93 (0.87 to 0.97) [100/107]	0.81 (0.76 to 0.86) [212/261]	61.8 (27.0 to 141.3)	P	C + H + Clin + T + X	?	?	?	?
	*	ADA	p/s		0.30	226	0.93 (0.84 to 0.98) [63/68]	0.72 (0.64 to 0.79) [114/158)	32.6 (12.3 to 86.5)						
Momi, 2002[407]	*,†	ADA	pf	40	0.32	127	0.63 (0.47 to 0.78) [26/41]	0.81 (0.72 to 0.89) [70/86]	7.6 (3.3 to 17.5)	P	C + H + Clin + T	?	?	?	?
Nagesh, 2001[212]	*,†	ADA	pf	50	0.33	60	0.55 (0.32 to 0.77) [11/20]	0.55 (0.38 to 0.71) [22/40]	1.5 (0.5 to 4.4)	R	H + T + X	Y	P	Y	?
Ocana, 1986[408]	*,†	ADA	pf	50	0.51	74	1.00 (0.91 to 1.00) [38/38]	0.97 (0.85 to 1.00) [35/36]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	N
Orphanidou, 1996[409]	*,†	ADA	pf	40.6	0.34	97	0.79 (0.61 to 0.91) [26/33]	0.94 (0.85 to 0.98) [60/64]	55.7 (15.0 to 206.9)	P	C + H	?	?	?	N
	*		sr	39.4			0.33 (0.18 to 0.52) [11/33]	0.94 (0.85 to 0.98) [60/64]	7.5 (2.2 to 26.0)						
Perez-Rodriguez, 1999[410]	*,†	ADA	pf	40	0.26	103	0.89 (0.71 to 0.98) [24/27]	0.92 (0.84 to 0.97) [70/76]	93.3 (21.6 to 402.5)	P	C + H	?	P	?	?
	*	ADA/ADA1 ratio	pf	0.42			1.00 (0.87 to 1.00) [27/27]	0.99 (0.93 to 1.00) [75/76]	0.0 (0.0 to 0.0)						
Pettersson, 1984[411]	*,†	ADA	pf	50	0.21	90	1.00 (0.82 to 1.00) [19/19]	0.85 (0.74 to 0.92) [60/71]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	?	?	N
	*		pf/sr	2.5			0.79 (0.54 to 0.94) [15/19]	0.85 (0.74 to 0.92) [60/71]	20.5 (5.7 to 73.3)						
Reechaipichitkul, 2001[412]	*,†	ADA	pf	48	0.38	132	0.80 (0.66 to 0.90) [40/50]	0.80 (0.70 to 0.88) [66/82]	16.5 (6.8 to 39.9)	P	C + H + T	Y	P	Y	N

continued

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Riantawan, 1999[87]	*,†	ADA	pf	40	0.51	197	0.97 (0.91 to 0.99) [97/100]	0.84 (0.75 to 0.90) [81/97]	163.7 (46.1 to 581.7)	R	C + H + Clin	Y	P	Y	?
	†			60			0.95 (0.89 to 0.98) [95/100]	0.96 (0.90 to 0.99) [93/97]	441.8 (115.0 to 1,696.4)						
Richter, 1994[413]	*	ADA	pf	10	0.95	118	0.97 (0.91 to 0.99) [109/112]	50.0 (0.12 to 0.88) [3/6	36.3 (5.1 to 260.3)	P	C + H + T + TST	?	P	?	?
San Jose, 1992[414]	*	ADA	sr	30	0.20	271	0.87 (0.75 to 0.95) [46/53]	0.55 (0.48 to 0.62) [120/218]	8.0 (3.5 to 18.6)	P	C + H + Clin	?	?	?	N
	*	ADA/lysozyme	pf/sr	3.3			0.79 (0.66 to 0.89) [42/53]	0.95 (0.91 to 0.97) [207/218]	71.9 (29.2 to 176.6)						
	*	ADA/total protein	pf	11.5			0.92 (0.82 to 0.98) [49/53]	0.95 (0.91 to 0.97) [207/218]	230.5 (70.4 to 754.7)						
Sharma, 2001[415]	*,†	ADA	pf	35	0.64	75	0.83 (0.70 to 0.93) [40/48]	0.67 (0.46 to 0.83) [18/27]	10.0 (3.3 to 30.1)	P	C + H + Clin + T	Y	P	?	?
	†			100			0.40 (0.26 to 0.55) [19/48]	1.00 (0.87 to 1.00) [27/27]	0.0 (0.0 to 0.0)						
Sinha, 1987[416]	*,†	ADA	pf	30	0.70	53	1.00 (0.91 to 1.00) [37/37]	1.00 (0.79 to 1.00) [16/16]	0.0 (0.0 to 0.0)	P	C + Clin + H + X	?	?	?	N
Strankinga, 1987[417]	*,†	ADA	pf	79	0.12	86	1.00 (0.69 to 1.00) [10/10]	0.87 (0.77 to 0.94) [66/76]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	N
Valdes, 1993[418]	*,†	ADA	pf	47	0.22	405	1.00 (0.96 to 1.00) [91/91]	0.95 (0.92 to 0.97) [298/314]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	N
	*		pf/sr	1.5	0.18	276	0.86 (0.73 to 0.94) [42/49]	0.89 (0.84 to 0.93) [202/227]	48.5 (19.7 to 119.4)						
Valdes, 1995[419]	*,†	ADA	pf	47	0.63	129	1.00 (0.96 to 1.00) [81/81]	0.88 (0.75 to 0.95) [42/48]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	?
Valdes, 1996[420]	*	2′-deoxyadenosine deaminase	pf	22	0.22	350	0.95 (0.87 to 0.99) [72/76]	0.92 (0.89 to 0.95) [253/274]	216.9 (72.1 to 652.0)	P	H	?	?	?	?
	*,†	ADA		47			1.00 (0.95 to 1.00) [76/76]	0.91 (0.87 to 0.94) [249/274]	0.0 (0.0 to 0.0)						
	*	ADA2		40			1.00 (0.95 to 1.00) [76/76]	0.96 (0.93 to 0.98) [263/274]	0.0 (0.0 to 0.0)						
Villegas, 2000[213]	*,†	ADA	pf	45.5	0.44	140	0.87 (0.76 to 0.94) [53/61]	0.86 (0.76 to 0.93) [68/79]	41.0 (15.4 to 109.0)	P	C + H + Clin + T	?	P	?	N

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Villena, 1996[421]	*,†	ADA	pf	33	0.21	228	0.90 (0.78 to 0.97) [44/49]	0.95 (0.91 to 0.98) [170/179]	166.2 (53.0 to 521.0)	P	C + H + Clin + T	Y	P	Y	N

[a] Primary analysis: * indicates data set included in primary analysis; † indicates data sets used in secondary analysis to compare test cut-offs.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 15

Serodiagnostic and biochemical test evaluations in pleural TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Anti-TB antibody tests – commercial															
Chierakul, 2001[208]	*	ICT test	sr		0.56	119	0.46 (0.34 to 0.59) [31/67]	0.60 (0.45 to 0.73) [31/52]	1.3 (0.6 to 2.6)	L	C + H	Y	?	?	?
	*		pf				0.25 (0.16 to 0.37) [17/67]	0.90 (0.79 to 0.97) [47/52]	3.2 (1.1 to 9.4)						
Ghelani, 1999[206]	*	Inhouse (A60)	pf		0.67	81	0.91 (0.80 to 0.97) [49/54]	0.56 (0.35 to 0.75) [15/27]	12.3 (3.7 to 40.4)	P	C + H + T	?	?	?	Y
Kunter, 2003[207]	*	Anda TB IgG	sr	0.464	0.70	125	0.26 (0.17 to 0.37) [23/88]	0.86 (0.71 to 0.95) [32/37]	2.3 (0.8 to 6.5)	R	C + H	?	?	?	N
	*	Anda TB IgM		0.624			0.48 (0.37 to 0.59) [42/88]	0.92 (0.78 to 0.98) [34/37]	10.3 (3.0 to 36.2)						
	*	Anda TB IgG	pf	0.614	0.70	125	0.42 (0.32 to 0.53) [37/88]	0.76 (0.59 to 0.88) [28/37]	2.3 (1.0 to 5.3)						
	*	Anda TB IgM		0.614			0.77 (0.67 to 0.86) [68/88]	0.95 (0.82 to 0.99) [35/37]	59.5 (13.1 to 269.3)						
Antigen tests															
Dhand, 1988[209]	*	MTB	pf	0.2	0.42	36	0.80 (0.52 to 0.96) [12/15]	0.38 (0.18 to 0.62) [8/21]	2.5 (0.5 to 11.5)	P	C + H + Clin + T + TST	Y	P	Y	?
Cytokine tests															
Aoki, 1994[396]	*	IFN-γ	pf		0.28	39	1.00 (0.72 to 1.00) [11/11]	1.00 (0.88 to 1.00) [28/28]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	?
Chiang, 1994[210]	*	IL-2R	sr	5000	0.29	93	0.74 (0.54 to 0.89) [20/27]	0.94 (0.85 to 0.98) [62/66]	44.3 (11.7 to 167.1)	P	C+H	?	?	?	N
Momi, 2002[407]	*	TNF-α	pf	55	0.32	127	0.71 (0.54 to 0.84) [29/41]	0.76 (0.65 to 0.84) [65/86]	7.5 (3.3 to 17.2)	P	C + H + Clin + T	?	?	?	?
Orphanidou, 1996[409]	*	IL-1	pf	1	0.34	97	0.48 (0.31 to 0.66) [16/33]	0.66 (0.53 to 0.77) [42/64]	1.8 (0.8 to 4.2)	P	C + H	?	?	?	N
	*		sr	1			0.58 (0.39 to 0.75) [19/33]	0.55 (0.42 to 0.67) [35/64]	1.6 (0.7 to 3.8)						
	*	TNF	pf	40.4			0.70 (0.51 to 0.84) [23/33]	0.94 (0.85 to 0.98) [60/64]	34.5 (9.8 to 121.0)						
	*		sr	27			0.21 (0.09 to 0.39) [7/33]	0.97 (0.89 to 1.00) [62/64]	8.3 (1.6 to 42.9)						
Ribera, 1988[422]	*	IFN-γ	pf	2	0.37	80	1.00 (0.88 to 1.00) [30/30]	(1.00 (0.93 to 1.00) 50/50	0.0 (0.0 to 0.0)	P	C + H	?	?	?	?

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Richter, 1994[413]	*	Total protein	pf		0.95	118	0.82 (0.74 to 0.89) [92/112]	0.83 (0.34 to 1.00) [5/6]	23.0 (2.5 to 207.8)	P	C + H + T + TST	?	P	?	?
Silva-Mejias, 1995[423]	*	IL-1B	pf	200	0.19	102	0.05 (0.00 to 0.26) [1/19]	0.81 (0.71 to 0.89) [67/83]	0.2 (0.0 to 1.9)	P	C + H	?	?	?	?
Valdés, 1993[418]	*	IFN-γ	pf	140	0.24	145	0.94 (0.81 to 0.99) [33/35]	0.92 (0.85 to 0.96) [101/110]	185.2 (38.1 to 900.6)	P	C+H	?	?	?	N
Villegas, 2000[213]	*	IFN-γ	pf		0.42	137	0.78 (0.65 to 0.87) [45/58]	0.97 (0.91 to 1.00) [77/79]	133.3 (28.8 to 617.6)	P	C + H + Clin + T	?	P	?	N
Wongtim, 1999[424]	*	IFN-γ	pf	240	0.59	66	0.95 (0.83 to 0.99) [37/39]	0.96 (0.81 to 1.00) [26/27]	481.0 (41.4 to 5,587.1)	P	C + H + T	Y	P	?	?
				83			0.93 (0.80 to 0.98) [38/41]	0.96 (0.80 to 1.00) [24/25]	304.0 (29.9 to 3,094.0)						
Lysozyme tests															
Asseo, 1982[425]	*	Lysozyme	pf/sr	1	0.36	118	1.00 (0.92 to 1.00) [42/42]	0.96 (0.89 to 0.99) [73/76]	0.0 (0.0 to 0.0)	R	C + H + Clin + T + X	?	?	?	N
	*		pf	10			0.62 (0.46 to 0.76) [26/42]	0.97 (0.91 to 1.00) [74/76]	60.1 (12.9 to 279.5)						
Caballero, 1999[400]	*	Lysozyme	pf/pl	2	0.07	92	0.83 (0.36 to 1.00) [5/6]	0.70 (0.59 to 0.79) [60/86]	11.5 (1.3 to 103.7)	P	C + Clin + T	?	?	?	?
Fontan Bueso, 1988[401]	*	Lysozyme	pf/sr	1.2	0.44	138	1.00 (0.94 to 1.00) [61/61]	0.95 (0.87 to 0.99) [73/77]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	?	?	?
Klockars, 1979[426]	*	Lysozyme	pf	15	0.25	110	0.79 (0.59 to 0.92) [22/28]	0.90 (0.82 to 0.96) [74/82]	33.9 (10.6 to 108.3)	P	C + H+ Clin + T + X	?	?	Y	?
	*		pf/sr	1.1			0.86 (0.67 to 0.96) [24/28]	0.90 (0.82 to 0.96) [74/82]	55.5 (15.3 to 200.7)						
San Jose, 1992[414]	*	Lysozyme	sr	13	0.20	271	0.89 (0.77 to 0.96) [47/53]	0.30 (0.24 to 0.36) [65/218]	3.3 (1.4 to 8.2)	P	C + H + Clin	?	?	?	N
	*	Lysozyme/total protein	pf	5	0.19	270	0.60 (0.45 to 0.73) [31/52]	0.42 (0.36 to 0.49) [92/218]	1.1 (0.6 to 2.0)						
Valdés, 1993[418]	*	Lysozyme	pf/sr	1.1	0.18	276	0.67 (0.52 to 0.80) [33/49]	0.90 (0.86 to 0.94) [205/227]	19.2 (9.2 to 40.3)	P	C + H	?	?	?	N
	*		pf	15			0.86 (0.73 to 0.94) [42/49]	0.62 (0.55 to 0.68) [140/227]	9.7 (4.2 to 22.4)						
Villena, 1996[421]	*	Lysozyme	pf/sr	1.7	0.21	228	0.71 (0.57 to 0.83) [35/49]	0.92 (0.87 to 0.96) [165/179]	29.5 (12.9 to 67.3)	P	C + H + Clin + T	Y	P	Y	N

continued

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Miscellaneous tests															
Aoki, 1994[396]	*	CA125	pf	35	0.37	19	1.00 (0.59 to 1.00) [7/7]	0.75 (0.43 to 0.95) [9/12]	0.0 (0.0 to 0.0)	P	C + H	?	?	?	?
Ribera, 1990[211]	*	IFN-γ response (PPD)	sr	≥10	0.38	40	0.47 (0.21 to 0.73) [7/15]	0.56 (0.35 to 0.76) [14/25]	1.1 (0.3 to 4.0)	P	C + H	?	?	?	?
	*		pf	≥10			0.93 (0.68 to 1.00) [14/15]	0.72 (0.51 to 0.88) [18/25]	36.0 (4.0 to 327.7)						
Yorgancioglu, 1996[427]	*	TBSA	pf		0.52	21	0.55 (0.23 to 0.83) [6/11]	0.80 (0.44 to 0.97) [8/10]	4.8 (0.7 to 33.8)	R	C + H + T	?	?	?	N
Ribera, 1990[211]	*	Lymphocytes	sr	≥2	0.38	40	0.87 (0.60 to 0.98) [13/15]	0.60 (0.39 to 0.79) [15/25]	9.8 (1.8 to 52.8)	P	C + H	?	?	?	?
				≥4			0.67 (0.38 to 0.88) [10/15]	0.64 (0.43 to 0.82) [16/25]	3.6 (0.9 to 13.7)						
				≥6			0.33 (0.12 to 0.62) [5/15]	0.72 (0.51 to 0.88) [18/25]	1.3 (0.3 to 5.1)						
	*	Lymphocytes	pf	≥6	0.38	40	0.80 (0.52 to 0.96) [12/15]	0.96 (0.80 to 1.00) [24/25]	96.0 (9.0 to 1,023.8)						
				≥2			1.00 (0.78 to 1.00) [15/15]	0.60 (0.39 to 0.79) [15/25]	0.0 (0.0 to 0.0)						
				≥4			0.93 (0.68 to 1.00) [14/15]	0.80 (0.59 to 0.93) [20/25]	56.0 (5.9 to 533.0)						

[a] Primary analysis: * indicates data set included in primary analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 16

NAAT evaluations in TB meningitis – study characteristics

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Study	Test[a]	% AFB+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Commercial													
Bemer-Melchoir, 1998[377]	Amplicor – Manual	8	0.06	17	0.00 (0.00 to 0.97) [0/1]	1.00 (0.79 to 1.00) [16/16]	0.00 P (0.00 to 0.00)	C alone		?	R	?	Y
Bonington, 1998,[428] 2000[429]	Amplicor – Cobas	12	0.26	69	0.33 (0.13 to 0.59) [6/18]	0.98 (0.90 to 1.00) [50/51]	25.00 (2.75 to 227.62)	P	C + Clin	?	P	?	Y
	Amplicor – Manual				0.50 (0.26 to 0.74) [9/18]	0.98 (0.90 to 1.00) [50/51]	50.00 (5.63 to 444.32)						
Brienze, 2001[430]	Amplicor – Manual	11	0.33	46	0.27 (0.08 to 0.55) [4/15]	0.94 (0.79 to 0.99) [29/31]	5.27 (0.84 to 33.00)	R	C + Clin	Y	P	?	Y
Chedore, 2002[431]	AMTD – Enhanced	3	0.05	311	0.94 (0.70 to 1.00) [15/16]	0.99 (0.98 to 1.00) [293/295]	2,197.50 (188.51 to 25,616.98)	L	C alone	?	R	?	Y
Ehlers, 1996[306]	AMTD – Standard		0.12	51	0.67 (0.22 to 0.96) [4/6]	0.98 (0.88 to 1.00) [44/45]	88.00 (6.47 to 1,196.26)	L	C alone	?	?	?	Y
Gamboa, 1997[378]	AMTD – Standard		0.47	17	0.63 (0.24 to 0.91) [5/8]	1.00 (0.66 to 1.00) [9/9]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	?
Lang, 1998[432]	AMTD – Standard	0	0.29	84	0.83 (0.63 to 0.95) [20/24]	1.00 (0.94 to 1.00) [60/60]	0.00 (0.00 to 0.00)	P	C + Clin + T	?	?	?	Y
	Cut-off ≥ 11,000 RLU				0.83 (0.63 to 0.95) [20/24]	1.00 (0.94 to 1.00) [60/60]	0.00 (0.00 to 0.00)						
	Cut-off ≥ 30,000 RLU				0.33 (0.16 to 0.55) [8/24]	1.00 (0.94 to 1.00) [60/60]	0.00 (0.00 to 0.00)						
Osumi, 1995[321]	AMTD – Standard		0.33	6	1.00 (0.16 to 1.00) [2/2]	1.00 (0.40 to 1.00) [4/4]	0.00 (0.00 to 0.00)	P	C + Clin	Y	?	?	?
Rajo, 2002[433]	LcX assay	1	0.10	87	0.56 (0.21 to 0.86) [5/9]	0.99 (0.93 to 1.00) [77/78]	96.25 (8.99 to 1,030.34)	R	C alone	?	P	?	?
Shah, 1998[382]	Amplicor – Manual		0.01	402	0.67 (0.09 to 0.99) [2/3]	1.00 (0.99 to 1.00) [398/399]	796.00 (35.84 to 17,679.98)	L	C alone	?	?	?	Y
Zambardi, 1995[333]	Amplicis Myco B (IS6110)		0.08	13	0.00 (0.00 to 0.97) [0/1]	0.92 (0.62 to 1.00) [11/12]	0.00 (0.00 to 0.00)	P	C + Clin	Y	?	Y	?
In-house													
Ahuja, 1994[434]	target NS		0.39	36	0.86 (0.57 to 0.98) [12/14]	0.36 (0.17 to 0.59) [8/22]	3.43 (0.61 to 19.35)	?	Clin + H + T	?	?	?	Y
Brienze, 2001[430]	MPB64	11	0.23	100	0.48 (0.27 to 0.69) [11/23]	0.97 (0.91 to 1.00) [75/77]	34.38 (6.77 to 174.61)	R	C + Clin	Y	P	?	Y

continued

Study	Test[a]	% AFB+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Caws, 2000[435]	IS6110		0.13	131	0.47 (0.23 to 0.72) [8/17]	0.99 (0.94 to 1.00) [91/92]	80.89 (9.06 to 721.90)	L	C + Clin + T	?	P	?	N
Ceyhan, 1996[222]	IS6110		0.37	57	0.29 (0.11 to 0.52) [6/21]	0.97 (0.85 to 1.00) [35/36]	14.00 (1.55 to 126.57)	P	C alone	?	?	?	Y
Hooker, 2003[436]	Target NS (LCR)	2	0.40	57	0.22 (0.07 to 0.44) [5/23]	0.91 (0.76 to 0.98) [31/34]	2.87 (0.61 to 13.45)	P	C alone	?	P	?	Y
	Target NS (PCR)		0.47	49	0.04 (0.00 to 0.22) [1/23]	1.00 (0.87 to 1.00) [26/26]	0.00 (0.00 to 0.00)						
Kolk, 1992[349]	IS986	5	0.07	102	0.86 (0.42 to 1.00) [6/7]	0.72 (0.61 to 0.80) [68/95]	15.11 (1.74 to 131.49)	L	C alone	Y	?	Y	Y
Kox, 1994[350]	IS6110	7	0.13	15	1.00 (0.16 to 1.00) [2/2]	0.92 (0.64 to 1.00) [12/13]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	N
Kox, 1995[437]	IS6110	7	0.55	42	0.48 (0.27 to 0.69) [11/23]	1.00 (0.82 to 1.00) [19/19]	0.00 (0.00 to 0.00)	L	C + Clin + T	Y	?	N	Y
Narayanan, 2001[438]	IS6110		0.70	96	0.81 (0.69 to 0.89) [54/67]	0.79 (0.60 to 0.92) [23/29]	15.92 (5.39 to 47.05)	?	C + Clin	?	?	?	Y
	TRC4				0.91 (0.82 to 0.97) [61/67]	0.76 (0.56 to 0.90) [22/29]	31.95 (9.68 to 105.50)						
Nguyen, 1996[439]	IS6110	1	0.49	136	0.35 (0.24 to 0.48) [23/66]	0.87 (0.77 to 0.94) [61/70]	3.63 (1.53 to 8.60)	R	C + Clin + T	Y	?	N	Y
Portillo-Gomez, 2000[387]	IS6110	13	0.23	146	0.94 (0.80 to 0.99) [31/33]	1.00 (0.97 to 1.00) [113/113]	0.00 (0.00 to 0.00)	L	C + Clin + H + T	?	P	?	Y

[a] Test evaluated and any subgroup information.
[b] Percentage of AFB-positive samples tested.
[c] Prevalence of TB in sample tested.
[d] Total number of patients tested with a given test.
[e] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[f] Specificity (95% confidence interval) [number true negative/total number without disease].
[g] Diagnostic odds ratio (95% confidence interval).
[h] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[i] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[j] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[k] Study design: P, prospective; R, retrospective; ?, can't tell.
[l] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 17

Serodiagnostic and biochemical evaluations in TB meningitis – study characteristics

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Adenosine deaminase group															
Blake, 1982[398]	*	ADA	pf	30	0.41	202	0.92 (0.73 to 0.99) [22/24]	0.96 (0.91 to 0.99) [106/110]		R	C + H + Clin + T + X	?	?	?	?
Eintracht, 2000[214]	*,†	ADA	csf	6	0.18	61	0.91 (0.59 to 1.00) [10/11]	0.94 (0.83 to 0.99) [47/50]	156.7 (14.7 to 1,665.7)	P	C alone	Y	P	?	N
	*	ADA2		>80	0.33	33	1.00 (0.72 to 1.00) [11/11]	0.86 (0.65 to 0.97) [19/22]	0.0 (0.0 to 0.0)						
				>90			0.36 (0.11 to 0.69) [4/11]	0.95 (0.77 to 1.00) [21/22]	12.0 (1.1 to 126.1)						
Gambhir, 1999[440]	*,†	ADA	csf	>7	0.60	60	0.69 (0.52 to 0.84) [25/36]	0.63 (0.41 to 0.81) [15/24]	3.8 (1.3 to 11.3)	P	C + H + Clin	?	?	?	N
	†			≥ 8			0.44 (0.28 to 0.62) [16/36]	0.75 (0.53 to 0.90) [18/24]	2.4 (0.8 to 7.5)						
Kaur, 1992[225]	*,†	ADA	csf	10	0.21	136	0.39 (0.22 to 0.59) [11/28]	0.90 (0.83 to 0.95) [97/108]	5.7 (2.1 to 15.2)	P	C + H + T	Y	P	Y	N
Mann, 1982[441]	*,†	ADA	csf	>6	0.57	58	0.85 (0.68 to 0.95) [28/33]	0.84 (0.64 to 0.95) [21/25]	29.4 (7.0 to 123.0)	P	C + Clin + T + TST	?	R	?	?
				>4			0.88 (0.72 to 0.97) [29/33]	0.84 (0.64 to 0.95) [21/25]	38.1 (8.5 to 169.8)						
				>5			0.79 (0.61 to 0.91) [26/33]	0.84 (0.64 to 0.95) [21/25]	19.5 (5.0 to 75.7)						
Pettersson, 1991[442]	*,†	ADA	csf	20	0.04	85	1.00 (0.29 to 1.00) [3/3]	0.99 (0.93 to 1.00) [81/82]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	?	?	N
Rohani, 1995[443]	*,†	ADA	csf	9	0.12	119	1.00 (0.77 to 1.00) [14/14]	0.88 (0.80 to 0.93) [92/105]	0.0 (0.0 to 0.0)	P	C + Clin + X	?	?	?	?
Anti-TB antibody tests															
Prabhakar, 1987[215]	*	BCG	csf conc 1:500		0.10	260	0.48 (0.28 to 0.69) [12/25]	0.92 (0.88 to 0.95) [217/235]	11.1 (4.4 to 27.9)	P	C + Clin + T	Y	?	?	?
	*		conc 1:200				0.40 (0.21 to 0.61) [10/25]	0.97 (0.93 to 0.99) [227/235]	18.9 (6.5 to 55.0)						
	*	H37Rv	conc 1:500				0.72 (0.51 to 0.88) [18/25]	0.91 (0.87 to 0.95) [215/235]	27.6 (10.3 to 74.1)						
	*		conc 1:200				0.72 (0.51 to 0.88) [18/25]	0.92 (0.88 to 0.95) [216/235]	29.2 (10.9 to 78.8)						

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Antigen tests															
Bal, 1983[444]	*	H37Rv	csf	0.15	0.20	41	1.00 (0.63 to 1.00) [8/8]	0.97 (0.84 to 1.00) [32/33]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	?	?	?
Donald, 1987[445]	*	MTB	csf	>0.05	0.42	53	1.00 (0.85 to 1.00) [22/22]	0.81 (0.63 to 0.93) [25/31]	0.0 (0.0 to 0.0)	P	C + Clin + X	?	?	?	N
				>0.075			0.86 (0.65 to 0.97) [19/22]	0.87 (0.70 to 0.96) [27/31]	42.8 (8.6 to 213.4)						
Miscellaneous tests															
Mann, 1982[441]	*	Bromide partition test	csf	1.6	0.57	58	0.88 (0.72 to 0.97) [29/33]	0.96 (0.80 to 1.00) [24/25]	174.0 (18.2 to 1,662.6)	P	C + Clin + T + TST	?	R	?	?
Wiggelinkhuizen, 1980[216]	*	Bromide partition test	sr&csf	1.6	0.61	83	0.94 (0.84 to 0.99) [48/51]	0.88 (0.71 to 0.96) [28/32]	112.0 (23.4 to 537.2)	P	C + H + Clin + T	?	R	?	Y

[a] Primary analysis: * indicates data set included in primary analysis; † indicates data sets used in secondary analysis to compare test cut-offs.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 18

NAAT evaluations in lymphatic TB – study details

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Study	Test[a]	% Sm+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]
Commercial													
Baek, 2000[217]	Amplicor – Manual		0.59	29	0.76 (0.50 to 0.93) [13/17]	1.00 (0.74 to 1.00) [12/12]	0.00 (0.00 to 0.00)	P	T + H	?	?	N	Y
Bemer-Melchoir, 1998[377]	Amplicor – Manual	8	0.33	33	0.73 (0.39 to 0.94) [8/11]	0.82 (0.60 to 0.95) [18/22]	12.00 (2.16 to 66.55)	P	C alone	?	R	?	Y
Ehlers, 1996[306]	AMTD – Standard		0.48	29	0.93 (0.66 to 1.00) [13/14]	1.00 (0.78 to 1.00) [15/15]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Gamboa, 1997[378]	AMTD – Standard		0.61	28	0.82 (0.57 to 0.96) [14/17]	0.64 (0.31 to 0.89) [7/11]	8.17 (1.42 to 47.02)	P	C alone	?	?	?	?
Gamboa, 1998[379]	AMTD – Enhanced	15	0.47	38	0.78 (0.52 to 0.94) [14/18]	1.00 (0.83 to 1.00) [20/20]	0.00 (0.00 to 0.00)	P	C + X	?	?	?	Y
	AMTD – Standard				0.89 (0.65 to 0.99) [16/18]	1.00 (0.83 to 1.00) [20/20]	0.00 (0.00 to 0.00)						
Gamboa, 1998[380]	LcX assay	12	0.3	113	0.88 (0.73 to 0.97) [30/34]	1.00 (0.95 to 1.00) [79/79]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Rimek, 2002[446]*	Amplicor – Cobas	7	0.38	39	0.40 (0.16 to 0.68) [6/15]	0.92 (0.73 to 0.99) [22/24]	7.33 (1.24 to 43.41)	R	C alone	?	?	?	Y
Shah, 1998[382]	Amplicor – Manual		0.22	45	0.90 (0.55 to 1.00) [9/10]	1.00 (0.90 to 1.00) [35/35]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
In-house													
Brisson-Noel, 1989[219]	65-kDa		0.75	4	1.00 (0.29 to 1.00) [3/3]	1.00 (0.03 to 1.00) [1/1]	0.00 (0.00 to 0.00)	?	C + Clin + T	?	?	?	Y
Goel, 2001[218]	65-kDa	50	0.75	52	0.95 (0.83 to 0.99) [37/39]	0.92 (0.64 to 1.00) [12/13]	222.00 (18.46 to 2,670.22)	P	C+T	Y	?	Y	?
Manitchotpisit, 1999[447]	MPB64	28	0.76	33	0.84 (0.64 to 0.95) [21/25]	0.75 (0.35 to 0.97) [6/8]	15.75 (2.30 to 107.93)	P	C + H + T	?	?	?	Y
Narayanan, 2000[448]	IS6110	11	0.6	101	0.69 (0.56 to 0.80) [42/61]	0.45 (0.29 to 0.62) [18/40]	1.81 (0.79 to 4.13)	R	C + H	?	R	?	?
	TRC4		0.61	100	0.79 (0.66 to 0.88) [48/61]	0.44 (0.28 to 0.60) [17/39]	2.85 (1.18 to 6.89)						
Rimek, 2002[446]*	IS6110	6	0.4	40	0.88 (0.62 to 0.98) [14/16]	1.00 (0.86 to 1.00) [24/24]	0.00 (0.00 to 0.00)	R	C alone	?	?	?	Y
Yassin, 2003[34]	IS6110		0.68	71	0.71 (0.56 to 0.83) [34/48]	0.35 (0.16 to 0.57) [8/23]	1.30 (0.45 to 3.74)	P	Cytology	?		?	Y

continued

Study	Test[a]	% AFB+[b]	Prevalence[c]	Total[d]	Sens % (95% CI) [tp/dis][e]	Spec % (95% CI) [tn/nodis][f]	DOR (95% CI)[g]	Setting[h]	Reference test[i]	Index blinded[j]	Design[k]	Ref blinded[l]	Pt repr[m]

[a] Test evaluated and any subgroup information.
[b] Percentage of smear-positive samples tested.
[c] Prevalence of TB in sample tested.
[d] Total number of patients tested with a given test.
[e] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[f] Specificity (95% confidence interval) [number true negative/total number without disease].
[g] Diagnostic odds ratio (95% confidence interval).
[h] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[i] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[j] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[k] Study design: P, prospective; R, retrospective; ?, can't tell.
[l] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 19

Serodiagnostic and biochemical test evaluations in lymphatic TB – study details

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
Anti-TB antibody tests															
Kiran, 1982[220]	*	H37Ra	l	2.5	0.23	126	0.55 (0.36 to 0.73) [17/31]	0.95 (0.90 to 0.98) [103/108]	25.0 (8.0 to 78.4)	P	C + H	?	?	?	Y
Antigen tests															
Jain, 2003[221]	*	MTB	l		0.77	124	0.92 (0.84 to 0.96) [88/96]	0.86 (0.67 to 0.96) [24/28]	66.0 (18.3 to 237.9)	P	C alone	?	?	?	Y

[a] Primary analysis: * indicates data set included in primary analysis.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 20

Peritoneal TB – study characteristics

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Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr.[o]
NAAT Tests															
Ceyhan, 1996[222]	*	IS6110	a		0.43	7	1.00 (0.29 to 1.00) [3/3]	1.00 (0.40 to 1.00) [4/4]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	Y
Adenosine deaminase tests															
Bhargava, 1990[449]	*,†	ADA	a	36	0.20	87	1.00 (0.80 to 1.00) [17/17]	0.97 (0.90 to 1.00) [68/70]	0.0 (0.0 to 0.0)	P	C + H + Clin	?	P	?	N
	†			29			1.00 (0.80 to 1.00) [17/17]	0.87 (0.77 to 0.94) [61/70]	0.0 (0.0 to 0.0)						
	†			32			1.00 (0.80 to 1.00) [17/17]	0.91 (0.82 to 0.97) [64/70]	0.0 (0.0 to 0.0)						
	*	ADA	a/sr	0.984	0.33	43	0.79 (0.49 to 0.95) [11/14]	0.86 (0.68 to 0.96) [25/29]	22.9 (4.4 to 120.1)						
				0.974			0.86 (0.57 to 0.98) [12/14]	0.97 (0.82 to 1.00) [28/29]	168.0 (13.9 to 2,034.3)						
				1.26			0.57 (0.29 to 0.82) [8/14]	0.86 (0.68 to 0.96) [25/29]	8.3 (1.9 to 37.2)						
	*	ADA	sr	54	0.33	43	0.79 (0.49 to 0.95) [11/14]	0.97 (0.82 to 1.00) [28/29]	102.7 (9.6 to 1,096.3)						
				43			0.93 (0.66 to 1.00) [13/14]	0.97 (0.82 to 1.00) [28/29]	364.0 (21.1 to 6,285.5)						
				48			0.86 (0.57 to 0.98) [12/14]	0.93 (0.77 to 0.99) [27/29]	0.93 (0.77 to 0.99) (10.2 to 644.9)						
Brant, 1995[223]	*,†	ADA	a	31	0.18	44	1.00 (0.63 to 1.00) [8/8]	0.92 (0.78 to 0.98) [33/36]	0.0 (0.0 to 0.0)	P	C + H	?	P	?	N
Burgess, 2001[450]	*,†	ADA	a	≥30	0.10	178	0.94 (0.73 to 1.00) [17/18]	0.92 (0.87 to 0.96) [147/160]	192.2 (23.7 to 1,562.0)	P	C + H + Clin + T	?	P	?	N
				≥25			0.94 (0.73 to 1.00) [17/18]	0.87 (0.81 to 0.92) [139/160]	112.5 (14.2 to 890.3)						
	†			≥35			0.83 (0.59 to 0.96) [15/18]	0.94 (0.89 to 0.97) [150/160]	75.0 (18.6 to 302.7)						
	†			≥40			0.83 (0.59 to 0.96) [15/18]	0.96 (0.92 to 0.99) [154/160]	128.3 (29.1 to 565.9)						
Dwivedi, 1990[451]	†	ADA	a	33	0.39	49	1.00 (0.82 to 1.00) [19/19]	0.97 (0.83 to 1.00) [29/30]	0.0 (0.0 to 0.0)	P	C + H + T + X	?	?	?	N

continued

Study	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded I[n]	Pt repr[o]
Kaur, 1992[225]	*,†	ADA	a	15	0.09	140	0.83 (0.52 to 0.98) [10/12]	0.81 (0.73 to 0.88) [104/128]	21.7 (4.5 to 105.4)	P	C + H + T	Y	P	Y	N
Ribera, 1991[224]	†	ADA	a	40	0.19	86	1.00 (0.79 to 1.00) [16/16]	0.97 (0.90 to 1.00) [68/70]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	P	?	N
Cytokine tests															
Brant, 1995[223]	*	Total protein	a	3.5	0.18	44	0.75 (0.35 to 0.97) [6/8]	0.53 (0.35 to 0.70) [19/36]	3.4 (0.6 to 18.9)	P	C + H	?	P	?	N
Ribera, 1991[224]	*	IFN-γ	a	3	0.19	86	1.00 (0.79 to 1.00) [16/16]	1.00 (0.95 to 1.00) [70/70]	0.0 (0.0 to 0.0)	P	C + H + Clin + T	?	P	?	N
Miscellaneous tests															
Brant, 1995[223]	*	LDH	a	240	0.18	44	1.00 (0.63 to 1.00) [8/8]	0.64 (0.46 to 0.79) [23/36]	0.0 (0.0 to 0.0)	P	C + H	?	P	?	N
	*	Lymphocyte proliferation	a	70			1.00 (0.63 to 1.00) [8/8]	0.47 (0.30 to 0.65) [17/36]	0.0 (0.0 to 0.0)						
	*	Lymphocytes	a	1000			0.13 (0.00 to 0.53) [1/8]	0.72 (0.55 to 0.86) [26/36]	0.4 (0.0 to 3.4)						

[a] Primary analysis: * indicates data set included in primary analysis; † indicates data sets used in secondary analysis to compare test cut-offs.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; s, sputum; sr, serum; r, respiratory; u, urine.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 21

Pericardial TB – study characteristics

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Study[a]	Pr analysis[a]	Test[b]	Sample type[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
NAATS tests															
Lee, 2002[226]	*	Amplicor – Cobas	a		0.18	67	0.75 (0.43 to 0.95) [9/12]	1.00 (0.94 to 1.00) [55/55]	0.00 (0.00 to 0.00)	P	C + Clin + T + H	Y	?	?	?
Ceyhan, 1996[222]	*	IS6110	a		0.57	7	0.25 (0.01 to 0.81) [1/4]	1.00 (0.29 to 1.00) [3/3]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	Y
Adenosine deaminase test															
Burgess, 2002[227]	*	ADA	p	30	0.58	110	0.94 (0.85 to 0.98) [60/64]	0.67 (0.52 to 0.80) [31/46]	31.0 (9.5 to 101.4)	P	C + H + Clin + T + X	?	P	?	?
Koh, 1997[452]	*	ADA	p	40	0.41	51	0.86 (0.64 to 0.97) [18/21]	0.87 (0.69 to 0.96) [26/30]	39.0 (7.8 to 195.7)	P	C + Clin + T + H	Y	P	?	N
Komsuoglu, 1995[453]	*	ADA	p	70	0.19	108	1.00 (0.83 to 1.00) [20/20]	0.91 (0.83 to 0.96) [80/88]	0.0 (0.0 to 0.0)	R	C + H + T + X	?	?	?	N
Lee, 2002[226]	*	ADA	p	40	0.18	67	0.83 (0.52 to 0.98) [10/12]	0.78 (0.65 to 0.88) [43/55]	17.9 (3.4 to 93.1)	P	C + H + Clin + T	Y	?	?	?
Cytokine test															
Burgess, 2002[227]	*	IFN-γ	p	200	0.63	30	1.00 (0.82 to 1.00) [19/19]	1.00 (0.72 to 1.00) [11/11]	0.0 (0.0 to 0.0)	P	C + H + Clin + T + X	?	P	?	?

[a] Primary analysis: * indicates study compares in-house and commercial NAAT tests.
[b] Test evaluated and any subgroup information.
[c] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[d] Cut-off used to define positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[l] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 22

Genito-urinary TB – study characteristics

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Study	Test[a]	Sample type[b]	% Sm+[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
NAAT – Commercial															
Gamboa, 1997[378]	AMTD – Standard	u		30,000	0.45	40	0.50 (0.26 to 0.74) [9/18]	1.00 (0.85 to 1.00) [22/22]	0.00 (0.00 to 0.00)	P	C alone	?	?	?	?
Gamboa, 1998[379]	AMTD – Enhanced	u	4.1	30,000	0.19	73	0.79 (0.49 to 0.95) [11/14]	1.00 (0.94 to 1.00) [59/59]	0.00 (0.00 to 0.00)	P	C + X	?	?	?	Y
Gamboa, 1998[379]	AMTD – Standard	u	5.9	30,000	0.19	73	0.64 (0.35 to 0.87) [9/14]	1.00 (0.94 to 1.00) [59/59]	0.00 (0.00 to 0.00)	P	C + X	?	?	?	Y
Gamboa, 1998[380]	LcX assay	u	11.6		0.29	69	0.70 (0.46 to 0.88) [14/20]	1.00 (0.93 to 1.00) [49/49]	0.00 (0.00 to 0.00)	L	C alone	?	?	?	Y
Zambardi, 1995[333]	Amplicis Myco B	u			0.05	22	0.00 (0.00 to 0.97) [0/1]	0.67 (0.43 to 0.85) [14/21]	0.00 (0.00 to 0.00)	P	C + Clin	Y	?	Y	?
NAAT – in-house															
Hemal, 2000[229]	MPB64	u			0.83	42	0.94 (0.81 to 0.99) [33/35]	0.86 (0.42 to 1.00) [6/7]	99.00 (7.71 to 1,272.03)	R	C+Clin+H	Y	?	Y	Y
Moussa, 2000[228]	16S rRNA	u	21		0.36	1000	0.87 (0.83 to 0.90) [316/363]	0.99 (0.98 to 1.00) [630/637]	605.11 (270.41 to 1,354.08)	L	C alone	?	?	?	Y
Moussa, 2000[228]	IS6110	u	21		0.36	1000	0.96 (0.93 to 0.97) [347/363]	0.98 (0.97 to 0.99) [625/637]	1,129.56 (528.31 to 2,415.07)	L	C alone	?	?	?	Y
van Vollenhoven, 1996[454]	IS6110	u			0.02	83	1.00 (0.16 to 1.00) [2/2]	1.00 (0.96 to 1.00) [81/81]	0.00 (0.00 to 0.00)	P	C + H	?	?	?	Y
Antigen tests															
Rattan, 1993[230]	H37Rv	sr		0.8	0.70	50	0.40 (0.24 to 0.58) [14/35]	0.93 (0.68 to 1.00) 914/15]	9.3 (1.1 to 79.2)	P	Clin + lap	?	?	?	N

[a] Test evaluated and any subgroup information.
[b] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sr, serum; u, urine.
[c] Percentage of smear-positive samples tested.
[d] Cut-off used to define test positivity, if reported.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.

continued

Study	Test[a]	Sample type[b]	% Sm+[c]	Cut-off[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]

[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

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Appendix 23

Skeletal TB – study characteristics

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Study	Test[a]	Sample type[b]	% sputum[c]	% Sm+[d]	Prevalence[e]	Total[f]	Sens (95% CI) [tp/dis][g]	Spec (95% CI) [tn/nodis][h]	DOR (95%CI)[i]	Setting[j]	Reference test[k]	Index blinded[l]	Design[m]	Ref blinded[n]	Pt repr[o]
van der Spoel van Dijk, 2000[231]	IS6110	sb	0	0	45	0.29	0.79 (0.49 to 0.95) [11/14]	0.89 (0.71 to 0.98) [24/27]	29.33 (5.09 to 169.18)	R	Clin + H	?	?	?	Y

[a] Test evaluated and any subgroup information.
[b] Sample tested: B, BAL or bronchial aspirate; g, gastric aspirate; la, lung aspirate; m, mixed (respiratory and non-respiratory); pf, pleural fluid; r, respiratory; s, sputum; sb, spinal biopsy; sr, serum; u, urine.
[c] Percentage of total samples tested that were sputum.
[d] Percentage of smear-positive samples tested.
[e] Prevalence of TB in sample tested.
[f] Total number of patients tested with a given test.
[g] Sensitivity (95% confidence interval) [number true positive/total number of diseased].
[h] Specificity (95% confidence interval) [number true negative/total number without disease].
[i] Diagnostic odds ratio (95% confidence interval).
[j] Study setting: L, laboratory; P, primary hospital; R, referral hospital; ?, unknown/not clear.
[k] Reference test used: C, culture; Clin, clinical diagnosis; H, histology; T, treatment trial; X, X-ray.
[l] Index test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[m] Study design: P, prospective; R, retrospective; ?, can't tell.
[n] Reference test interpreted blinded?: Y, yes; N, no; ?, can't tell.
[o] Patient sample representative of population to whom test will be applied in practice?: Y, yes; N, no; ?, can't tell.

Appendix 24

Fully automated liquid culture tests – study details

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Study	Reference test[a]	No. of specimens[b]	Recruit-ment[c]	Sample type[d]	% respiratory[e]	Contamination rate (%)[f]	% NTM[g]	Total isolates detected[h] (%)	% smear-positive isolates[i]	False-negative rate[j]	Time to detection[k]
MGIT 960											
Alcaide, 2000[120]	PCR-RFLP + B + C + A	1068 (?)	C?	M	76	3	2	All: 120 (11%)	47% (56/120)	18% (21/120)	13.2 (4–40)
								MTB: 96 (9%)	53% (51/96)	12% (12/96)	12.6 (4–37)
Hanna, 1999[77]	A, HPLC, B in Sm+; G in Sm–	3330 (2346)	R	M	66	8	7	All: 353 (11%)	43% (51/119)	18% (64/353)	11.1 (paired)
								MTB: 132 (4%)	nr	23% (30/132)	14.4 (paired)
Idigoras, 2000[232]	A, B and other genetic assays	2832 (?)	C	R	100	8	4	All: 321 (11%)	nr	11% (34/321)	nr
								MTB: 201 (7%)	66% (132/201)	7% (14/201)	13 (3–47)
Kanchana, 2000[455]	A on Sm+; plus 'identification methods'	1742 (?)	C?	M	68	10.5–6.4[l]	3	All: 104 (6%)	52% (54/104)	23% (24/104)	nr
								MTB: 59 (3%)	68% (40/59)	8% (5/59)	10.5 (SD 4.6)
Lu, 2002[456]	A on Sm+; NTM forwarded to myco lab	6062 (?)	C	M	78	nr	4	All: 278 (5%)	nr	10% (29/278)	nr
								MTB: 65 (1%)	nr	6% (4/65)	nr
Tortoli, 1999[89]	A on Sm+, HPLC + B if A–	2567 (1631)	C	M	69	10	2	All: 236 (9%)	55% (129/236)	19% (46/236)	13.3
								MTB: 169 (7%)	71% (80/113[m])	12% (20/169)	14.3
MB/BacT											
Alcaide, 2000[120]	PCR-RFLP (hsp65) + B + C +A	1068 (?)	C?	M	76	3	2	All: 120 (11%)	47% (56/120)	17% (20/120)	15.9 (6–44)
								MTB: 96 (9%)	53% (51/96)	11% (11/96)	15.9 (6–40)
Benjamin, 1998[457]	A in C+	488 (302)	C?	M	83	7	4	All: 44 (9%)	nr	11% (5/44)	nr
								MTB: 24 (5%)	65% (15/23)	4% (1/24)	11.9 (1–25)
Brunello, 1999[458]	A + B + MB/BacT	1830 (689)	nr	M	76	4	3	All: 173 (9%)	62% (107/173)	3% (6/173)	11.7 (2–50)
								MTB: 114 (6%)	84% (96/114)	1% (1/114)	13.3 (8–35)
Gil-Setas, 2004[76]	MTD + B	2101 (?)	C	M	77	9	3	All: 158 (8%)	43% (68/158)	10% (11/111)	nr
								MTB: 111 (5%)	60% (nr)	nr	16 (CI: 14.5, 17.4)
Harris, 2000[460]	A (NTM) + conv (MTB); plus A on all MB/BacT+	686 (?)	nr	M	67	7	6	All: 67 (10%)	88% (52/59)	13% (9/67)	13.4 (3–33)
								MTB: 23 (3%)	nr	4% (1/23)	15.8 (7–30)
Palacios, 1999[461]	A on Sm+ plus B	5208 (1960)	C	M	77	10	1	All: 301 (6%)	45% (136/301)	5% (14/301)	nr
								MTB: 257 (5%)	53% (135/257)	4% (10/257)	16.4 (SD 7.2)
Piersimoni, 2001[462], 2002[463]	A + NAP + C + B	1093 (611)	C	M	62	nr	7	All: 122 (11%)	nr	41% (50/122)	nr
								MTB: 47 (4%)	74% (34/46)	9% (4/47)	18.1 (6–47)

continued

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Study	Reference test[a]	No. of specimens[b]	Recruit-ment[c]	Sample type[d]	% respiratory[e]	Contamination rate (%)[f]	% NTM[g]	Total isolates detected[h] (%)	% smear-positive isolates[i]	False-negative rate[j]	Time to detection[k]
Roggenkamp, 1999[464]	A + sequencing of 16S rRNA gene	3700 (1503)	C	M	65	7	1	All: 123 (3%)	25% (31/123)	27% (33/123)	nr
								MTB: 71 (2%)	35% (25/71)	20% (14/71)	17.2
Rohner, 1997[465]	A for liquid C; B for solid	1078 (583)	nr	M	29	4	1	All: 73 (7%)	68% (50/73)	14% (10/73)	17.5 (SD 6.4)
								MTB: 67 (6%)	nr	12% (8/67)	nr
Somoskovi, 2000[466]	A + B on Sm+	377 (243)	C	M	90	4	<1	All: 57 (15%)	25% (14/57)	4% (2/57)	nr
								MTB: 55 (15%)	nr	4% (2/55)	14.3 (6–24)
BACTEC 9000											
Van Griethuysen, 1996[467]	A on Sm+, myco lab	1216	S	M		6	2	All: 148 (12%)	53% (107/202[n])	4% (6/148)	17.6 (SD 8.7)
								MTB: 127 (10%)	nr	2% (2/127)	
ESP II											
Tortoli, 1998[468]	A + B, C or HPLC for A negative –	2673 (?)	nr	M	58	8	3	All: 219 (8%)	52% (114/219)	21% (46/219)	18.1 (SD 9.3)
								MTB: 129 (5%)	nr	15% (19/129)	19.1 (SD 8.7)
Williams-Bouyer, 2000[469]	A + B if Sm+, A – snt for HPLC and B	3151 (1688)	C?	M	56	19	5	All: 233 (7%)	nr	29% (67/233)	16.9 (2–45)
								MTB: 65 (2%)	48% (31/65[o])	26% (17/65)	18.7 (3–39)
Woods, 1997[470]	A + B + HPLC	2283	C?	M	71	9	5	All: 149 (7%)	nr	13% (19/149)	13.1 (2–39)
								MTB: 53 (2%)	68% (36/53***)	11% (6/53)	15.5 (2–34)
BACTEC 460											
Alcaide, 2000[120]	PCR-RFLP (hsp65) + B + C + A	1068 (?)	C?	M	76	2	2	All: 120 (11%)	47% (56/120)	20% (24/120)	12.6 (3–40)
								MTB: 96 (9%)	53% (51/96)	19% (18/96)	11.8 (3–30)
Benjamin, 1998[457]	A in C+	488 (302)	C?	M	83	4	4	All: 44 (9%)	nr	9% (4/44)	nr
								MTB: 24 (5%)	65% (15/23)	0% (0/24)	11.9 (1–25)
Brunello, 1999[458]	A + B + MB/BacT	1830 (689)	nr	M	76	3	3	All: 173 (9%)	62% (107/173)	<1% (1/173)	11.2 (2–53)
								MTB: 114 (6%)	84% (96/114)	0% (0/114)	9.6 (3–30)
Hanna, 1999[77]	A, HPLC, B in Sm+; G in Sm–	3330 (2346)	R	M	66	45	7	All: 353 (11%)	43% (51/119)	23% (82/353)	11.3 (paired)
								MTB: 132 (4%)	nr	10% (13/132)	143.2 (paired)
Harris, 2000[460]	A (NTM) + conv (MTB); plus A on all MB/BacT+	686 (?)	nr	M	67	2	6	All: 67 (10%)	88% (52/59)	9% (6/67)	9.2 (2–35)
								MTB: 23 (3%)	nr	0% (0/23)	11.6 (4–35)

continued

Study	Reference test[a]	No. of specimens[b]	Recruit-ment[c]	Sample type[d]	% respiratory[e]	Contamination rate (%)[f]	% NTM[g]	Total isolates detected[h] (%)	% smear-positive isolates[i]	False-negative rate[j]	Time to detection[k]
Kanchana, 2000[455]	A on Sm+; plus 'identification methods'	1742 (?)	C?	M	68	5.1–2.9*	3	All: 104 (6%)	52% (54/104)	10% (10/104)	nr
								MTB: 59 (3%)	68% (40/59)	3% (2/59)	16 (SD 9.8)
Piersimoni, 2001[462], 2002[463]	A + NAP + C+ B	1093 (611)	C	M	62	nr	7	All: 122 (11%)	nr	18% (22/122)	nr
								MTB: 47 (4%)	74% (34/46)	4% (2/47)	14.2 (2–34)
Roggenkamp, 1999[464]	A + sequencing of 16S rRNA gene	3700 (1503)	C	M	65	3	1	All: 123 (3%)	25% (31/123)	9% (11/123)	nr
								MTB: 71 (2%)	35% (25/71)	3% (2/71)	15.4
Rohner, 1997[465]	A for liquid C; B for solid	1078 (583)	nr	M	29	3	1	All: 73 (7%)	68% (50/73)	8% (6/73)	14.3 (SD 8.2)
								MTB: 67 (6%)	nr	7% (5/67)	nr
Somoskovi, 2000[466]	A + B on Sm+	377 (243)	C	M	90	3	<1	All: 57 (15%)	25% (14/57)	11% (6/57)	
								MTB: 55 (15%)	nr	7% (4/55)	16.6 (8–23)
Tortoli, 1998[468]	A + B, C or HPLC for A –	2673 (?)	nr	M	58	4	3	All: 219 (8%)	52% (114/219)	11% (24/219)	17.8 (SD 10.2)
								MTB: 129 (5%)	nr	2% (3/129)	18.6 (SD 9.7)
Tortoli, 1999[89]	A on Sm+, HPLC + B if A–	2567 (1631)	C	M	69	4	2	All: 236 (9%)	55% (129/236)	15% (35/236)	14.8
								MTB: 169 (7%)	71% (80/113[m])	9% (16/169)	14.9
Woods, 1997[470]	A + B + HPLC	2283	C?	M	71	4	5	All:149 (7%)	nr	19% (28/149)	14.4 (2–36)
								MTB: 53 (2%)	68% (36/53[o])	8% (4/53)	16.6 (4–36)
Lowenstein–Jensen											
Alcaide, 2000[120]	PCR-RFLP (hsp65) + B + C + A	1068 (?)		M	76	4	2	All: 120 (11%)	47% (56/120)	30% (36/120)	22.2 (13–45)
								MTB: 96 (9%)	53% (51/96)	27% (26/96)	22.1 (13–45)
Brunello, 1999[458]	A + B + MB/BacT	1830 (689)	nr	M	76	5	3	All: 173 (9%)	62% (107/173)	4% (7/173)	26.8 (7–47)
								MTB: 114 (6%)	84% (96/114)	2% (2/114)	29.7 (16–41)
Kanchana, 2000[455]	A on Sm+; plus 'identification methods'	1742 (?)	C?	M	68	20.5 tp 12.4	3	All: 104 (6%)	52% (54/104)	41% (43/104)	nr
								MTB: 59 (3%)	68% (40/59)	15% (9/59)	25.2 (SD 7.5)
Lu, 2002[456]	A on Sm+; NTM forwarded to myco lab	6062 (?)	C	M	78	nr	4	All: 278 (5%)	nr	38% (106/278)	nr
								MTB: 65 (1%)	nr	26% (17/65)	nr
Palacios, 1999[461]	A on Sm+ plus B	5208 (1960)	C	M	77	4	1	All: 301 (6%)	45% (136/301)	34% (101/301)	nr
								MTB: 257 (5%)	53% (135/257)	27% (70/257)	20 (SD 8.2)

continued

Study	Reference test[a]	No. of specimens[b]	Recruit-ment[c]	Sample type[d]	% respiratory[e]	Contamination rate (%)[f]	% NTM[g]	Total isolates detected[h] (%)	% smear-positive isolates[i]	False-negative rate[j]	Time to detection[k]
Piersimoni, 2001,[462] 2002[463]	A + NAP + C + B	1093 (611)	C	M	62	nr	7	All: 122 (11%)	nr	42% (51/122)	nr
								MTB: 47 (4%)	74% (34/46)	23% (11/47)	22.6 (7–62)
Roggenkamp, 1999[464]	A + sequencing of 16S rRNA gene	3700 (1503)	C	M	65	5	1	All: 123 (3%)	25% (31/123)	46% (57/123)	nr
								MTB: 71 (2%)	35% (25/71)	32% (23/71)	29.8
Somoskovi, 2000[466]	A + B on Sm+	377 (243)	C	M	90	1	<1	All: 57 (15%)	25% (14/57)	19% (11/57)	nr
								MTB: 55 (15%)	nr	18% (10/55)	35.8 (14–58)
Tortoli, 1998[468]	A + B, C or HPLC for A –	2673 (?)	nr	M	58	9	3	All: 219 (8%)	52% (114/219)	36% (78/219)	27.8 (SD 11.5)
								MTB: 129 (5%)	nr	17% (22/129)	28.6 (SD 10.8)
Tortoli, 1999[89]	A on Sm+, HPLC + B if A–	2567 (1631)	C	M	69	17	2	All: 236 (9%)	55% (129/236)	29% (69/236)	25.7
								MTB: 169 (7%)	71% (80/113[m])	27% (45/169)	25.1
Van Griethuysen, 1996[467]	A on Sm+, myco lab	1216	S	M		6	2	All: 148 (12%)	53% (107/202[n])	20% (30/148)	29.4 (SD 12.2)
								MTB: 127 (10%)	nr	16% (21/127)	nr
Other solid media											
Gil-Setas, 2004[76] (M 7h11)	MTD + B	2101 (?)	C	M	77	7	3	All: 158 (8%)	43% (68/158)	nr	nr
								MTB: 111 (5%)	60% (nr)	11% (12/111)	10.9 (CI: 9.8, 12.1)
Hanna, 1999[77] (M 7h11+ LJ)	A, HPLC, B in Sm+; G in Sm–	3330 (2346)	R	M	66	21	7	All: 353 (11%)	43% (51/119)	29% (103/353)	nr
								MTB: 132 (4%)	nr	20% (27/132)	nr
Harris, 2000[460] (Egg-based)	A (NTM) + conv (MTB); plus A on all MB/BacT+	686 (?)	nr	M	67	5	6	All: 67 (10%)	88% (52/59)	15% (10/67)	15.6 (14–42)
								MTB: 23 (3%)	nr	17% (4/23)	18.9 (14–28)
Idigoras, 2000[232] (M 7h11)	B, A and other genetic assays	2832 (?)	C	R	100	8	4	All: 321 (11%)	nr	49% (158/321)	nr
								MTB: 201 (7%)	66% (132/201)	24% (48/201)	13 (3–47)
Rohner, 1997[465] (Egg-based)	A for liquid C; B for solid	1078 (583)	nr	M	29	nr	1	All: 73 (7%)	68% (50/73)	21% (15/73)	nr
								MTB: 67 (6%)	nr	21% (14/67)	nr
Williams-Bouyer, 2000[469] (M 7h11)	A + B if Sm+, A– sent for HPLC and B	3151 (1688)	C?	M	56	11	5	All: 233 (7%)	nr	38% (89/233)	19.2 (5–56)
								MTB: 65 (2%)	48% (31/65[o])	12% (8/65)	19.2 (6–56)
Woods, 1997[470] (M 7h11)	A + B + HPLC	2283 (?)	C?	M	71	1	5	All: 149 (7%)	nr	35% (52/149)	17.8 (2–36)
								MTB: 53 (2%)	68% (36/53[o])	11% (6/53)	18.3 (12–36)

continued

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Study	Reference test[a]	No. of specimens[b]	Recruit-ment[c]	Sample type[d]	% respiratory[e]	Contamination rate (%)[f]	% NTM[g]	Total isolates detected[h] (%)	% smear-positive isolates[i]	False-negative rate[j]	Time to detection[k]

[a] Reference test used: A, Accuprobe on cultured isolates; susc, 'susceptibility testing'; B, biochemical tests; C, culture; conv, 'conventional methods', e.g. colonial morphology, production of niacin; G, Gram stain; HPLC, high-performance liquid chromatography; NAP, radiometric *p*-nitro-α-acetylamino-β-hydroxypropiophenone test; PCR-RFLP, PCR-restriction fragment length polymorphism analysis; Sm+, smear positive; Sm–, smear negative.
[b] No of specimens (no of patients)
[c] Recruitment: C, consecutive; C?, appears consecutive, i.e. samples submitted within a described period of time; R, random; S, selected inclusion (to maximise mycobacterial yield).
[d] Type of samples recruited: M, mixed respiratory and non-respiratory; R, respiratory only.
[e] Percentage of samples included that were respiratory in origin.
[f] Contamination rate: percentage of samples contaminated.
[g] Percentage of total specimens analysed that were NTM.
[h] Total number of isolates detected (as percentage of total analysed).
[i] Percentage of isolates detected that were smear positive.
[j] False-negative rate.
[k] Mean time to detection, with SD, 95% CI or range, depending on what was reported in the paper.
[l] Rate changed due to changes in decontamination procedure.
[m] Paired samples only.
[n] Smear status only reported for total isolates detected by any method.
[o] Numerator is largest no. detected by any one culture method, not reported across all methods used.

Appendix 25

Search strategy to identify relevant citations for a systematic review of interferon-γ assays

Medline (1966–2004)

- Tests
  interferon type II [MeSH Terms] OR interferon gamma[Text Word] OR ELISPOT[All Fields] OR quantiferon[All Fields] OR esat-6[All Fields] OR cfp10[All Fields]

AND

- Tuberculosis
  mycobacterium TB [MeSH Terms] OR mycobacterium TB[Text Word] OR TB[MeSH Terms] OR TB[Text word]

AND

- Sensitive diagnostic search filter
  sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [Title/Abstract] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]

Embase (1980–2004)

- Tests
  interferon gamma.mp OR interferon gamma/ OR quantiferon.mp OR ELISPOT.mp OR esat-6.mp OR cfp10.mp

AND

- Tuberculosis
  mycobacterium TB.mp OR mycobacterium TB/ OR TB.mp OR TB/

AND

- Sensitive diagnostic search filter
  sensitiv$ OR detec$ OR accura$ OR specific$ OR reliab$ OR positive OR negative OR diagnos$

CAB Abstracts (1973–2004)

- Tests
  interferon OR quantiferon OR ELISPOT OR esat* OR cfp10 OR cfp 10 OR cfp-10 [Title/ Keyword/ Abstract]

AND

- Tuberculosis
  TB OR tuberc* [Title/ Keyword/ Abstract]

AND

- Sensitive diagnostic search filter
  sensitiv* OR diagnos* OR accura* OR reliab* [Title/ Keyword/ Abstract]

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Appendix 26

Data collection sheet: a systematic review of interferon-γ assays

Reviewer ID ..... **Title** .....

.....

Authors .....

Source ..... *Year* ..... *Volume* .....

Pages ..... *Country* ..... *Language* .....

Selection or rejection: (must have all four as yes)

a) **Population** *People with latent TB or exposure to TB* Y/N

.....

b) **Tests** *Interferon gamma assays* Y/N

.....

Tuberculin skin test for latent TB Y/N

c) **Verification of exposure to TB, BCG or HIV** Y/N

Select this diagnostic test study? *If this is* Y *complete the form* Y/N

If N *must describe why not selected* .....

Data collection (if more than one visual feature fill additional forms)

Population

Number ..... *Child/Adult*

Mean age (range) .....

Ethnic origin .....

Asian ..... *White* ..... *Black* ..... *Other* .....

Risk factors for TB exposure .....

Vaccination: .....

HIV status *Pos(%)* ..... *Neg(%)* ..... *Don't know* .....

Other .....

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Test – interferon gamma assay (use another form if more than one tests evaluated)

Test name .....

.....

Description of index test .....

.....

a) Complete ..... *b) Incomplete* ..... *c) Can't tell* .....

Definition of test result .....

.....

Tuberculin skin test

Test name .....

Description of test .....

.....

a) Complete ..... *b) Incomplete* ..... *c) Can't tell* .....

Definition of + test result .....

Definition of – test result .....

Verification of exposure:

Subgroup	*Direct/Indirect*	*Duration*	*Location*	*Other*
A (Intense)				
B (Moderate)				
C (Low)				
D (Very low)				

Details of description (location, time, etc.)

.....

.....

History of household TB contact .....

Born in high prevalent country .....

Study quality

Patient enrolment: consecutive/arbitrary/unreported/other .....

Data collection: retrospective/prospective/unreported/other .....

Blinding of test results from exposure: yes/no/unreported/other .....

Description of index test: adequate/inadequate/unreported/other .....

Description of TST: adequate/inadequate/unreported/other .....

Description of exposure status (where applicable): adequate/inadequate/unreported/other .....

Completeness of verification of exposure (where applicable): adequate/inadequate/unreported/other .....

Results

Number of subjects with data available .....

All subjects .....

Test Specify	*TST Positive*	*TST Negative*	*Total*
Positive			
Negative			
Total			

Subgroups (exposure status) .....

Test Specify	*TST Positive*	*TST Negative*	*Total*
Positive			
Negative			
Total			

Subgroups (exposure status) .....

Test Specify	*TST Positive*	*TST Negative*	*Total*
Positive			
Negative			
Total			

Subgroups .....

Test Specify	*TST Positive*	*TST Negative*	*Total*
Positive			
Negative			
Total			

Subgroups .....

Test Specify	*TST Positive*	*TST Negative*	*Total*
Positive			
Negative			
Total			

Subgroups based on vaccination .....

Test Specify	*Vaccinated*	*Unvaccinated*	*Total*
Positive			
Negative			
Total			

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Subgroups based on vaccination .....

Test Specify	*Vaccinated*	*Unvaccinated*	*Total*
Positive			
Negative			
Total			

Subgroups based on HIV status .....

Test Specify	*HIV Positive*	*HIV Negative*	*Total*
Positive			
Negative			
Total			

Subgroups based on HIV status .....

Test Specify	*HIV Positive*	*HIV Negative*	*Total*
Positive			
Negative			
Total			

Appendix 27

Characteristics of studies included in systematic review of interferon-γ assays in diagnosis of latent tuberculosis

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Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Studies assessing RD1-specific antigen-based assays and PPD **ELISPOT based on RD1-specific antigens and PPD**					
Lalvani *et al.*,[166] 2001 Contact Tracing Clinic, London, UK Study period not reported	Healthy adult contacts of patients with sputum smear-positive pulmonary TB attending the clinic (clinic held once per week and is attended by individuals though to have been in contact with newly identified case of TB) No exclusion criteria 50 participants included in review, 20 out of 50 participants were contacts of one index case	Four groups based on proximity and frequency of exposure to index cases **High exposure** (A) Intense, close prolonged exposure at workplace or household (B) Moderate, regular intermittent exposure **Low exposure** (C) Low, casual intermittent exposure (D) Very low, no known contact	ELISPOT response to ESAT-6; and response to PPD Positive result: ≥10 spot-forming cells compared with control wells	Heaf test: 6 needle disposable head Heaf gun with PPD TU/ml (equivalent to 10 TU Mantoux); response graded after 1 week Positive result: grade 3–4 equivalent to >15 mm of Mantoux test	BCG vaccination reported 82% vaccinated HIV status not reported
Richeldi *et al.*,[177] 2004 University Hospital Modena, Italy Study period not reported	Hospital contacts of a patient with sputum smear-positive MDR-TB on a maternity unit and household contacts. Contacts included mothers, newborn babies and visiting relatives No exclusion criteria 92 participants included in review	Four groups based on proximity and frequency of exposure to index case in a hospital outbreak investigation **High exposure** (A) Very intense, household contacts (B) Intense, same hospital room **Low exposure** (C) Moderate, contact but not same hospital room (D) Low, same ward but no direct contact	ELISPOT response to ESAT-6 and CFP-10; and response to PPD Positive result: ≥5 spot-forming cells compared with control wells	Tuberculin PPD with 5 TU recorded after 72 h Positive result: ≥5 mm	BCG vaccination reported 10% vaccinated HIV status reported, but data not identified according to test

continued

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Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Hill *et al.*,[258] 2004 Government health centre and MRC Labs Greater Banjul, The Gambia Study period from May 2002 to April 2003	Household contacts of patients with sputum smear-positive TB attending the health centre or MRC outpatient clinic Excluded if treated for TB in last 1 year, if recruited 60 days after index case had been recruited, if diagnosis of TB within 1 month of recruitment or cough longer than index case 735 participants included in review	Three groups based on proximity (average amount of time spent daily and where contacts slept) to index cases **High exposure** (A) Intense, same room (B) Moderate, different room **Low exposure** (C) Low, different house	ELISPOT response to ESAT-6 and CFP-10; and response to PPD RT49 Positive result: ≥10 spot-forming units compared with control wells	PPD RT 23 with 2 TU, response recorded after 48–72 h Positive result: >10 mm induration	BCG vaccination reported, but data not identified according to test HIV status reported, but data not identified according to test
Unspecified assay based on RD1-specific antigen and PPD					
Vekemans *et al.*,[260] 2001 Serrekunda Health Centre, The Gambia Study period not reported	Patients with sputum smear-positive pulmonary TB, healthy household contacts and community controls Excluded if HIV positive 58 participants included in review excluding patients with ATB	Two groups based on exposure to ATB **High exposure** (A) Intense, household contacts **Low exposure** (B) Low, community controls	Unspecified assay response to ESAT-6; and response to PPD Positive result: IFN-γ concentration above mean and 3 SD of concentration of control wells	PPD RT 23 with 2 TU Response recorded after 48–72 h Positive result: >10 mm induration	BCG vaccination not reported HIV status reported as all patients HIV negative

continued

Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Studies assessing RD1-specific antigen-based assays **ELISPOT based on RD1-specific antigens**					
Ewer *et al.*,[178] 2003 Secondary School, Leicester, UK Study period 2001	Students (aged 11–15 years) at same secondary school as a single index case of sputum smear-positive pulmonary TB. All students invited to participate; consenting students who also underwent Heaf test by local health authority and who were interviewed by school nurse about place of birth and history of TB exposure outside school were included No exclusion criteria 535 participants included in review	Four groups based on proximity and shared activities with index case in a school outbreak investigation **High exposure** (A) Intense, same class (B) Moderate, same year who shared classes with index case **Low exposure** (C) Low, same year who shared only weekly events with index case (D) Very low, same school but different years	ELISPOT response to ESAT-6 and CFP-10 Positive result: ≥5 spot-forming cells compared with control wells	Heaf test: 6 needle disposable head Heaf gun with PPD TU/ml (equivalent to 10 TU Mantoux); response graded after 1 week Positive result: If BCG vaccinated >15 mm; if unvaccinated ≥5 mm	BCG vaccination reported 87% vaccinated HIV status not reported
Whole blood ELISA based on RD1-specific antigens					
Brock *et al.*,[256] 2004 Community High School, Denmark Study period 2002	Students at same community high school as a single index case of sputum smear-positive pulmonary TB, household contacts and contacts at the local choir, which the index case regularly attended No exclusion criteria 125 participants included in review	Two groups based on exposure to ATB in a school outbreak investigation **High exposure** (A) Intense, high exposure in same class, household or local choir **Low exposure** (B) Low, other classes in same school	Whole blood ELISA based on ESAT-6 and CFP-10 Whole blood ELISA based on PPD. Not possible to compute 2 × 2 table Positive result: 0.35 IU/ml of IFN-γ	Tuberculin PPD with 2 TU recorded after 72 h Positive result: >10 mm induration	BCG vaccination reported, however TST not done in vaccinated group 32% vaccinated HIV status not reported

continued

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Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Studies assessing PPD-based assays **Whole blood ELISA based on PPD**					
Pottumarthy *et al.*,[155] 1999 New Zealand Study period from November 1996 to February 1998	1. Immigrants from countries with a high TB prevalence 2. Healthcare workers undergoing employment screening at occupational health clinics and microbiology lab. staff at Auckland and Green Lane hospitals 3. Patients with suspected ATB infection or *Mycobacterium avian complex* (MAC) No exclusion criteria 364 participants included in review excluding ATB/MAC	Two groups based on exposure to ATB **High exposure** (A) Moderate, immigrants from high-prevalence countries **Low exposure** (B) Low, healthcare workers and microbiology staff with low risk	Whole blood ELISA assay based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Mantoux test according to CDC guidelines	BCG vaccination not reported HIV status reported as all HIV negative
Mazurek *et al.*,[158] 2001 5 US hospitals Study period from March 1998 to June 1999	Adult participants recruited at five hospitals 1. Pre-employment or preschool enrolment TST 2. Considered high risk for LTBI 3. ATB clinically suspected who had undergone <6 weeks anti-TB therapy 4. ATB patients, completing therapy within previous 2 years Excluded if self-reported as pregnant or HIV positive, had history of severe reaction to tuberculin, were immunocompromised or had taken immunosuppressive drugs 1045 participants included in review excluding ATB	Two groups based on exposure to ATB **High exposure** (A) Intense, high risk for LTBI **Low exposure** (B) Low, pre-employment and school screening	Whole blood ELISA assay based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Tuberculin PPD with 5 TU recorded after 48–72 h Positive result: >10 mm	BCG vaccination reported 17% vaccinated HIV status not reported, however, self-reported HIV excluded

continued

Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Fietta *et al.*,[154] 2003 Clinic of Respiratory Diseases University school of Medicine Pavia,Italy Study period from February 1999 to December 2000	Adult patients recruited 1. Clinically suspected active TB 2. Healthcare workers in daily contact with infectious TB 3. Household contacts 4. Individuals requesting pre-employment or preschool enrolment TST Excluded if self-reported as pregnant or HIV positive, history of severe reaction to tuberculin, TST in previous 12 months 201 participants included in review excluding ATB	Two groups based on exposure **High exposure** (A) Intense, household contacts and healthcare workers in contact **Low exposure** (B) Low, pre-employment and school screening	Whole blood ELISA assay based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Tuberculin PPD with 2 TU recorded after 72 h Positive result: >10 mm	BCG vaccination reported 42% vaccinated HIV status not reported, however, self-reported HIV excluded
Studies without information on TB exposure but with useful information on HIV status					
Converse *et al.*,[257] 1997 USA Study period not reported	Random sample of participants from a longitudinal cohort study of HIV infection among inner-city drug users (ALIVE study) 1 patient excluded due to late return 66 participants included in review	No information on exposure reported	Whole blood ELISA based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Tuberculin PPD with 5 TU recorded after 48–72 h Positive result >5 mm induration: for HIV-positive patients >10 mm induration for HIV-negative patients	BCG vaccination not reported HIV status reported 52% HIV positive
Kimura *et al.*,[259] 1999 USA Study period not reported	Volunteers from participants in longitudinal cohort study of the of HIV infection among inner-city drug users (ALIVE study) No exclusion criteria 467 participants	No information on exposure reported	Whole blood ELISA assay based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Tuberculin PPD with 5 TU recorded after 48–72 h Positive result >5 mm induration:for HIV-positive patients >10 mm induration for HIV-negative patients	BCG vaccination not reported HIV status reported 36% HIV positive

continued

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Study Country Study period	Study population including exclusion criteria Number of subjects included in review	TB exposure categories and classification in high- and low-exposure groups in review	Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)	TST	BCG vaccination status and HIV status
Bellete *et al.*,[255] 2002 Research Institute, Ethiopia John Hopkins University Baltimore USA Study period not reported	Baltimore participants: 1. Students and employees for pre-enrolment or pre-employment enrolment TST screening 2. TB contacts or persons from high TB prevalence countries 3. ATB and treated previous TB Volunteers from employees at Faculty of Medicine, Addis Ababa University and persons attending the TB Center for screening for TB (with negative chest X-ray and sputum examination for ATB) Excluded if inadequate blood sample, no detectable IFN-γ response, chest X-ray abnormalities other than TB, positive culture for MAC 248 participants included in review excluding Baltimore subjects since no 2 × 2 table possible	Not possible to construct 2 × 2 tables for exposures reported	Whole blood ELISA assay based on PPD Positive result: (human–nil)/(mitogen–nil) > 15% and (human–nil) – (avian–nil)/(human–nil) > –10%	Tuberculin PPD with 5 TU recorded after 48–72 h Positive result >5 mm induration	BCG vaccination reported, but not identified according to test HIV status reported 22% HIV positive

continued

Study **Country** **Study period**	**Study population including exclusion criteria** **Number of subjects included in review**	**TB exposure categories and classification in high- and low-exposure groups in review**	**Interferon-γ assay* (ELISPOT, whole blood ELISA or unspecified)**	**TST**	**BCG vaccination status and HIV status**
Chapman *et al.*,[153] 2002 University Teaching Hospital, Lusaka, Zambia Oxford, UK Study period not reported	1. Zambian patients with active pulmonary TB on less than 1 month of anti-TB treatment 2. Healthy Zambian adults attending casualty department with minor injuries 3. Healthy adults recruited in Oxford, UK Excluded (2) if history of TB, symptoms of TB, known TB contact, symptoms of TB, abnormal chest X-ray Excluded (3) if history of TB, resident in TB endemic area, known TB contact 49 participants from Zambia included in review, others excluded since no combined TST/ ELISPOT data available, UK participants excluded since no TST data; ATB excluded	No information on exposure reported	ELISPOT response to ESAT-6 and CFP-10 Positive result: if the test well contained at least 5 spot-forming cells more than negative controls	PPD RT 23 with 5TU recorded after 48–72 h. Positive result: >10 mm induration	BCG vaccination reported, but not identified according to test HIV status reported 22% HIV positive

Appendix 28

Methodological features of studies included in systematic review of interferon-γ assays for latent tuberculosis

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Study	Study design	Recruitment of subjects	Blinding of test results	Description of tests and thresholds	Ascertainment of exposure status	Overall satisfactory features[a]
RD1-based antigen assays						
Vekemans *et al.*,[260] 2001[b]	Prospective	Non-consecutive	Unclear	Adequate	Limited detail	2/5
Lalvani *et al.*,[166] 2001[b]	Prospective	Consecutive	Blinded	Adequate	Detailed, using interview by project nurse	5/5
Chapman *et al.*,[153] 2002	Prospective	Unclear	Non-blinded	Adequate	Not applicable	3/4
Ewer *et al.*,[178] 2003	Prospective	Consecutive	Blinded	Adequate	Detailed, using interview by school nurse in an outbreak	5/5
Hill *et al.*,[258] 2004[b]	Prospective	Random inclusion	Blinded	Adequate	Detailed	4/5
Richeldi *et al.*,[177] 2004[b]	Prospective	Unclear	Blinded	Adequate	Detailed, using structured questionnaire in an outbreak	4/5
Brock *et al.*,[256] 2004	Prospective	Unclear	Unclear	Adequate	Detailed, using interview	3/5
PPD-based assays						
Converse *et al.*,[257] 1997	Prospective	Random inclusion	Unclear	Adequate	Not applicable	2/4
Pottumarthy *et al.*,[155] 1999	Prospective	Unclear	Unclear	Adequate	Limited detail	2/5
Kimura *et al.*,[259] 1999	Prospective	Unclear	Unclear	Adequate	Not applicable	2/4
Mazurek *et al.*,[158] 2001	Prospective	Unclear	Unclear	Adequate	Limited detail, interview with standardised questionnaire used	2/5
Bellete *et al.*,[255] 2002	Prospective	Unclear	Unclear	Adequate	Not applicable	2/4
Fietta *et al.*,[154] 2003	Prospective	Unclear	Unclear	Adequate	Limited detail	2/5

[a] Studies satisfying >66% of the quality features were considered to be of high quality.
[b] Studies also containing information on PPD-based assays.

Appendix 29

Data on association of interferon-γ assays and TSTs with exposure to tuberculosis (studies subgrouped according to assay type)

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Study	TB exposure comparison Test type	Exposure high Test +	 Test –	Exposure low Test +	 Test –	OR[a]	ROR[b]	Dose–response gradient[c] Test	 Assay vs TST
Assays based on PPD									
ELISPOT									
Lalvani *et al.*,[166] 2001	*Intense + moderate vs low + very low*								
	ELISPOT	26	1	16	2	3.25	0.86	$p = 0.001$	–
	TST	16	11	5	13	3.78[d]		$p = 0.09$	
Hill *et al.*,[258] 2004	*Intense + moderate vs low*								
	ELISPOT	323	166	152	94	1.20	0.51	$p = 0.04$	–
	TST	231	255	68	178	2.37[d]		$p < 0.0001$	
Richeldi *et al.*,[177] 2004	*Intense + moderate vs low + very low*								
	ELISPOT	10	3	37	42	3.78	1.79	$p = 0.02$	–
	TST	1	12	3	76	2.11		$p = 0.53$	
Whole blood ELISA									
Pottumarthy *et al.*,[155]	*Moderate vs low*								
1999	Whole blood ELISA	71	166	47	80	0.73	0.78	–	–
	TST	86	151	48	79	0.94		–	
Mazurek *et al.*,[158] 2001	*Intense vs low*								
	Whole blood ELISA	219	728	8	90	3.38[d]	0.23	–	–
	TST	225	722	2	96	14.96[d]		–	
Fietta *et al.*,[154] 2003	*Intense vs low*								
	Whole blood ELISA	75	84	3	39	11.61[d]	1.34	–	–
	TST	48	111	2	40	8.65[d]		–	
Unspecified assay									
Vekemans *et al.*,[260]	*Intense vs low*								
2001	Unspecified assay	23	5	27	3	0.51	0.05	–	–
	TST	24	4	11	18	9.82[d]		–	
Assays based on RD1-specific antigens									
ELISPOT (ESAT-6)									
Lalvani *et al.*,[166] 2001	*Intense + moderate vs low + very low*								
	ELISPOT	17	10	0	18	61.67[d]	16.18	$p = 0.001$	–
	TST	16	11	5	13	3.78[d]		$p = 0.05$	
	ELISPOT[e]	17	10	0	18	61.2[d]	18.83	$p = 0.001$	–
	ELISPOT (PPD)	26	1	16	2	3.25		$p = 0.09$	

continued

Study	TB exposure comparison / Test type	Exposure high Test +	Exposure high Test –	Exposure low Test +	Exposure low Test –	OR[a]	ROR[b]	Dose–response gradient[c] Test	Dose–response gradient[c] Assay vs TST
Unspecified assay (ESAT-6)									
Vekemans *et al.*,[260] 2001	*Intense vs low*								
	Unspecified assay	20	8	9	21	5.83[d]	0.59	–	–
	TST	24	4	11	18	9.82[d]		–	
	Unspecified assay[e]	20	8	9	21	5.83[d]	11.41	–	–
	Unspecified assay (PPD)	23	5	27	3	0.51		–	
ELISPOT(ESAT-6 and CFP-10)									
Ewer *et al.*,[178] 2003	*Intense + moderate vs low + very low*								
	ELISPOT	63	38	84	350	6.91[d]	1.37	$p < 0.001$	$p = 0.03$
	TST	59	42	95	339	5.01[d]		$p < 0.001$	
Hill *et al.*,[258] 2004	*Intense + moderate vs low*								
	ELISPOT	160	329	58	188	1.58[d]	0.66	$p = 0/02$	–
	TST	231	255	68	178	2.37[d]		$p < 0.0001$	
	ELISPOT[e]	160	329	58	188	1.58[d]	1.30	$p = 0/02$	–
	ELISPOT (PPD)	323	166	152	94	1.20		$p = 0/04$	
Richeldi *et al.*,[177] 2004	*Intense + moderate vs low + very low*								
	ELISPOT	7	6	10	69	8.05[d]	3.81	$p = 0.02$	–
	TST	1	12	3	76	2.11		$p = 0.53$	
	ELISPOT[e]	7	6	10	69	8.05[d]	2.13	$p = 0.02$	–
	ELISPOT (PPD)	10	3	37	42	3.78		$p = 0.02$	
Whole blood ELISA (ESAT-6 and CFP-10)									
Brock *et al.*,[256] 2004	*High vs low*								
	Whole blood ELISA	24	21	2	38	21.71[d]	1.93	–	–
	TST	25	20	4	36	11.25[d]		–	

CFP, culture filtrate protein; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; ESAT, early secretory antigen target; TST, tuberculin skin test.

[a] ORs computed using RevMan software, 0.5 added to zero cells in 2×2 tables, value >1 indicates test more strongly associated with TB exposure (see *Figure 2*).

[b] Ratio value >1 indicates assay more strongly associated with exposure than TST, i.e. assay more accurate than TST (see *Figure 3*).

[c] Relating results of tests to degree of TB exposure, *p*-values as reported in the original papers with more than two exposure categories only.

[d] *p*-Value significant (<0.05).

[e] Direct comparison of RD1-specific antigen-based assay with PPD-based assay.

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Appendix 30

Data on association of interferon-γ assays and TSTs with BCG vaccination status among those exposed to tuberculosis (studies subgrouped according to assay type)

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Study	Test type	BCG + Test +	BCG + Test –	BCG – Test +	BCG – Test –	OR[a]	ROR[b]
Assays based on PPD							
ELISPOT							
Lalvani *et al.*,[166] 2001	ELISPOT	38	2	6	2	6.33	0.60
	TST	21	16	1	8	10.50[c]	
Richeldi *et al.*,[177] 2004	ELISPOT	Not reported	Not reported	Not reported	Not reported	–	–
	TST	3	6	1	78	39[c]	
Whole blood ELISA							
Mazurek *et al.*,[158] 2001	Whole blood ELISA	68	89	119	651	4.18[c]	0.42
	TST	91	66	93	677	10.04[c]	
Fietta *et al.*,[154] 2003	Whole blood ELISA	34	32	41	52	1.35	2.25
	TST	16	51	33	63	0.6	
Assays based on RD1-specific antigens							
ELISPOT(ESAT-6)							
Lalvani *et al.*,[166] 2001	ELISPOT[d]	16	24	3	6	1.33	0.13
	TST	21	16	1	8	10.5[c]	
	ELISPOT[d]	16	24	3	6	1.33	0.21
	ELISPOT (PPD)	38	2	6	2	6.33	
ELISPOT (ESAT-6 and CFP-10)							
Ewer *et al.*,[178] 2003	ELISPOT	131	336	16	52	1.27	0.69
	TST	133	334	12	56	1.86	
Richeldi *et al.*,[177] 2004	ELISPOT	3	6	13	66	2.54	0.06
	TST	3	6	1	78	39.0[c]	
Whole blood ELISA (ESAT-6 and CFP-10)							
Brock *et al.*,[256] 2004	Whole blood ELISA	6	34	26	59	0.40	–
	TST	Not reported	Not reported	29	56	–	

CFP, culture filtrate protein; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; ESAT, early secretory antigen target; TST, tuberculin skin test.
[a] ORs computed using Revman software, value >1 indicates test more strongly associated with BCG vaccination (see *Figure 5*).
[b] Ratio value <1 indicates false-positive result more likely with TST than with assay (see *Figure 6*).
[c] *p*-Value significant (<0.05).
[d] Direct comparison of RD1-specific antigen-based assay with PPD-based assay.

Appendix 31

Data on association of interferon-γ assays and TSTs with HIV status among those exposed to tuberculosis (studies subgrouped according to assay type)

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Study	Test type	HIV + Test +	HIV + Test –	HIV – Test +	HIV – Test –	OR[a]	ROR[b]
Assays based on PPD							
Whole blood ELISA							
Converse *et al.*,[257] 1997	Whole blood ELISA	17	17	26	6	0.23[c]	0.34
	TST	9	25	11	21	0.69	
Kimura *et al.*,[259] 1999	Whole blood ELISA	32	135	177	123	0.16[c]	0.48
	TST	16	151	71	229	0.34[c]	
Bellete *et al.*,[255] 2002	Whole blood ELISA	15	39	112	82	0.28[c]	0.54
	TST	28	26	131	63	0.52[c]	
Assays based on RD1-specific antigens							
ELISPOT(ESAT-6 and CFP-10)							
Chapman *et al.*,[153] 2002	ELISPOT	6	8	24	11	0.34	2.5
	TST	5	9	28	7	0.14[c]	

CFP, culture filtrate protein; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; ESAT, early secretory antigen target; TST, tuberculin skin test.
[a] ORs computed using Revman software, value >1 indicates test more strongly associated with HIV infection (see *Figure 4*).
[b] Ratio value >1 indicates false-negative result more likely with TST than with assay (see *Figure 5*).
[c] *p*-Value significant (<0.05).

Appendix 32

Costs of antituberculosis drugs

BNF 46 (2003)[471] states regimens based on the Joint Tuberculosis Committee and British Thoracic Society guidelines for the treatment of tuberculosis in the UK. Out of interest, the Department of Health prescription data (PCA) for community-dispensed prescriptions 2002 reports data for BNF Section 5.1.9 'Antituberculosis drugs' for 81,000 prescriptions at an overall cost of £1.95 million (isoniazid expenditure at £232,000 in PCA 2002).

Regimen	Maximum drug cost, 6 months (£)
Recommended dosage for standard unsupervised 6-month treatment: Rifater® (rifampicin, isoniazid, and pyrazinamide) (for 2-month initial phase only) Ethambutol (for 2-month initial phase only)[a]	173.38 (drug sensitive)
Rifinah® or Rimactazid® (rifampicin and isoniazid) (for 4-month continuation phase following initial treatment with Rifater®)	281.84 (drug resistant)
Recommended dosage for standard supervised 6-month treatment: These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) 3 times per week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times per week for a further 4 months Recommended dosage for intermittent supervised 6-month treatment; isoniazid, 3 times per week (for 2-month initial and 4-month continuation phases) Rifampicin, 3 times per week (for 2-month initial and 4-month continuation phases) Pyrazinamide, 3 times per week (for 2-month initial phase only) [l]Ethambutol, 3 times per week (for 2-month initial phase only)	221.34 (drug sensitive) 438.26 (drug resistant)
Proportion of patients expected to be drug resistant = 5%	(5%)
Proportion of patients expected to require supervised treatment = 5%	(5%)
Mean patient drug cost (6 months) (applying the above '5%' assumptions)	181.47

[a] Ethambutol may be omitted from the regimen if the risk of isoniazid resistance is low. Most ATB cases in the UK are treated with 4 drugs (i.e. ethambutol is included for the first 2 months). Hence, it is better to assume the costs are £281.84 and £438.26.

[b] Drug administration needs to be fully supervised (directly observed therapy) in patients who cannot comply reliably with the treatment regimen.

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Appendix 33

Costs of laboratory investigations

These are based on the price list from the Public Health Laboratory Mycobacterium Reference Unit.

Method	Purpose	Cost(£)
Culture and first-line sensitivity on solid media	Identification and sensitivity	30
Rapid (Accuprobe) TB complex identification	Rapid TB identification	15
Rapid (Accuprobe) identification of non-MTB mycobacteria	Identification	15
	Standard culture	16
Culture using rapid liquid culture methods	Rapid culture	26
PCR identification of TB complex and molecular rifampicin testing (including culture and identification)	Fastrack	120

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Feedback

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We look forward to hearing from you.

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