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Diagnostic accuracy of the Xpert® MTB/RIF cycle threshold level to predict smear positivity: a meta-analysis

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SUMMARY

SETTING: Xpert® MTB/RIF is the most widely used molecular assay for rapid diagnosis of tuberculosis (TB). The number of polymerase chain reaction cycles after which detectable product is generated (cycle threshold value, C_T) correlates with the bacillary burden.

OBJECTIVE: To investigate the association between Xpert C_T values and smear status through a systematic review and individual-level data meta-analysis.

DESIGN: Studies on the association between C_T values and smear status were included in a descriptive systematic review. Authors of studies including smear, culture and Xpert results were asked for individual-level data, and receiver operating characteristic curves were calculated.

RESULTS: Of 918 citations, 10 were included in the descriptive systematic review. Fifteen data sets from studies potentially relevant for individual-level data meta-analysis provided individual-level data (7511 samples from 4447 patients); 1212 patients had positive Xpert results for at least one respiratory sample (1859 samples overall). ROC analysis revealed an area under the curve (AUC) of 0.85 (95%CI 0.82–0.87). Cut-off C_T values of 27.7 and 31.8 yielded sensitivities of 85% (95%CI 83–87) and 95% (95%CI 94–96) and specificities of 67% (95%CI 66–77) and 35% (95%CI 30–41) for smear-positive samples.

CONCLUSION: Xpert C_T values and smear status were strongly associated. However, diagnostic accuracy at set cut-off C_T values of 27.7 or 31.8 would not replace smear microscopy. How C_T values compare with smear microscopy in predicting infectiousness remains to be seen.

KEY WORDS: systematic review; diagnosis; Xpert; cycle threshold value

THE XPERT® MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay is an automated real-time molecular assay for rapid diagnosis of tuberculosis (TB) and detection of rifampicin resistance, recommended for use as the initial diagnostic test in individuals with suspected multidrug-resistant TB (MDR-TB) or human immu-

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nodeficiency virus associated TB.[1] Xpert was first endorsed by the World Health Organization (WHO) in December 2010. In 2013, the WHO recommended that Xpert be used as the initial diagnostic test for all adults and children with signs and symptoms of TB, rather than microscopy and culture.[1,2] A recently updated Cochrane review estimated pooled Xpert sensitivity to be 89% (95% confidence interval [CI] 85–92) and pooled specificity to be 99% (95%CI 98–99).[3] Xpert, which has a lower biohazard risk[4] and is less operator-dependent than conventional smear microscopy, is undergoing a major global roll-out in a number of high-burden countries, and has already replaced smear microscopy in South Africa.[5]

The Xpert assay uses molecular beacon technology to detect DNA sequences amplified in a hemi-nested real-time polymerase chain reaction (PCR) assay. The analytical limit of detection of Xpert, defined as the minimum number of bacilli that can be detected with 95% confidence, is 131 (95%CI 106–176) colony forming units per ml of clinical sputum sample.[6,7] Xpert thus has a limit of detection that is 50–100 times greater than that of smear microscopy, and is half as sensitive as liquid culture.[8,9] The assay's cycle threshold value (C_T), which is the number of PCR cycles after which each of the five probes is considered positive, provides a semiquantitative measure of bacillary burden in sputum.[6,10] *Mycobacterium tuberculosis* bacillary load therefore correlates with smear status, time to culture positivity using liquid culture systems and Xpert C_T values.[11]

The correlation between smear status and bacillary load as a marker of infectiousness is used to guide public health and treatment decisions.[12] However, smear status provides a rather crude estimate of bacillary burden and can only coarsely dichotomise samples into positive and negative. In settings where smear microscopy is no longer performed, quantitative Xpert C_T may be used to identify infectious TB patients for contact tracing as recommended by the WHO.[13] Quantitative Xpert C_T values may also help to cost-effectively guide targeted contact tracing of the most infectious TB patients,[14] and thus prioritise contact tracing.

The present study investigates the association between Xpert C_T values and smear status through a systematic review of the available literature, and a meta-analysis using individual-level data provided by primary studies to establish a receiver operating characteristic (ROC) curve and optimal cut-offs for C_T values.

METHOD

The review was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (PRISMA).[15] The protocol was registered with PROSPERO (CRD42014013315), and ethical approval was provided by the ethics committee of the London School of Hygiene & Tropical Medicine, London, UK (Ref 7071).

Inclusion and exclusion criteria

Cohort, cross-sectional, diagnostic studies, prevalence surveys and published and non-published laboratory validation studies were eligible for inclusion if they reported on respiratory samples (spontaneous sputum, induced sputum, broncho-alveolar lavage, tracheal aspirates, pleural fluid) and provided culture (either solid or liquid), microscopy (auramine or Ziehl-Neelsen) and Xpert C_T values. Studies were included if all three diagnostic tests (microscopy, culture and Xpert) were performed and if the culture isolate was identified as *M. tuberculosis* complex using either nucleic-acid amplification test or antigen testing. Studies reporting the association between Xpert C_T values and smear status were included in the descriptive analysis. Authors of studies included in the descriptive analysis and authors of studies presenting Xpert, smear microscopy and culture results were contacted and asked to provide individual-level data. Studies were excluded if sample sets were not random or consecutive. We did not exclude studies that assessed patients during treatment.

Search strategy

A search strategy was developed (see Appendix*) to identify all relevant studies, regardless of language or publication status. Medline, Embase, Global Health, Current Controlled Trials and the Cochrane database were searched. All references were imported into EndNote (Thomson Reuters, New York, NY, USA), duplicates were removed and abstracts were examined independently by two reviewers. Full-text articles of all potentially relevant studies were obtained, and inclusion criteria were applied. Studies included in three published reviews investigating the diagnostic accuracy of Xpert were also screened for inclusion.[3,16,17] Reference lists of the studies identified by the above methods were examined. All authors of potentially eligible studies were asked at least twice to provide data sets with individual patient information (see Appendix for further information on data extraction).

Risk of bias

Risk of bias for all included studies was assessed independently (BL and KK). The Cochrane Guidelines on Systematic Reviews on Diagnostic Test Accuracy were followed,[18] and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies

*The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000005/art00005

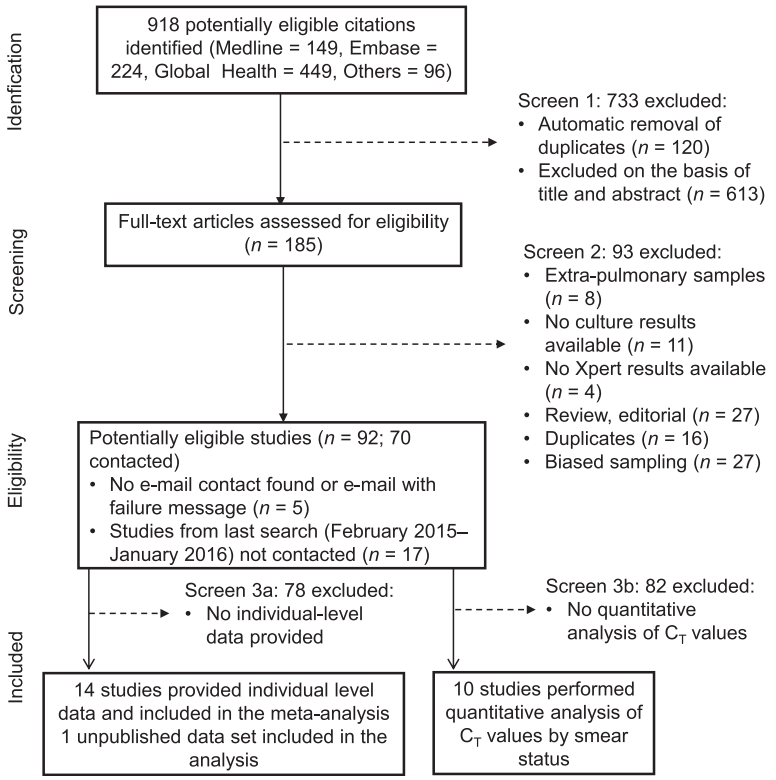

Figure 1 Selection process for the inclusion of studies. CT = cycle threshold.

2) tool was adapted to assess the risk of bias[19] (Appendix).

Data analysis

Meta-analysis was performed using individual-level data provided by authors. For studies providing Xpert C_T values for each of the probes, a mean C_T value was calculated. For isolates with *rpo*B mutation, mean C_T values were calculated disregarding the probe with a C_T value of 0. Mean Xpert C_T values for smear-positive and smear-negative, culture-positive samples were calculated. Linear regression was used to investigate the association between C_T values and smear positivity, smear grading and days to culture positivity. ROC analysis, stratified by human immunodeficiency virus (HV) status, was performed to determine the optimal C_T value, taking into account clustering by patient and study site. Sensitivity and specificity with corresponding 95% confidence intervals (CIs) were calculated for differing cut-off values. All analysis was conducted using Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

Study selection

Individual patient data

The last search was performed in February 2016. Of 918 unique citations identified, 92 were deemed potentially relevant for inclusion in the individual patient data meta-analysis (Figure 1; Appendix, information on all studies) and authors were contacted. Fourteen study teams provided anonymised individual-level data from 15 studies for the meta-analysis (Table 1).[21,25,27,29,30–39]

Descriptive systematic review on association between C_T values and smear status

Ten studies investigated the association between smear status and C_T values (Figure 1).[11,20,21,26,33–40] Seven of the ten studies were conducted in sub-Saharan Africa, and HIV prevalence among study participants ranged from 3% to 60%. Two studies did not provide information on HIV prevalence.[27,36] Overall studies were of moderate to good quality, although they did not always report on their efforts to minimise bias. Most, however, were consecutive or random collections of samples, and nearly all, except three, did report on the flow of patients in the study (Table 1).[20,34,36]

The mean C_T values of smear-positive samples were significantly lower (difference of mean C_T values 3–10) than smear-negative samples.[35,36,41] Two studies assessed the association between smear grade and C_T values and found a moderate to good inverse correlation (Spearman correlation coefficient range 0.7–0.9).[21,36] Three studies performed ROC analysis and proposed an optimal cut-off C_T value for the detection of smear-positive samples. Cut-offs

Table 1 Summary table of the included studies as well as studies providing individual data points (see Appendix for all studies contacted for individual data points)

Author, year, reference	Country	HIV %	Specimen type	Samples *n*	Culture-positive samples (culture medium: LG/MGIT) *n*	Xpert-positive *n*	Smear-positive (staining method, concentration) *n*
Alnimr, 2014[20]	Saudi Arabia	NR	Sputum	714	21 (MGIT)	20	17 (Kinyoun staining, NR)
Blakemore, 2011[21]*	Lima, Peru; Baku, Azerbaijan; Cape Town and Durban, South Africa; and Mumbai, India	40	Sputum	2223	2223 (LG + MGIT)	2008	1532 (ZN, concentrated and unconcentrated)
Friedrich, 2013[22]	South Africa, Tanzania	South Africa 3%, Tanzania 18%	Sputum	2741	NR (MGIT)	NR	221 (auramine, NR)
Friedrich, 2011[23]	South Africa	NR	Sputum	140	140 (MGIT)	130	120 (auramine, NR)
Hanrahan, 2013[24]	South Africa	60	Sputum	2406	406 (MGIT)	373	210 (auramine, concentrated)
Nikolayevskyy, 2015[25]*	Russia, Lithuania, Latvia	2–15	Sputum	1937	MGIT	NR	NR
Rachow, 2011[26]	Tanzania	59	Sputum	292	69 (MGIT + LJ)	61	51 (ZN, NR)
Theron, 2012[27]*	South Africa	30	Sputum	496	141 (MGIT)	130	96 (auramine, concentrated)
Theron, 2013[28]	South Africa	35	BAL	156	27 (MGIT)	21	16 (auramine, concentrated)
Theron, 2014[29]*	South Africa	NR	Sputum, BAL	865	172 (MGIT)	NR	67
Additional studies providing data for individual-level analysis							
Armand, 2011[30]*	France	NR	Sputum, BAL	80	60 (LJ)	44	28 (auramine, unconcentrated)
Al-Darraji, 2013[31]*	Malaysia	100%	Sputum	125	15 (MGIT)	8	1 (auramine, unconcentrated)
Balcells, 2012[32]*	Chile	100	Sputum	166	12 (MGIT and LJ)	11	5 (ZN, NR)
Clemente, 2011[33]*	Spain	NR	Sputum, BAL	614	81 (MGIT and LJ)	76	37 (ZN, NR)
Miller, 2011[34]*	Canada	NR	Sputum	89	29 (MGIT + LJ)	26	2 (auramine)
Ntinginya, 2012[35]*	Tanzania	NR	Sputum	219	9 (MGIT + LJ)	10	7 (ZN, NR)
Ozkutuk, 2014[36]*	Turkey	NR	Sputum, tracheal aspirate, gastric lavage	1611 (1269 patients)	125 (MGIT + LJ)	101	84 (ZN, concentrated)
Porcel, 2013[37]*	Spain	NR	Pleural fluid	67	5 (LJ)	3	1 (auramine)
Sohn, 2014[38]*	Canada	2.4	Sputum	502	25 (MGIT)	12	7 (auramine, NR)
Teo, 2011[39]*	Singapore	NR	Sputum, BAL	131	67 (MGIT)	61	54 (ZN, concentrated)

* Included in the individual-patient data analysis.
HIV = human immunodeficiency virus; LJ = Löwenstein-Jensen; MGIT™ = Mycobacteria Growth Indicator Tube; C_T = threshold concentration; ROC = receiver operator characteristic; NR = not reported; AUC = area under the ROC curve; ZN = Ziehl-Neelsen; BAL = bronchoalveolar lavage.

derived using Youden's index (aiming at optimising sensitivity and specificity) were estimated to be respectively 27.7, 27.1 and 27.5.[21,33,37] The corresponding sensitivity for smear positivity using these C_T value cut-offs ranged from 82% to 98%.[21,33,37] One study performed an analysis stratified by HIV status, and reported an optimal cut-off of 26.7 for samples from HIV-infected and 28.8 for non-HIV-infected patients.[37]

Meta-analysis of individual-level data

Individual-level data from 14 studies and one unpublished data set were included (Table 1; see Appendix for description of unpublished data set).[21,25,27,29,30–39] Collectively this amounted to 7511 respiratory samples from 4447 patients. A total of 1406 patients had at least one culture-positive sample, 1212 of whom had at least one Xpert-positive sample, 636 had two Xpert-positive samples and 11 patients more than three. The total number of Xpert-positive samples included in the meta-analysis was 1859. The majority of the samples were from males (64%); 20% of the samples were smear-negative, and among those patients with known HIV (44%) status, 14% were HIV-infected (Table 2).

The mean C_T value for smear-positive samples was significantly lower (22.0, 95%CI 21.5–22.6) than for smear-negative samples (29.3, 95%CI 28.1–30.5) (Appendix). Regression analysis revealed a decrease in C_T value of 7.4 (95%CI −8.1 to −6.8) for smear-positive samples, with 25% of the variability explained by smear status. Analysis adjusted for sex, age

Table 1 *(continued)*

Correlation between C_T value and bacterial load	C_T value cut-off (ROC analysis)	Sensitivity for proposed C_T cut-off	Specificity for proposed C_T cut-off	Risk of bias	Storage
Spearman's correlation coefficient $r = 0.9$ (C_T value and time to culture positivity)	NR	NR	NR	Moderate	Fresh samples
$r = -0.77$ (C_T value and smear microscopy grading)	27.7 suggested as most predictive cut off; 25 for higher specificity; AUC NR (only samples with internal control C_T value of <34)	C_T value 27.7: 98% C_T value 25: 95%	C_T value 27.7: 48% C_T value 25: 65%	Low	Fresh samples,
$r = -0.74$ (C_T value and smear microscopy grading) $r = 0.73$ (C_T value and days to culture positivity)	Different cut-offs throughout treatment	NR	NR	Moderate	Fresh samples
$r = -0.40$ (C_T value and smear microscopy grading) $r = 0.54$ (C_T value and days to culture positivity)	NR	NR	NR	Moderate	Fresh samples
$r = 0.58$ (C_T value and days to culture positivity)	Overall: 27.5, HIV+:26.7, HIV−: 28.8 AUC NR	Overall: 69%, HIV+: 79%, HIV−: 56	NR	Low	One fresh, one frozen
$r = 0.61$ (C_T value and days to culture positivity)	NR	NR	NR	Moderate	Fresh samples
$\beta = -5.02$ (C_T value and smear microscopy grading) $\beta = 1.19$ (C_T value /days to culture positivity)	NR	NR	NR	Moderate	Frozen samples
Smear+: C_T value 22 Smear−:C_T value 32.6	C_T value 27.1 cut off suggested as most predictive C_T value < 31.8 suggested as a rule out AUC 0.86	C_T 27.1: 82%, C_T 31.8: 96%	C_T 27.1:79% C_T 31.8:47%	Low	Frozen samples
$r = 0.50$ (C_T value and time to culture positivity)	NR	NR	NR	Low	Frozen samples
$r = 0.50$ (C_T value and days to culture positivity)	NR	NR	NR	NR	Fresh samples
NR	NR	NR	NR	Moderate	Fresh samples
NR	NR	NR	NR	Low	Fresh samples
NR	NR	NR	NR	Low	Fresh samples
NR	NR	NR	NR	Moderate	Fresh samples
NR	NR	NR	NR	Moderate	Frozen samples
NR	NR	NR	NR	Moderate	Fresh samples
NR	NR	NR	NR	Moderate	Fresh samples
NR	NR	NR	NR	Moderate	Frozen samples
NR	NR	NR	NR	Low	Fresh samples
NR	NR	NR	NR	High	Fresh samples

and HIV status including 812 samples revealed similar results (–7.5, 95%CI –8.4 to –6.5). Sputum samples of HIV-infected individuals had higher C_T values than non-HIV-infected individuals (regression coefficient 2.7, 95%CI 1.2–4). A sensitivity analysis disregarding the biggest sample set[21] yielded a coefficient of –6.9 for smear-positive samples; another sensitivity analysis disregarding frozen or archived samples yielded a coefficient of –7.1 (Table 3).

Smear grading and C_T values

Smear grading was available for 1428 samples. A subanalysis adjusted for sex, age and HIV status including 621 records showed a linear association between smear grade and C_T values. Using scanty smears as the reference, the regression coefficients were respectively –3.2 (95%CI –4.1 to –2), –5.3 (95%CI –6·6 to –4) and –9.4 (95%CI –10.6 to –8.3) for 1+, 2+ and 3+ smear-positive samples (Table 3, Figure 2A). Including smear grade as a linear variable yielded a regression coefficient of –3.1 (95%CI –3.4 to –2.8).

C_T value and days to culture positivity

Data on days to culture positivity were provided for 1424 samples. A linear regression of C_T value and days to culture positivity showed evidence of a positive association ($P < 0.001$). The average increase in C_T value was 0.18 for each extra day to culture positivity (95%CI 0.12–0.24) in a linear regression accounting for clustering by participants and adjusting for HIV, sex, age and study location ($n = 776$) (Figure 2B and Table 3).

Receiver operator characteristic analysis

ROC analysis, adjusted for study location and accounting for clustering by patient, was performed

Table 2 Baseline characteristics for individual-level data of patients with culture-positive and Xpert-positive samples*

	Smear-negative *n* (%)	Smear-positive *n* (%)	Unknown *n* (%)	Total *n* (%)
Age, years, median†	37	32	44	33
Sex				
Male	159 (64)	554 (59)	15(62)	728 (60)
Female	70 (28)	243 (26)	9 (37)	322 (27)
Missing	18 (7)	144 (15)	0	162 (14)
HIV status				
Negative	62 (25)	318 (34)	12 (50)	392 (32)
Positive	50 (20)	91 (10)	11 (46)	152 (13)
Missing	153 (55)	532 (57)	1 (4)	668 (55)
Treatment status				
Unknown	107 (43)	461 (38)	23 (96)	591 (49)
Treatment not yet started	102 (41)	339 (36)	1 (4)	442 (36)
Completed treatment	37 (15)	105 (11)	0	142 (12)
Stopped treatment	1 (1)	36 (4)	0	37 (3)
Specimen				
Sputum	224 (91)	898 (95)	24 (100)	1146 (95)
BAL	20 (8)	39(4)	0	59 (5)
Tracheal aspirate	0	2 (1)	0	2 (0.2)
Pleural fluid	3 (1)	2 (1)	0	5 (0.2)
Author, reference, country				
Al-Darraji,[30] Malaysia	5 (2)	1 (0.1)	0	6 (0.5)
Armand,[28] France	17 (8)	27 (4)	0	44 (5)
Balcells,[25] Chile	5 (3)	6 (1)	0	11 (1)
Blakemore,[21] Peru, Azerbaijan, South Africa, India	126 (51)	504 (54)	0	630 (52)
Clemente,[22] Spain	19 (9)	31 (4)	1 (4)	51 (5)
Kalmambetova, Kyrgyzstan (unpublished)	11 (5)	103 (11)	0	114 (9)
Miller,[33] Canada‡	2 (1)	9 (1)	0	11 (1)
Ntinginya,[23] Tanzania	1 (0.5)	5 (0.7)	0	6 (1)
Nikolayevskyy,[20] Russia, Lithuania, Latvia	4 (2)	27 (3)	0	31 (3)
Ozkutuk,[31] Turkey	17 (7)	67 (7)	0	84 (7)
Porcel,[32] Spain‡	1 (0.4)	1 (0.1)		2 (0.2)
Sohn,[29] Canada	4 (2)	6 (1)	0	10 (1)
Theron,[42] South Africa‡	8 (4)	23 (3)	23 (95)	54 (5)
Teo,[24] Singapore	5 (2)	42 (6)	0	47 (5)
Theron,[42] South Africa	22 (9)	89 (10)	0	111 (9)
Total, *n*	247	941	24	1212 (100)

* No missing values for smear status.
† Missing values: smear-negative ($n = 18$), smear-positive ($n = 103$).
‡ Data include frozen samples processed for Xpert, see Table 3 for sensitivity analysis.
HIV = human immunodeficiency virus; BAL = bronchoalveolar lavage.

to determine the area under the curve (AUC) and sensitivity and specificity for specific C_T value cut-offs (Figure 3). The overall AUC was 0.85 (95%CI 0.82–0.87), and remained the same when stratified by HIV status. Sensitivity and specificity for different C_T value cut-offs stratified by HIV status are shown in Table 3. Overall, a C_T value cut-off at 27.7 would provide a sensitivity of 85% (95%CI 83–87) and a specificity of 67% (95%CI 66–77). In non-HIV-infected individuals, the same cut-off would have a

Table 3 Random effects linear regressions on C_T value, smear status, smear grading and days to culture positivity

Explanatory variable as measure for bacillary load		β coefficient	*P* value	95%CI
Smear status (1827 samples from 1167 patients) (crude*)†	Smear-positive	−7.4	<0.001	−8.1 to −6.8
Smear status (812 samples from 515 patients)*‡§	Smear-positive	−7.5	<0.001	−8.4 to −6.5
Time to culture positivity in days (776 samples from 528 patients)*‡	1 day	0.18	<0.001	0.12 to 0.24
Smear grade (621 samples from 393 patients)*‡				
	Scanty	Baseline		
	1+	−3.2	<0.001	−4.4 to −2
	2+	−5.3	<0.001	−6.6 to −4
	3+	−9.4	<0.001	−10.6 to −8.3

* Clustering by patient and study site accounted for.
† In a sensitivity analysis, a variable for storage conditions (frozen vs. fresh samples) was included in the linear regression of 1827 samples from 1167 patients. The regression coefficient for smear-positive samples did not change and there was no evidence for an association of C_T values as to whether samples were frozen or not ($P = 0.81$).
‡ Adjusted for sex, age and HIV status.
§ In a sensitivity analysis removing the biggest study (>50% of samples, Blakemore),[21] performing the same regression analysis on 208 samples from all other studies, the β coefficient for smear-positive samples compared to smear-negative samples was −6.9 (95%CI −8.3 to −5.5).
C_T = threshold concentration; CI = confidence interval; HIV = human immunodeficiency virus.

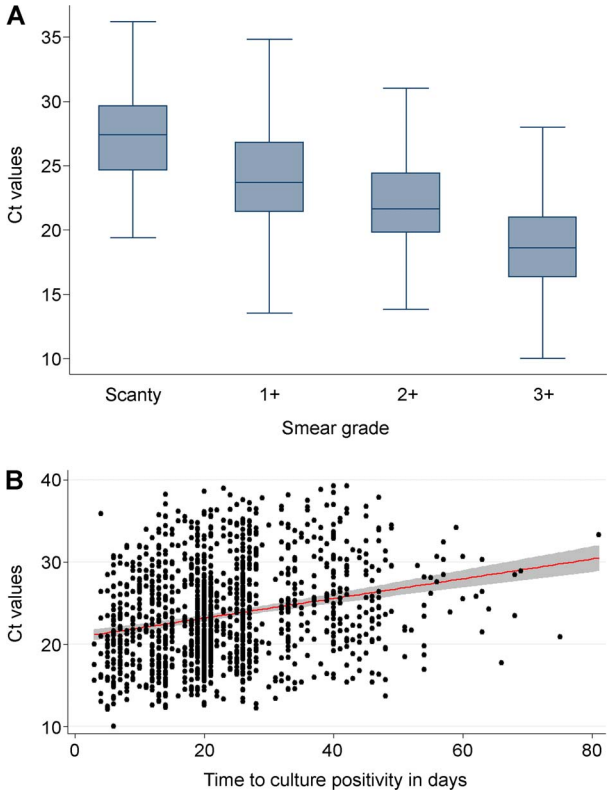

Figure 2 Association between **A)** C_T values (medians, 25 and 75 percentiles and ranges) and smear grading; **B)** C_T values and days to culture positivity (grey line = regression; grey area = area of 95% confidence intervals. C_T = threshold concentration. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000005/art00005

sensitivity of 83% (95%CI 79–86) and a specificity of 62% (95%CI 51–71), while in HIV-infected patients sensitivity would be 79% (95%CI 70–85) and specificity 79% (95%CI 65–88). To raise sensitivity to 95% (95%CI 94–96), the overall cut-off would have to be set at 31.8, resulting in a specificity of 35% (95%CI 30–41) (Table 4 and Figure 3).

DISCUSSION

Key findings

This review confirms the consistent, strong association between Xpert C_T values and the bacillary load, through both a descriptive review of the literature and a meta-analysis of 1859 samples. Three of 10 studies included in the descriptive review conducted ROC analysis and reported C_T value cut-offs of between 27.1 and 27.7 for optimal specificity (48–79%) and sensitivity (82–98%). Data on 1859 Xpert-positive respiratory samples from 1212 patients were included in the meta-analysis. The mean difference in C_T values between smear-positive and smear-negative samples was 7.4. The ROC curve showed good diagnostic accuracy (AUC 0.85).

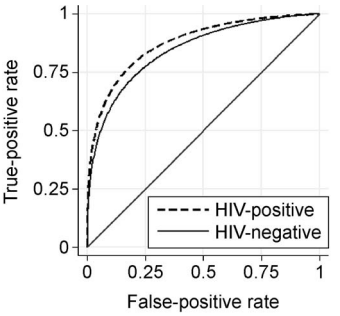

Figure 3 ROC of C_T value on smear, adjusting for study location and taking into account patient clustering by HIV status. HIV = human immunodeficiency virus; C_T = threshold concentration; ROC = receiver operating characteristic.

Strengths and limitations

The strengths of this review include a broad search strategy across different databases without any restrictions with regard to language and setting. Despite our best efforts, only 14/92 potentially eligible studies and one previously unpublished data set could be included in the meta-analysis. While some studies could not be included due to the lack of C_T values, authors of other studies presenting data on C_T values and smear status were unable to provide individual-level data.[34–36] The data included in the meta-analysis thus presents a selection, and might be prone to bias. One study provided >50% of all samples, which might have disproportionately influenced our results. However, sensitivity analysis excluding this study revealed similar results. The overall quality of the included studies was moderate to good, and risk of bias within studies was low.

Interpretation of findings

The general association between Xpert C_T values and bacillary load is not new, and mirrors what individual studies have shown.[11,21] Our meta-analysis allows for detailed and context-dependent analysis of this relationship for programmatic purposes. The moderate diagnostic accuracy of C_T values compared to smear in this meta-analysis, as well as different needs in contexts with varying prevalence of smear positivity, might preclude the use of C_T values as a replacement for smear in every context.

Deciding which C_T cut-off to use will differ according to the required objectives and context. To detect 95% of smear-positive patients, a cut-off of 31.8 would have to be chosen, resulting in a low (35%) specificity and lower positive predictive value. In the context of scarce resources, patients with the lowest C_T value, such as 20.7, might be prioritised for isolation. A recent cost-effectiveness study from the United States suggested that the use of Xpert in guiding decisions on patient isolation could substantially reduce isolation time as well as costs.[42]

In the context of contact tracing, C_T cut-offs may

Table 4 AUC, sensitivity and specificity with 95%CIs for smear positivity with different C_T value cut-offs in the meta-analysis on individual-level data derived from 15 different studies

AUC*	Cut-off (C_T value)	Sensitivity 95%CI†	Specificity % (95%CI)†	PPV (95%CI)	NPV (95%CI)	LR+	LR−
HIV-positive (233 samples from 152 patients)							
0.85 (0.77–0.92)							
	20.7	34 (26–44)	93 (81–97)	91 (77–97)	40 (31–49)	4.7	0.7
	25.3	67 (58–75)	87 (74–95)	92 (83–96)	55 (44–66)	5	0.4
	27.7	79 (70–85)	79 (65–88)	89 (80–94)	63 (51–74)	3.6	0.3
	31.8	93 (88–96)	49 (36–63)	80 (72–86)	76 (60–86)	1.8	0.1
HIV-negative (617 samples from 392 patients)							
0.84 (0.78–0.89)							
	20.7	45 (40–50)	97 (90–99)	99 (96–100)	24 (19–29)	14	0.6
	25.3	73 (69–77)	81 (71–88)	96 (93–97)	35 (28–42)	3.9	0.3
	27.7	83 (79–86)	62 (51–71)	92 (89–95)	40 (31–48)	2.1	0.3
	31.8	94 (92–97)	32 (23–42)	89 (85–91)	50 (37–64)	1.4	0.2
All (1827 samples from 1167 patients)‡§							
0.85 (0.82–0.87)							
	20.7	43 (41–46)	95 (92–97)	97 (95–98)	30 (27–33)	8.8	0.6
	25.3	75 (73–78)	83 (76–87)	94 (92–95)	46 (41–50)	4	0.3
	27.7	85 (83–87)	64 (66–77)	91 (89–92)	53 (48–58)	2.4	0.2
	31.8	95 (94–96)	35 (30–40)	85 (83–87)	64 (57–71)	1.5	0.1

* Taking into account clustering by patient and by study.
† Calculated with robust standard errors to take into account clustering by patients.
‡ Only 840 samples had information on HIV available; the AUC in those with HIV status available was 0.84 (95%CI 0.80–0.88); 1039 samples had no information on HIV available; the AUC for these was 0.85 (95%CI 0.81–0.88).
§ A sensitivity analysis disregarding the two biggest studies with 208 samples yielded an AUC of 0.84 (CI95 0.78–0.9).
AUC = area under the curve; CI = confidence interval; C_T = threshold concentration; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; + = positive; − = negative; HIV = human immunodeficiency virus.

be chosen according to resource availability. A C_T value cut-off of 27.7 would result in 59% of individuals being labelled as 'highly infectious' in a setting where 50% of patients with pulmonary TB are smear-positive. The C_T value cut-off would thus identify a similar number of highly infectious index cases as smear microscopy, and result in a similar number of contact tracing activities. However, 28% of these index cases identified by C_T value cut-off would be smear-negative, and 15% of the index cases identified as less infectious would be smear-positive. The sensitivity of C_T value cut-offs will always be less than 100%. However, smear positivity alone is itself an imperfect measure of infectiousness,[12,43] and transmission from smear-negative, culture-positive index cases is well described.[44] C_T values are generated in a consistent automated fashion, are less operator-dependent than smear microscopy, produce a timely available read-out, do not require any interpretation and are thus more objective. Whether smear status or Xpert C_T values predict infectiousness more accurately remains to be shown in prospective controlled studies.

With regard to treatment monitoring, C_T values provide a theoretical advantage of being able to compare numerical values over time rather than comparing two broad categories. In this paper, we did not specifically assess C_T values for their value in treatment monitoring. However, a multicentre trial conducted in sub-Saharan Africa failed to show any association between Xpert results and treatment outcomes in patients with drug-susceptible TB, despite good correlation between Xpert C_T values and smear status.[38] It is therefore difficult at this point to judge the usefulness of C_T values for serial testing of patients as part of treatment monitoring.[2]

A limitation inherent to smear microscopy and Xpert is the inability to differentiate between viable and dead bacilli. This differentiation is particularly important in patients on treatment. This has been addressed in the context of the Xpert test that uses propidium monoazide.[20] C_T values of samples treated with propidium monoazide were consistently lower than C_T values of untreated samples. Further research is needed to assess whether Xpert, with or without propidium monoazide pretreatment, could substitute smear microscopy for the purpose of treatment monitoring.

In conclusion, this meta-analysis provides further evidence that Xpert C_T values are strongly associated with smear status. However, the important question of whether Xpert C_T values predict infectiousness, transmission and treatment response remains unanswered. The correlation between Xpert C_T values and bacillary load is biologically plausible and supported by the results of this review. Given that mycobacillary burden on an individual level is linked to onward *M. tuberculosis* transmission, it may even be that aggregated Xpert C_T values at a community level (akin to community mycobacterial load) could potentially be used as a marker of ongoing community transmission, a concept similar to community viral load in the context of HIV.[45]

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APPENDIX

Search strategy for systematic review

We searched the following databases: 1) Medline, 2) Embase, 3) Global Health, 4) Current Controlled Trials, and 5) Cochrane Database of Systematic Reviews. The search strategy for Medline is given below. Search strategies were adapted to the databank used, but essentially we tried to retrieve all references that covered tuberculosis as well as the use of Xpert® MTB/RIF. We only searched for references from 2006 onward, as Xpert was not in use before that. We did not restrict by language or country.

Table A.1 Search strategy for systematic review

Databank	Category	Search terms
Medline	Xpert® MTB/RIF	Xpert.mp
		Genexpert.mp
		Cepheid.mp
		gene adj1 xpert.mp
		qRT adj1 PCR.mp
	Tuberculosis	exp Tuberculosis
		exp Mycobacterium tuberculosis
		Tuberculosis.mp
		TB.mp
		Tb.mp
		Mycobacteriosis.mp
		Mycobacterium.mp
		Mtb.mp

Data extraction and management

Data were extracted independently in duplicate using a standardised data extraction form. Data regarding setting, laboratory procedures (culture and microscopy methods), study population eligibility (inclusion and exclusion) criteria, population size, human immunodeficiency virus status, number of samples and diagnostic results (Xpert threshold concentration [C_T] value, smear result, smear grading, culture result, time to culture positivity) were determined. For studies included in the descriptive analysis, the following additional information was obtained where applicable: C_T value cut-offs for smear-positive samples determined by receiver operating characteristic (ROC) analysis, Spearman's correlation coefficient, regression coefficient and mean C_T values for smear-positive and smear-negative samples. Authors were asked to provide the following essential information for the data sets included in the meta-analysis: patient identifier, name and location of the laboratory, type of specimen, date of culture, date of microscopy, microscopy method, culture method, Xpert processing date, culture result, microscopy result, Xpert result, Xpert C_T value. Where authors provided all sample C_T values on individual probes A–E, a mean was calculated; C_T values of individual probes rifampicin-resistant (and therefore 0) were excluded. Authors were asked to provide any of the additional information if available: sex and age of the patient, human immunodeficiency virus (HIV) status, treatment status, smear grading, time to culture positivity on liquid culture.

Information on the unpublished data set

The data set contains data on 170 successive samples of 170 patients from the National Reference Laboratory in Kyrgyzstan from 2013 and 2014. Only samples with information available on culture, microscopy and Xpert results were provided, in an anonymised manner. No information on HIV status or time to culture positivity was available. The data set was provided by G Kalmambetova, Head of the Laboratory.

Table A.2 All studies potentially able to provide individual level patient data:[83–92] studies included in the descriptive systematic review on C_T values, in grey studies contributing individual-level data to the meta-analysis

Study data

Author, reference	Study title	Journal	Country	Year	Samples/patients *n*	Study population
Al-Darraji[1]	The diagnostic performance of a single Xpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia	PLOS ONE (electronic resource)	Saudi Arabia	2013	125 patients	125 HIV infected prisoners
Al-Ateah[2]	Evaluation of direct detection of *Mycobacterium tuberculosis* complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert system	Saudi Med J	Saudi Arabia	2012	239 total, 172 respiratory samples, 62 samples positive by culture	Patients tested for TB
Al Johani[3]	Rapid molecular detection of tuberculosis and rifampin resistance using Xpert MTB/RIF	Conference abstract	Saudi Arabia	2011	26 culture-positive, 16 smear-positive, 40 persons without TB	Patients tested for TB
Antonenka[4]	Comparison of Xpert MTB/RIF with ProbeTec ET DTB and COBAS TaqMan MTB for direct detection of *M. tuberculosis* complex in respiratory specimens	BMC Infect Dis	Germany	2013	121 sputum samples, 68 culture-positive	Patients tested for TB
Archontakis[5]	Evaluation of GeneXPERT MTB/RIF assay in respiratory and non-respiratory specimens for the rapid detection of *Mycobacterium tuberculosis*	Conference abstract	Greece	2011	250 samples, 50 culture-positive, 24 *M. tuberculosis* complex, 14 respiratory samples	Patients tested for TB
Armand[6]	Comparison of the Xpert MTB/RIF test with an IS*6110*-TaqMan real-time PCR assay for direct detection of *Mycobacterium tuberculosis* in respiratory and non-respiratory specimens	J Clin Microbiol	France	2011	117 clinical specimens (97 culture-positive and 20 culture-negative, 60 respiratory and 37 non-respiratory specimens	Unclear
Atehortua[7]	Xpert MTB/RIF test performance assay in respiratory samples at real work settings in a developing country	Biomedica	Colombia	2015	152 eligible, 103 patients included	Patients tested for TB
Aurin[8]	Molecular approaches for detection of the multi-drug resistant tuberculosis (MDR-TB) in Bangladesh	PLOS ONE	Bangladesh	2014	300 samples, 193 RMP resistance detected	Patients tested for TB with suspicion of resistance
Balcells[9]	Rapid molecular detection of pulmonary tuberculosis in HIV-infected patients in Santiago, Chile	Int J Tuberc Lung Dis	Chile	2012	12 culture-positive samples	166 HIV-positive patients
Barnard[10]	The diagnostic performance of the GenoType MTBDR*plus* version 2 line probe assay is equivalent to that of the Xpert MTB/RIF assay	J Clin Microbiol	South Africa	2012	282 samples	NR
Barnard[11]	The utility of Xpert MTB/RIF performed on bronchial washings obtained in patients with suspected pulmonary tuberculosis in a high prevalence setting	BMC Pulm Med	South Africa	2015	112 patients for bronchial lavage, 39 culture-positive	Patients tested for TB with negative or scarce smear
Barreales[12]	GeneXpert MTB/RIF system in pulmonary and extra-pulmonary specimens: comparison with other nucleic acid technologies	Conference abstract	Spain	2012	90 samples, 50 respiratory, 11 smear-positive, 79 smear-negative	NR
Bilgin[13]	Comparison of a real-time polymerase chain reaction-based system and Erlich-Ziehl-Neelsen method with culture in the identification of *Mycobacterium tuberculosis*	Turk J Med Sci	Turkey	2016	243 respiratory samples	Patients tested for tuberculosis
Bodmer[14]	Diagnosing pulmonary tuberculosis in a low prevalence setting—the Xpert MTB/RIF tes	Conference abstract		2010	231 specimens, 6 culture-positive	149 patients tested for TB
Boehme[15]	Rapid molecular detection of tuberculosis and rifampin resistance	N Engl J Med	Multisite	2010	732 culture-positive patients, 561 smear-positive, 171 smear-negative	NR
Boehme[16]	Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation stud	Lancet	Multisite	2011		6648 participants evaluated for TB
Bowles[17]	Xpert MTB/RIF, a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis	Int J Tuberc Lung Dis	The Netherlands	2011	72 samples	Patients tested for TB
Bunsow[18]	Evaluation of GeneXpert MTB/RIF for the detection of *Mycobacterium tuberculosis* and resistance to rifampin in clinical specimens	J Infect	Spain	2014	595 clinical samples, 290 respiratory, 81 culture-positive	Patients tested for TB
Carriquiry[19]	A diagnostic accuracy study of Xpert MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru	PLOS one	Peru	2012		131 HIV positive Patients tested for TB
Celik[20]	Applicability of Xpert MTB/RIF assay for routine diagnosis of tuberculosis: a four-year single-center experience	Turk J Med Sci	Turkey	2015	7407 samples from patients without suspicion of TB, 411 samples from patients with high risk of TB	Patients screened for TB
Ciftci[21]	[Evaluation of Xpert MTB/RIF results for the detection of *Mycobacterium tuberculosis* in clinical samples]	Mikrobiyol Bul	Turkey	2011	85 samples, 25 culture-positive	
Clemente[22]	Evaluation of the Xpert MTB/RIF test for rapid detection of *Mycobacterium tuberculosis*	Conference abstract	Spain	2011	1039 samples, 614 pulmonary, 81 culture-positive	930 patients tested for TB
Darwish[23]	Diagnostic assessment of Xpert MTB/RIF in a sample of *Mycobacterium tuberculosis* Egyptian patients	Afr J Microbiol Res	Egypt	2013	50 samples	Patients tested for TB
Davis[24]	The clinical and public health impact of automated nucleic acid testing for TB evaluation in San Francisco	Conference abstract	US	2011	20 samples	20 patients tested for TB on empiric treatment
Davis[25]	Impact of GeneXpert MTB/RIF on patients and tuberculosis programs in a low-burden setting. a hypothetical trial	Am J Respir Crit Care Med	US	2014	156 patients, 59 empiric TB treatment	Patients tested for TB
Deforges[26]	Application of the rapid detection system for *M. tuberculosis* complex and rifampicin resistance Xpert MTB/RIF in decontaminated respiratory specimens, non-respiratory specimens and cultures	Conference abstract	France	2010	15 pulmonary samples, 10 culture-negative, 2 NTM-positive, 3 culture-positive	Patients tested for TB

Table A.2 *(continued)*

Study data	Xpert sensitivity and specificity					Inclusion criteria for this systematic review				
HIV %	Sensitivity (vs. culture) %	Smear+ %	Smear−	Specificity (vs. culture)	Comments	Culture analysed	Smear analysed	Xpert analysed	C_T values reported or analysed	Median time to culture positivity
NR	53.3	100	NR	NR		Yes	Yes	Yes	No	No
NR	95.4	NR	NR	100	Respiratory and non-respiratory	Yes	Yes	Yes	No	No
NR	96.2	93.80	25	NR	Unclear number of people	Yes	Yes	Yes	No	No
NR	74.6	100	68	96.2	Frozen specimens	Yes	Yes	Yes	No	No
NR	100	NR	NR	NR	Very few respiratory samples	Yes	Unclear	Yes	No	No
NR	78.7	100	57	1		Yes	Yes	Yes	No	Yes
NR	91	NR	87	92	Spanish paper	Yes	Yes	Yes	NR	NR
NR	NR	NR	NR	NR	Mainly on RMP-resistant samples but not limited to these	Yes	Yes	Yes	No	No
100	11/12 (91.7) (95%CI 64.6–98.5)	8/12 (66.7) (95%CI 39.1–86.2)	NR	147/148 (99.3) (95%CI 96.3–99.9)		Yes	Yes	Yes	No	Yes
NR	71.2	NR	58	100		Yes	Yes	Yes	No	Yes
NR	92.3	NR	NR	87.7		Yes	Yes	Yes	NR	NR
NR	100	100	100	100		Yes	Yes	Yes	No	No
NR	100	NR	NR	98.7		Yes	Yes	Yes	NR	NR
	83.3 (95%CI 43.6–96.9)			100 (95%CI 98.3–100)		Yes	Yes	Yes	No	No
40.2	92	98.2	72.5	99.2		Yes	Yes	Yes	No	No
19	90.3		77	99		Yes	Yes	Yes	No	Yes
	93.8	NR	NR	92		Yes	Yes	Yes	No	No
NR	97.1	NR	NR	95		Yes	Yes	Yes	No	No
100	97.8 (95%CI 88.4–99.6)	NR	NR	84/86 (97.7) (95%CI 91.9–99.4)		Yes	Yes	Yes	No	No
NR	100	NR	NR	99		Yes	Yes	Yes	NR	NR
	96	NR	NR	NR	Article in Turkish	Yes	Yes	Yes	No	No
	93	1	92.3	100		Yes	Yes	Yes	No	No
NR	97.1	NR	NR	100		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR		Yes	Yes	Yes	No	No
NR	100	NR	NR	NR		Yes	Yes	Yes	No	No

Table A.2 *(continued)*

Study data

Author, reference	Study title	Journal	Country	Year	Samples/patients *n*	Study population
Deggim[27]	Integrating the Xpert MTB/RIF assay into a diagnostic workflow for rapid detection of *Mycobacterium tuberculosis* in a low-prevalence area	J Clin Microbiol	Switzerland	2013	79 samples, 57 sputum samples, 10 bronchial aspirates, 4 BAL, 8 non-respiratory samples	Patients tested for TB
Dorman[28]	Performance characteristics of the Cepheid Xpert MTB/RIF test in a tuberculosis prevalence survey	PLOS ONE	South Africa	2012	6893 samples, 187 culture-positive	6893 participants of prevalence survey
Gascoyne[29]	Comparison of on-demand PCR testing for *Mycobacterium tuberculosis* with culture and batched PCR	Conference abstract	UK	2012	96 samples	Patients tested for TB
Geleta[30]	Xpert MTB/RIF assay for diagnosis of pulmonary tuberculosis in sputum specimens in remote health care facility	BMC Microbiol	Ethiopia	2015	227 paired sputum samples	Patients tested for TB
Handel[31]	The impact of Xpert® MTB/RIF in sparsely populated rural settings	Int J Tuberc Lung Dis	South Africa	2015	1449 persons tested for TB	Patients tested for TB
Hanif[32]	GeneXpert MTB/RIF for rapid detection of *Mycobacterium tuberculosis* in pulmonary and extra-pulmonary samples	Int J Tuberc Lung Dis	Kuwait	2011	206 pulmonary (196 sputum, 6 BAL, 4 endotracheal aspirate), 60 pulmonary samples culture-positive	
Hanrahan[33]	Time to treatment and patient outcomes among patients tested for TB screened by a single point-of-care Xpert MTB/RIF at a primary care clinic in Johannesburg, South Africa	PLOS ONE (electronic resource)	South Africa	2013	641 patients with suspected TB, 50 Xpert-positive samples	
Helb[34]	Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology	J Clin Microbiol	Viet Nam	2010	107 clinical sputum samples	
Ionnaidis[35]	Cepheid GeneXpert MTB/RIF assay for *Mycobacterium tuberculosis* detection and rifampin resistance identification in patients with substantial clinical indications of tuberculosis and smear-negative microscopy results	J Clin Microbiol	Greece	2011	121 samples, 80 pulmonary and 41 extra-pulmonary, from 108 patients	Patients tested for TB
Jafari[36]	Comparison of molecular and immunological methods for the rapid diagnosis of smear-negative tuberculosis	Int J Tuberc Lung Dis	Germany	2013	96 patients tested for TB, BAL samples	Patients tested for TB
Kim[37]	The Xpert MTB/RIF assay evaluation in South Korea, a country with an intermediate tuberculosis burden	Int J Tuberc Lung Dis	South Korea	2012	71 specimens	TB patients
Kim[38]	Identification of *Mycobacterium tuberculosis* and rifampin resistance in clinical specimens using the Xpert MTB/RIF assay	Ann Clin Lab Sci	South Korea	2015	444 samples of 383 patients with suspected TB who were hospitalised	Patients with suspected TB
Kim[39]	Comparison of the Xpert MTB/RIF assay and real-time PCR for the detection of *Mycobacterium tuberculosis*	Ann Clin Lab Sci	South Korea	2015	52 samples	Patients with suspected tuberculosis
Kurbatova[40]	Performance of Cepheid® Xpert MTB/RIF® and TB-Biochip® MDR in two regions of Russia with a high prevalence of drug-resistant tuberculosis	Eur J Clin Microbiol Infect Dis		2013	238 specimens, 109 culture-positive, 67 RMP-resistant	Patients tested for TB
Kwak[41]	Diagnostic accuracy and turn-around time of the Xpert MTB/RIF assay in routine clinical practice	PLOS ONE (electronic resource)	South Korea	2013	681 patients	Patients tested for TB
Lawn[42]	Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study	PLOS ONE	South Africa	2011	839 samples, 81 culture-positive	515 HIV-positive patients tested for TB, 17.3% TB prevalence
Lee[43]	Diagnostic accuracy of Xpert® MTB/RIF on bronchoscopy specimens in patients with suspected pulmonary tuberculosis	Int J Tuberc Lung Dis	South Korea	2013	132 patients with Xpert, 38 culture-positive	Patients tested for TB
Lin[44]	Evaluation of Xpert MTB/RIF assay and amplified *Mycobacterium tuberculosis* Direct test in direct detection of pulmonary *M. tuberculosis* complex	Conference abstract	China	2010	38 smear positive samples, 27 culture-positive	Patients tested for TB
Lin[45]	Comparative evaluation of GeneXpert MTB/RIF assay and Gen-Probe amplified *Mycobacterium tuberculosis* Direct test for detection of *Mycobacterium tuberculosis* complex in smear-negative respiratory specimens	Conference abstract	China	2011	21 smear-negative culture-positive	Patients tested for TB
Lorent[46]	Active tuberculosis screening of close contacts among the urban poor: a Cambodian experience	Int J Tuberc Lung Dis	Cambodia	2014	1171 sputum samples from close contacts to TB	Close contacts
Luetkemeyer[47]	Xpert MTB/RIF versus AFB smear to determine respiratory isolation of US TB suspects	Conference abstract	US	2015	633 samples	Patients with suspected TB
Malbruny[48]	Rapid and efficient detection of *Mycobacterium tuberculosis* in respiratory and non-respiratory samples	Int J Tuberc Lung Dis	France	2011	91 respiratory, 17 culture-positive	132 patients tested for TB
Marlowe[49]	Comparison of three molecular methods for the direct detection of *Mycobacterium tuberculosis* complex from respiratory & non-respiratory specimens	Conference abstract	US	2010	76 specimen, 40 sputum, 11 bronchial	Patients tested for TB
Marlowe[50]	Evaluation of the Cepheid Xpert MTB/RIF assay for direct detection of *Mycobacterium tuberculosis* complex in respiratory specimens	J Clin Microbiol	US	2011	217 specimens	Patients tested for TB
Matabane[51]	Performance evaluation of three commercial molecular assays for the detection of *Mycobacterium tuberculosis* from clinical specimens in a high TB-HIV-burden setting	BMC Infect Dis	South Africa	2015	90 samples, 81 analysable	Persons tested for TB
Miller[52]	Performance of Xpert MTB/RIF RUO assay and IS*6110* real-time PCR for *Mycobacterium tuberculosis* detection in clinical samples	J Clin Microbiol	US	2011	112 specimen, 89 pulmonary, 29 culture-positive pulmonary	90 patients tested for TB

Table A.2 *(continued)*

Study data	Xpert sensitivity and specificity					Inclusion criteria for this systematic review				
HIV %	Sensitivity (vs. culture) %	Smear+ %	Smear−	Specificity (vs. culture)	Comments	Culture analysed	Smear analysed	Xpert analysed	C_T values reported or analysed	Median time to culture positivity
NR	NR	100	NR	NR		Yes	Yes	Yes	No	No
8.7 self-reported positive	62.6 (95%CI 55.2–69.5)	97.0 (95%CI 84.2–99.9)	55.2 (95%CI 47.0–63.2)	99.6 (95%CI 99.4–99.7), 81.3 (95%CI 73.9–87.3)		Yes	Yes	Yes	No	No
NR	96	NR	NR	98		Yes	Yes	Yes	No	No
NR	65.5	NR	31	NR		Yes	Yes	Yes	NR	NR
	91–99 (depending on centralisation)	NR	NR	NR		Yes	Yes	Yes	NR	NR
NR	92	98	69			Yes	Yes	Yes	No	No
69	66	NR	NR	NR		Yes	Yes	Yes	No	Yes
NR	91	100	84.6			Yes	Yes	Yes	No	No
NR	90.6	NR	NR	93.5	NR	Yes	Yes	Yes	No	No
NR	60	NR	NR	97	Compared to T. SPOT	Yes	Yes	Yes	No	No
0	100	NR	NR	NR	NR	Yes	Yes	Yes	No	Yes
	74	NR	NR	NR		Yes	Yes	Yes	NR	NR
NR	75.5	93.8	65.5	NR		Yes	Yes	Yes	NR	NR
NR	95.3 (95%CI 90.0–98.3)	NR	NR	86.0 (95%CI 78.9–91.3)	NR	Yes	Yes	Yes	No	No
0.7	79.50	NR	NR	100	Median time to treatment markedly reduced in those with Xpert	Yes	Yes	Yes	No	7 days
NR	73.3	100	43.4 (one sample); 62.3 (two sample)	NR		Yes	Yes	Yes	No	Yes
0.8	81.60	NR	NR	100		Yes	Yes	Yes	No	No
NR	92.6	NR	NR	NR		Yes	Yes	Yes	No	No
NR	NR	NR	52.4	NR		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR		Yes	Yes	Yes	No	No
38	82	NR	NR	NR		Yes	Yes	Yes	NR	NR
NR	100	NR	NR	100		Yes	Yes	Yes	No	No
NR	97.7	NR	NR	100	Archived samples	Yes	Yes	Yes	No	No
NR	0.96	0.98	0.72			Yes	Yes	Yes	No	No
	89.1	NR	NR	NR		Yes	Yes	Yes	NR	NR
NR	93	100	60	97		Yes	Yes	Yes	No	No

Table A.2 *(continued)*

Study data

Author, reference	Study title	Journal	Country	Year	Samples/patients *n*	Study population
Mokkaddas[53]	Comparison of two nucleic acid amplification assays, the ProbeTec ET assay and Xpert MTB/RIF assay, for detection of *Mycobacterium tuberculosis* in pulmonary and extra-pulmonary specimens	Conference Abstract	Kuwait	2012	989 specimen, 90 smear-positive, 66 smear-negative, 833 culture-negative	NR
Mokkaddas[54]	Evaluation of Gene Xpert MTB/RIF system for the direct detection of rifampicin-resistant *Mycobacterium tuberculosis* from pulmonary and extra-pulmonary specimens in the National Tuberculosis Reference Laboratory in Kuwait	Conference Abstract	Kuwait	2011	236 specimens, pulmonary 196	NR
Myneedu[55]	Xpert® MTB/RIF assay for tuberculosis diagnosis: evaluation in an Indian setting	Int J Tuberc Lung Dis	India	2014	134 samples from patients	134 TB patients with suspicion of resistance
Naidoo[56]	Evaluation of GeneXpert MTB/RIF assay on pulmonary and extra-pulmonary samples in a high-throughput laboratory	Conference Abstract	South Africa	2010	1140 sputum samples	Patients tested for TB
Narute[57]	Comparative study of gene Xpert MTB/RIF, smear microscopy and TB MGIT culture in diagnosis of tuberculosis in India	Conference abstract	India	2015	63 pulmonary TB patients	
Nazli[58]	Evaluation of GeneXpert MTB/RIF assay for the diagnosis of tuberculosis and rapid detection of rifampin resistance in clinical specimens	Conference Abstract	Turkey	2011	232 specimen, 28 smear positive, 69 culture positive	228 patients
Nosova[59]	[Comparing performance of 'TB-BIOCHIP', 'Xpert MTB/RIF' and 'GenoType MTBDR*plus*' assays for fast identification of mutations in the *Mycobacterium tuberculosis* complex in sputum from TB patients]	Mol Biol (Mosk)	Russia	2013	NR	Patients tested for TB
Ntinginya[60]	Performance of the Xpert® MTB/RIF assay in an active case-finding strategy: a pilot study from Tanzania	Int J Tuberc Lung Dis	Tanzania	2012	219 enrolled contacts, 5 culture positive	Contacts
O'Grady[61]	Evaluation of the Xpert MTB/RIF assay at a tertiary care referral hospital in a setting where tuberculosis and HIV infection are highly endemic	Clinical Infect Dis	Zambia	2012		937 recruited suspects, 881 produced enough sputum
Okumu[62]	Comparison of performance between Ziehl Neelsen (ZN) microscopy and the Xpert MTB/RIF assay in detection of *M. tuberculosis* in sputum at KEMRI/CDC TB lab	Conference abstract	Kenya	2012	262 specimen, 34	HIV-positive patients, screened for TB
Ozkutuk[63]	[Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary and extra-pulmonary tuberculosis in an intermediate-prevalence setting]	Mikrobiyoloji Bult	Turkey	2014	2639 specimen, 1611 pulmonary	Patients tested for TB
Park[64]	Comparison of the Xpert MTB/RIF and Cobas TaqMan MTB assays for detection of *Mycobacterium tuberculosis* in respiratory specimens	J Clin Microbiol	Korea	2013	320 consecutive respiratory specimens	Patients tested for TB
Pimkina[65]	The Xpert® MTB/RIF assay in routine diagnosis of pulmonary tuberculosis: a multicentre study in Lithuania	Respiratory Medicine	Lithuania	2015	833 respiratory samples	Persons tested for tuberculosis
Pinto[66]	Evaluation of a point-of-care molecular test for *M. tuberculosis* detection in an emergency setting	Conference abstract	Portugal	2012	64 respiratory specimens	Patients tested for TB
Porcel[67]	Xpert® MTB/RIF in pleural fluid for the diagnosis of tuberculosis	Int J Tuberc Lung Dis	Spain	2013	67 patients	Patients tested for TB
Scott[68]	Dried culture spots for Xpert MTB/RIF external quality assessment: results of a phase 1 pilot study in South Africa	J Clin Microbiol	South Africa	2011	274 specimens	Patients tested for TB
Scott[69]	Comparison of Xpert MTB/RIF with other nucleic acid technologies for diagnosing pulmonary tuberculosis in a high HIV prevalence setting: a prospective study	PLOS Med	South Africa	2011	311 specimens	Patients tested for TB
Iram[70]	Rapid diagnosis of tuberculosis using Xpert MTB/RIF assay - report from a developing country	Pak J Med Sci	Pakistan	2015	205 persons of pulmonary TB	Persons tested for TB
Shah[71]	Xpert MTB/RIF under routine conditions in diagnosing pulmonary tuberculosis: a study in two hospitals in Pakistan	Public Health Action	Pakistan	2013	121 pulmonary TB	606 suspects
Shah[72]	Comparative performance of urinary lipoarabinomannan assays and Xpert MTB/RIF in HIV-infected individuals	AIDS	US	2014	103 culture-confirmed TB	TB patients
Sharma[73]	Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis	PLOS ONE	India	2015	1439 respiratory samples	Persons tested for TB
Siracuse[74]	GeneXpert MTB/RIF performance evaluation in respiratory specimens in Ecuador	Conference abstract	Ecuador	2015	1602 sputum samples	Persons tested for TB
Sohn[75]	Xpert MTB/RIF testing in a low tuberculosis incidence, high-resource setting: limitations in accuracy and clinical impact	Clin Infect Dis	Canada	2014	502 consecutive patients	Patients tested for TB
Teo[76]	Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified *Mycobacterium tuberculosis* Direct assay, for detection of *Mycobacterium tuberculosis* in respiratory and non-respiratory specimens	J Clin Microbiol	Singapore	2011	162 respiratory specimens	Patients tested for TB
Theron[77]	Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in a high HIV prevalence setting	Am J Respir Crit Care Med	South Africa	2012	496 patients	Patients tested for TB
Theron[78]	Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial	Lancet	Multisite	2014	744 patients in Xpert group, 182 culture-positive	Patients tested for TB
Tura[79]	Assessment of laboratory accuracy measures of the GeneXpert system for the detection of *Mycobacterium tuberculosis* (Mtb) in a Philippine tertiary hospital from October 2014 to February 2015	Conference abstract	The Philippines	2015	140 clinical samples	Persons tested for TB

Table A.2 *(continued)*

Study data		Xpert sensitivity and specificity				Inclusion criteria for this systematic review				
HIV %	Sensitivity (vs. culture) %	Smear+ %	Smear−	Specificity (vs. culture)	Comments	Culture analysed	Smear analysed	Xpert analysed	C_T values reported or analysed	Median time to culture positivity
NR	90	NR	65	100		Yes	Yes	Yes	No	No
NR	NR	100	0.6	100		Yes	Yes	Yes	No	No
NR	100	NR	NR	NR	Sensitivity for RMPresistance 98.2%, specificity 97%	Yes	Yes	Yes	No	No
NR	99.8	NR	NR	94.1		Yes	Yes	Yes	No	No
NR	96.9	NR	NR	NR	NR	Yes	Yes	Yes	NR	NR
NR	81.1	96.4	71.4	NR		Yes	Yes	Yes	No	No
NR	92	NR	NR	NR	Article in Russian	Yes	Yes	Yes	No	No
	100 (95%CI 47.81–100.0)	NR	NR	NR		Yes	Yes	Yes	No	No
70.9	86.1	NR	NR	95		Yes	Yes	Yes	No	Yes
NR	NR	NR	NR	NR	Author was contacted to see whether culture was performed, but no response	Unclear	Yes	Yes	No	No
NR	80.8	NR	NR	84.9	Article in Turkish	Yes	Yes	Yes	No	No
NR	67.9	67	69	100	NR	Yes	Yes	Yes	No	No
NR	93.7	97.8	82.5	91.7	NR	Yes	Yes	Yes	NR	NR
NR	91	NR	NR	100	NR	Yes	Yes	Yes	No	No
NR	15			100		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR	On dried culture spots	Yes	Yes	Yes	No	No
70	86 (95%CI 76–93)	NR	NR	NR		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR	Full-text not accessible, diagnostic accuracy not calculable	Yes	Yes	Yes	NR	NR
NR	NR	NR	NR	NR		Yes	Yes	Yes	No	No
NR	76	NR	NR	97		Yes	Yes	Yes	No	No
NR	95.7		77.7	99.3		Yes	Yes	Yes	NR	NR
NR	NR	92.7	NR	NR		Yes	Yes	Yes	NR	NR
2.4	46 (95%CI 26–67)	86 (95%CI 42–100)	28 (95%CI 10–56)	100		Yes	Yes	Yes	No	Yes
NR	90.1	NR	NR	89		Yes	Yes	Yes	No	No
NR	NR	89/94 (95) (95%CI 88–98)	12/22 (55) (95%CI 35–73)	NR		Yes	Yes	Yes	No	No
NR	83	NR	NR	95		Yes	Yes	Yes	No	No
NR	74.2	NR	NR	NR		Yes	Yes	Yes	NR	NR

Table A.2 *(continued)*

Study data

Author, reference	Study title	Journal	Country	Year	Samples/patients *n*	Study population
Williamson[80]	An evaluation of the Xpert MTB/RIF assay and detection of false-positive rifampicin resistance in *Mycobacterium tuberculosis*	Diagn Microbiol Infect Dis	New Zealand	2012	169 specimen	Patients tested for TB
Yoon[81]	Impact of Xpert MTB/RIF testing on tuberculosis management and outcomes in hospitalized patients in Uganda		Uganda	2012	477 patients, baseline 287 implementation 190	Patients tested for TB
Zeka[82]	Evaluation of the GeneXpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extra-pulmonary specimens	J Clin Microbiol	Turkey	2011	253 pulmonary samples	110 patients, 89 culture-positive, 21 culture-negative)
Alnimr[83]	Potential of two nucleic acid amplification assays for quantifying mycobacterial load in respiratory and non-respiratory specimens: a prospective study	Diagn Microbiol Infect Dis	Saudi Arabia	2014	714 samples, 44 culture positive	Patients tested for TB
Blakemore[84]	A multisite assessment of the quantitative capabilities of the Xpert MTB/RIF assay	Am J Respir Crit Care Med	Multisite	2011	2008 samples	TB patients
Friedrich[85]	Suitability of Xpert MTB/RIF and genotype MTBDR*plus* for patient selection for a tuberculosis clinical trial	J Clin Microbiol	South Africa	2011	120 smear positive tuberculosis patients with one sample	TB patients
Friedrich[86]	Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment	Lancet Respir Med	South Africa, Tanzania	2013	2741 samples from 221 patients	221 patients with smear positive tuberculosis
Hanrahan[87]	Xpert MTB/RIF as a measure of sputum bacillary burden. Variation by HIV status and immunosuppression	Am J Respir Crit Care Med	South Africa	2013	2406 sputum samples, 406 culture positive	Patients tested for TB
Nikolayevskyy[88]	Utility of propidium monoazide viability assay as a biomarker for a tuberculosis disease	Tuberculosis	Russia, Lithuania, Latvia	2014	1937 samples of 310 patients	Patients tested for TB
Rachow[89]	Rapid and accurate detection of *Mycobacterium tuberculosis* in sputum samples by Cepheid Xpert MTB/RIF assay—a clinical validation study	PLOS ONE	Tanzania	2011	292 adults	Patients tested for TB
Theron[90]	The use of an automated quantitative polymerase chain reaction (Xpert MTB/RIF) to predict the sputum smear status of tuberculosis patients	Clin Infect Dis	South Africa	2012	496; 141 culture-confirmed	Patients tested for TB
Theron[91]	Accuracy and impact of Xpert MTB/RIF for the diagnosis of smear-negative or sputum-scarce tuberculosis using bronchoalveolar lavage fluid	Thorax	South Africa	2013	160 patients	Patients tested for TB
Theron[92]	Determinants of PCR performance (Xpert MTB/RIF), including bacterial load and inhibition, for TB diagnosis using specimens from different body compartments	Nature Sci Rep	South Africa	2014	865 patients, 172 culture-confirmed samples	Patients tested for TB

C_T = threshold concentration; HIV = human immunodeficiency virus; + = positive; − = negative; NR = not reported; TB = tuberculosis; RMP = rifampicin; CI = confidence interval; NTM = non-tuberculous mycobacteria; BAL = bronchoalveolar lavage.

Table A.2 *(continued)*

Study data	Xpert sensitivity and specificity					Inclusion criteria for this systematic review				
HIV %	Sensitivity (vs. culture) %	Smear+ %	Smear−	Specificity (vs. culture)	Comments	Culture analysed	Smear analysed	Xpert analysed	C_T values reported or analysed	Median time to culture positivity
NR	100	NR	NR	100		Yes	Yes	Yes	No	No
NR	187/237 (79) (95%CI 73–84)	NR	34/81 (42) (95%CI 31–54)	190/199 (96) (95%CI 92–98)		Yes	Yes	Yes	No	No
NR	83	1	69	100		Yes	Yes	Yes	No	No
NR	NR	NR	NR	NR		Yes	Yes	Yes	Yes	Yes
NR	NR	NR	NR	NR	27.7 C_T cut-off predicted smear-positive	Yes	Yes	Yes	Yes	Yes
NR	92.9	NR	NR	NR	correlation found between C_T, time to positivity and microscopy smear grade	Yes	Yes	Yes	Yes	Yes
3% Cape Town, 18% Mbeya	97%	NR	NR	48.6		Yes	Yes	Yes	Yes	No
60	NR	NR	NR	NR		Yes	Yes	Yes	Yes	Yes
2–15	97.5	NR	NR	70.8		Yes	Yes	Yes	Yes	Yes
60	88.4 (95%CI78.4–94.9)	99 (95%CI 94.7–100.0)		97.8 (95%CI 88.2–99.9)		Yes	Yes	Yes	Yes	Yes
30	NR	NR	NR	NR		Yes	Yes	Yes	yes	yes
35	93	NR	NR	NR		Yes	Yes	Yes	Yes	Yes
NR	NR	NR	NR	NR	Uses data from other Theron studies	Yes	Yes	Yes	Yes	Yes

Table A.3 Risk of bias in those studies included or where additional individual level data was given*

		Patient selection Each item 1 point			Index test Each item 1 point		Patient flow Each item 1 point	Reference test Each item 1 point	
First author	Study title	Were samples triggered by another test, were they random or consecutive?	Was a case-control design avoided?	Were inappropriate exclusions, such as HIV-positive status avoided?	Could the conduct or interpretation of Xpert have introduced bias?	Was Xpert RIF interpreted without knowing about smear status?	Was smear and culture performed on everyone? Was everyone included in the analysis?	Was smear microscopy performed according to WHO guidelines?	Total risk of bias: 1–2 high 3–4 moderate 5–7 low
Alnimr[83]	Potential of two nucleic acid amplification assays for quantifying mycobacterial load in respiratory and non-respiratory specimens: a prospective study	NR	Yes	NR	No	NR	NR	Yes	3 (Moderate)
Armand[6]	Comparison of the Xpert MTB/RIF test with an IS*6110*-TaqMan real-time PCR assay for direct detection of *Mycobacterium tuberculosis* in respiratory and non-respiratory specimens	Not consecutive	No case control design	NR	NR	NR	Done on everyone, flow reported	Not clear	3 (Moderate)
Blakemore[84]	A multisite assessment of the quantitative capabilities of the Xpert MTB/RIF assay	Consecutive samples	No case control design	Yes	No	Yes	Flow reported	Yes	7 (Low)
Friedrich[86]	Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment	Subsample of a clinical trial	No case control design	Not reported	No	Not reported	Not reported	Yes	4 (Moderate)
Friedrich[85]	Suitability of Xpert MTB/RIF and GenoType MTBDR*plus* for patient selection for a tuberculosis clinical trial	Consecutive samples	No case control design	Severe comorbidities excluded	No	NR	Flow reported	Yes	5 (Moderate)
Hanrahan[38]	Xpert MTB/RIF as a measure of sputum bacillary burden. Variation by HIV status and immunosuppression	Consecutive samples	No case control design	No exclusion criteria reported, flow of participants reported	No	NR	Flow reported	According to Union guidelines	6 (Low)

Table A.3 *(continued)*

First author	Study title	Patient selection Each item 1 point: Were samples triggered by another test, were they random or consecutive?	Patient selection Each item 1 point: Was a case-control design avoided?	Patient selection Each item 1 point: Were inappropriate exclusions, such as HIV-positive status avoided?	Index test Each item 1 point: Could the conduct or interpretation of Xpert have introduced bias?	Index test Each item 1 point: Was Xpert RIF interpreted without knowing about smear status?	Patient flow Each item 1 point: Was smear and culture performed on everyone? Was everyone included in the analysis?	Reference test Each item 1 point: Was smear microscopy performed according to WHO guidelines?	Total risk of bias: 1–2 high 3–4 moderate 5–7 low
Nikolayevskyy[88]	Utility of propidium monoazide viability assay as a biomarker for a tuberculosis disease	NR	No case control design	No exclusion criteria reported	No	NR	NR	According to Union/ WHO guidelines	3 (Moderate)
Rachow[89]	Rapid and accurate detection of *Mycobacterium tuberculosis* in sputum samples by Cepheid Xpert MTB/RIF assay—a clinical validation study	NR	No case control design	No exclusion criteria reported	NR	NR	Flow reported	According to Union/ WHO guidelines	4 (Moderate)
Theron[90]	The use of an automated quantitative polymerase chain reaction (Xpert MTB/RIF) to predict the sputum smear status of tuberculosis patients	Consecutive	No case control design	No exclusion criteria	NR	NR	Flow reported	According to Union guidelines	5 (Low)
Theron[91]	Accuracy and impact of Xpert MTB/RIF for the diagnosis of smear-negative or sputum-scarce tuberculosis using bronchoalveolar lavage fluid	Not clear	No case control design	No exclusion criteria reported	No	NR	Flow reported	According to Union guidelines	5 (Low)
Theron[92]	Determinants of PCR performance (Xpert MTB/RIF), including bacterial load and inhibition, for TB diagnosis using specimens from different body compartments	Consecutive	No case control design	NR	No	NR	Flow reported	According to Union guidelines	5 (Low)

Table A.3 *(continued)*

First author	Study title	Patient selection Each item 1 point: Were samples triggered by another test, were they random or consecutive?	Patient selection Each item 1 point: Was a case-control design avoided?	Patient selection Each item 1 point: Were inappropriate exclusions, such as HIV-positive status avoided?	Index test Each item 1 point: Could the conduct or interpretation of Xpert have introduced bias?	Index test Each item 1 point: Was Xpert RIF interpreted without knowing about smear status?	Patient flow Each item 1 point: Was smear and culture performed on everyone? Was everyone included in the analysis?	Reference test Each item 1 point: Was smear microscopy performed according to WHO guidelines?	Total risk of bias: 1–2 high 3–4 moderate 5–7 low
Additional studies providing individual level data, without analysis of C_T values in the original publication									
Al-Darraji[1]	The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia	Consecutive	No case control	NR	No	NR	Flow reported	According to Union guidelines	5 (Low)
Balcells[9]	Rapid molecular detection of pulmonary tuberculosis in HIV-infected patients in Santiago, Chile	Consecutive	No case control design	Exclusion criteria: empiric antibiotic treatment up to 7 days before enrolment	No	Yes	Flow reported	NR	5 (Low)
Clemente[22]	Evaluation of the Xpert MTB/RIF test for rapid detection of *Mycobacterium tuberculosis*	Consecutive	No case control design	NR	No	NR	Flow reported	NR	4 (Moderate)
Miller[52]	Performance of Xpert MTB/RIF RUO assay and IS*6110* Real-Time PCR for *Mycobacterium tuberculosis* detection in clinical samples	NR	No case control design	NR	No	NR	NR	According to Union guidelines	3 (Moderate)
Ntinginya[60]	Performance of the Xpert® MTB/RIF assay in an active case-finding strategy: a pilot study from Tanzania	Consecutive	No case control	NR	No	NR	Flow reported	NR	4 (Moderate)

Table A.3 *(continued)*

First author	Study title	Patient selection Each item 1 point: Were samples triggered by another test, were they random or consecutive?	Patient selection Each item 1 point: Was a case-control design avoided?	Patient selection Each item 1 point: Were inappropriate exclusions, such as HIV-positive status avoided?	Index test Each item 1 point: Could the conduct or interpretation of Xpert have introduced bias?	Index test Each item 1 point: Was Xpert RIF interpreted without knowing about smear status?	Patient flow Each item 1 point: Was smear and culture performed on everyone? Was everyone included in the analysis?	Reference test Each item 1 point: Was smear microscopy performed according to WHO guidelines?	Total risk of bias: 1–2 high 3–4 moderate 5–7 low
Ozkutuk[63]	Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary tuberculosis in an intermediate-prevalence setting	NR	No case control	NR	No	NR	NR	According to Union guidelines	3 (Moderate)
Porcel[67]	Xpert MTB/RIF in pleural fluid for the diagnosis of TB	Consecutive	Not quite clear, reported as consecutive inclusion, but then described as a case-control design	Yes	No	Yes	NR	NR	4 (Moderate)
Sohn[75]	Xpert MTB/RIF testing in a low tuberculosis incidence, high-resource setting: limitations in accuracy and clinical impact	Consecutive	No case control design	Yes	No	NR	Flow reported	NR	5 (Low)
Teo[76]	Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF assay and the amplified *Mycobacterium tuberculosis* Direct assay, for detection of *Mycobacterium tuberculosis* in respiratory and non-respiratory specimens	NR	No case control	NR	No	NR	No flow reported	NR	2 (High)

* Each QUADAS-2 item rated as low risk of bias scored one point. Studies scoring 5–7 were considered low, 4–5 moderate and 1–3 high risk of bias.
HIV = human immunodeficiency virus; RIF = rifampicin; WHO = World Health Organization; NR = not reported; Union = International Union Against Tuberculosis and Lung Disease; QUADAS = Quality Assessment of Diagnostic Accuracy Studies.

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RESUME

CONTEXTE : L'Xpert® MTB/RIF est le test moléculaire le plus utilisé pour le diagnostic rapide de la tuberculose (TB). Le nombre de cycles de réaction par le polymérase en chaîne après lesquels un produit détectable est généré (valeur cycle seuil, C_T) est corrélé à la charge bacillaire.
OBJECTIF : Explorer l'association entre valeurs de C_T de l'Xpert et statut du frottis grâce à une revue systématique et à une méta-analyse au niveau individuel.
SCHÉMA : Les études consacrées à l'association entre valeurs de C_T et statut du frottis ont été incluses dans une revue systématique descriptive. On a demandé aux auteurs des études des données individuelles, incluant les résultats du frottis, de la culture et de l'Xpert, et les courbes de la fonction d'efficacité du récepteur (ROC) ont été calculées.
RÉSULTATS : Sur les 918 citations, 10 ont été incluses dans la revue descriptive systématique ; 15 ensembles de données émanant d'études potentiellement pertinentes pour la méta-analyse des données individuelles ont fourni des données pour 7511 échantillons et 4447 patients ; 1212 patients ont eu des résultats d'Xpert positifs pour au moins un échantillon respiratoire (1859 échantillons au total). L'analyse ROC a révélé un surface située sous la courbe de 0,85 (IC95% 0,82–0,87). Une valeur C_T seuil de 27,7 et 31,8 a abouti à une sensibilité de 85% (IC95% 83–87) et de 95% (IC95% 94–96) respectivement et à une spécificité de 67% (IC95% 66–77) et de 35% (IC95% 30–41) respectivement pour les échantillons à frottis positif.
CONCLUSION : Les valeurs C_T de l'Xpert et le statut du frottis ont été fortement associées. Cependant, la précision diagnostique à un seuil de valeur C_T de 27,7 ou 31,8 ne remplacerait pas la microscopie de frottis. Il reste à voir comment les valeurs C_T peuvent être comparées à la microscopie de frottis dans la prédiction de la contagiosité.

RESUMEN

MARCO DE REFERENCIA: La prueba Xpert® MTB/RIF es el método molecular de diagnóstico rápido de la tuberculosis (TB) más utilizado. El número de ciclos de la reacción en cadena de la polimerasa a partir del cual se genera un producto detectable (ciclo umbral, C_T) se correlaciona con la cantidad de micobacterias en la muestra.
OBJETIVO: Investigar la asociación entre el valor del C_T de la prueba Xpert y la calificación de la baciloscopia, mediante una revisión sistemática y el metanálisis de datos a escala individual.
MÉTODO: En una revisión sistemática descriptiva se incluyeron estudios sobre la asociación de los valores del C_T y la calificación de la baciloscopia. Se solicitó a los autores de los estudios que comportaban resultados de baciloscopias, cultivos y pruebas Xpert que comunicaran los datos a nivel individual y se calcularon la curvas de eficacia diagnóstica.
RESULTADOS: En la revisión sistemática descriptiva se incluyeron 10 de las 918 citas de artículos. Se obtuvieron los datos individuales de 15 conjuntos de datos de estudios que podían ser pertinentes en el metanálisis de datos individuales (7511 muestras de 4447 pacientes). En 1212 pacientes se observaron resultados positivos de la prueba Xpert de por lo menos una muestra respiratoria (1859 muestras en total). El análisis de la eficacia diagnóstica reveló un área bajo la curva de 0,85 (IC95% 0,82 a 0,87). Al adoptar valores límites del C_T de 27,7 y de 31,8 se obtuvieron respectivamente sensibilidades de 85% (IC95% de 83 a 87) y 95% (IC95% de 94 a 96) y especificidades de 67% (IC95% de 66 a 77) y 35% (IC95% de 30 a 41) para las muestras con baciloscopia positiva.
CONCLUSIÓN: El valor del C_T de la prueba Xpert y la clasificación de la baciloscopia exhibieron una fuerte correlación. Sin embargo, la precisión diagnóstica de la prueba cuando se define un valor límite del C_T de 27,7 o de 31,8 no remplazaría la baciloscopia. Queda por discernir cuál de los dos datos, el valor del C_T de la prueba Xpert o la baciloscopia, pronosticaría mejor la contagiosidad.