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Effect of previous treatment and sputum quality on diagnostic accuracy of Xpert® MTB/RIF

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SUMMARY

SETTING: In early studies, Xpert® MTB/RIF accurately detected culture-proven pulmonary tuberculosis (TB). Recent reports have, however, found a lower than expected specificity in previously treated TB patients.

OBJECTIVE: To investigate the diagnostic accuracy of Xpert in presumptive pulmonary TB patients in Southwestern Uganda.

DESIGN: We obtained demographic and clinical information and collected three sputum samples from each patient for smear microscopy, Xpert and culture. We estimated Xpert sensitivity and specificity against culture, and stratified the analysis by previous treatment and sputum quality status.

RESULTS: We analyzed results from 860 presumptive TB patients, including 109 (13%) with a previous history of anti-tuberculosis treatment; 205 (24%) were culture-positive. Xpert specificity was lower (91.8%, 95%CI 84.9–96.2) in previously treated than in new TB patients (97.5%, 95%CI 96.1–98.5; $P = 0.01$). In an adjusted analysis, patients with culture–, Xpert+ results were more likely to have been previously treated for TB (OR 8.3, 95%CI 2.1–32.0; $P = 0.002$), and to have mucosalivary sputum (OR 4.1, 95%CI 1.1–14.6; $P = 0.03$), but were less likely to self-report fever (OR 0.23, 95%CI 0.1–0.7; $P = 0.008$) than patients with concordant positive results.

CONCLUSION: Xpert specificity was lower in previously treated patients with suspected TB. The clinical and programmatic impact of culture–, Xpert+ results requires evaluation in future studies.

KEY WORDS: tuberculosis; Xpert® MTB/RIF; specificity; previous treatment; sputum quality

SINCE ITS INTRODUCTION IN 2010,[1] the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) has proved a major breakthrough in tuberculosis (TB) diagnostics by simultaneously detecting *Mycobacterium tuberculosis* and rifampin (RMP) resistance in <2 h. In 2010, the World Health Organization (WHO) recommended the use of Xpert for TB diagnosis,[2] and by 2014, >3000 GeneXpert modules and >10 million Xpert cartridges had been procured in 145 countries.[3]

One of the reported advantages of Xpert is its high accuracy in detecting *M. tuberculosis* in culture-positive respiratory samples.[1–4] In a meta-analysis of early studies, Xpert demonstrated a pooled specificity of 99%, and a sensitivity of 98% in acid-fast bacilli (AFB) smear-positive sputum specimens and 67% in AFB-negative specimens, mostly in high TB prevalence settings.[5] However, recent studies in programmatic conditions have suggested lower specificities of Xpert in previously treated patients (~90%).[6–9]

Patients with discordant culture–, Xpert+ results are currently thought to have 'false-positive' Xpert results as a result of remnant, non-viable bacilli after anti-tuberculosis treatment.[8,9] However, despite its known impact on the yield of other diagnostic methods such as AFB smear microscopy and culture,[10–12] limited attention has been placed on the effect of sputum quality on Xpert diagnostic performance. In the present study, we report our experience with Xpert among patients with suspected pulmonary TB in Southwestern Uganda.

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METHODS

The study represents a secondary analysis of a diagnostic study stratified by human immunodeficiency virus (HIV) status, designed to evaluate the diagnostic accuracy of a new AFB smear microscopy method and Xpert, using culture as the reference method.[13] A detailed description of the study population, experimental methods and results of the parent study are published elsewhere.[13]

Participants and clinical data

We enrolled adults with suspicion of pulmonary TB admitted to the Mbarara Regional Referral Hospital, Mbarara, Uganda, or attending out-patient clinics of the Municipality Health Centre in Mbarara, Uganda. HIV-infected and non-HIV-infected presumptive TB patients were enrolled independently. Uganda is on the WHO list of high-burden countries, with an estimated TB incidence of 166 cases per 100 000 population.[14] We included presumptive pulmonary TB patients aged $\geqslant$ 18 years, with cough of $\geqslant$2 weeks and at least one additional TB symptom (fever, weight loss or night sweats). We excluded patients who had received >2 days of anti-tuberculosis treatment within the last 60 days. We collected clinical and demographic data, performed HIV testing and CD4 cell count (HIV-infected only), and chest radiograph was interpreted by an experienced radiologist. Patients with a positive AFB, Xpert or culture result were referred to the closest TB clinic for treatment.

Sample collection, handling and processing

We obtained three sputum samples: one early morning and two spot specimens 1 day apart. Participants were instructed by a study nurse on how to provide an adequate specimen. Instructions were printed and handed to them in the sputum collection room. The volume and appearance of the specimen were assessed visually, and it was then placed in an iced-filled container before transportation to the laboratory within 3 h. Upon arrival, the sputum appearance was classified as salivary, mucoid, mucosalivary (mucoid/salivary group), or mucopurulent and prurulent (purulent group).[11] Spot samples were randomized in a 1:1 ratio using a block size of 4; one sample was tested using Xpert and one by the experimental smear method.[13] A direct smear was performed on the specimen used for Xpert before decontamination of the sample using *N*-acetyl-L-cysteine (NALC)/sodium hydroxide solution and then processed for culture and Xpert. The other two samples were decontaminated using NALC, and then processed for AFB smear microscopy and culture (Figure 1).

Laboratory methods

All testing was performed at the Epicentre/Médecins Sans Frontières Mbarara Research Centre laboratory in Mbarara, Uganda. Direct smear was performed using the auramine technique and graded according to WHO criteria.[15] After processing, 0.5 ml of the specimens was incubated using the manual MGIT™ (Mycobacterial Growth Indicator Tube; BD, Sparks, MD, USA) system for up to 6 weeks. Xpert testing was performed according to the manufacturer's instructions.

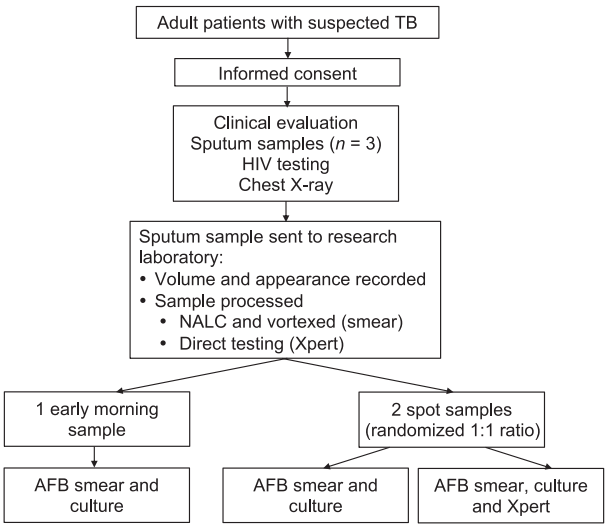

Figure 1 Diagrammatic representation of sample processing. TB = tuberculosis; HIV = human immunodeficiency virus; NALC = *N*-acetyl-L-cysteine; AFB = acid-fast bacilli.

Ethics approval

The study was approved by the Institutional Review Boards of Mbarara University of Science and Technology (Mbarara), the Uganda National Council for Science and Technology (Kampala, Uganda), the Comité de Protection des Personnes (St Germain-en-Laye, France) and the Boston University Medical Center (Boston, MA, USA), with oversight of statistical analysis by the Rutgers University Newark Institutional Review Board (Newark, NJ, USA). We obtained written informed consent from participants in accordance with guidelines from participating institutions.

Statistical analysis

We evaluated the performance of Xpert in detecting culture-positive TB. A positive result in $\geqslant$1 MGIT culture samples was considered as reference standard. We estimated sensitivities and specificities with 95% confidence intervals (CIs), and stratified analyses by previous TB treatment status (new vs. previously treated). Presumptive TB patients with discordant culture/Xpert results (e.g., culture–, Xpert+) were compared to those with concordant positive (culture+, Xpert+) results using the χ^2 test for categorical variables and Wilcoxon's rank sum for non-parametric numerical variables.[16] Variables with $P < 0.1$ and those considered to be clinically

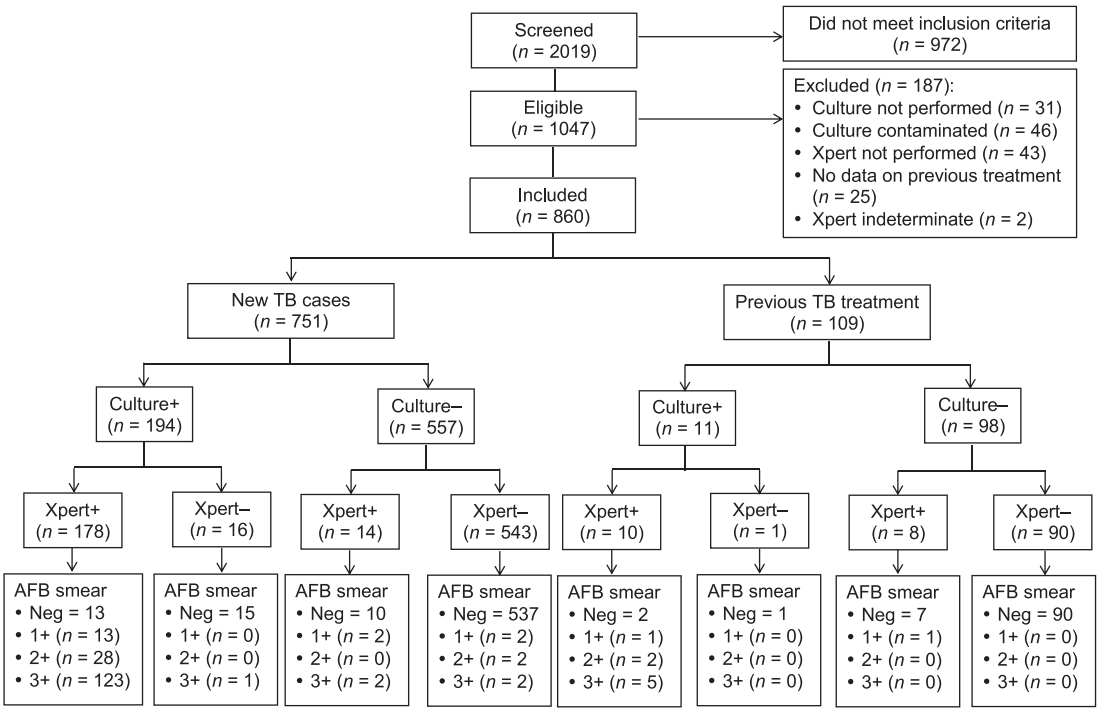

Figure 2 Study profile. TB = tuberculosis; AFB = acid-fast bacilli; + = positive; − = negative.

significant were included in multivariable logistic regression models. Crude and adjusted odds ratios (aORs) with their respective 95%CIs were estimated. All analyses were performed using Stata, v. 12.0 (StataCorp, College Station, TX, USA).

RESULTS

From September 2012 to April 2014, 2019 individuals were screened for study participation and 1047 presumptive TB patients were enrolled; 187 were excluded (Figure 2). The 860 presumptive TB patients included in this analysis were similar to those excluded in terms of age ($P = 0.14$), sex ($P = 0.68$), and previous anti-tuberculosis treatment ($P = 0.40$). The median age of the study population was 38 years (interquartile range [IQR] 29–49), 50% were male, 69% were HIV-infected, and 13% had a history of previous anti-tuberculosis treatment.

Sex, sputum volume and appearance

The median sputum volume produced was 5 ml (IQR 4–7); 48% participants produced purulent sputum (Table 1). Males had a higher sputum volume ($P = 0.02$) and more purulent sputum (72% vs. 54%, $P = 0.01$) than females (Appendix Table A.1).* Previously treated presumptive TB patients were similar to new patients with suspected TB in terms of sputum volume ($P = 0.13$), but had higher proportions of purulent sputum (67% vs. 57%, $P = 0.05$). Sputum characteristics by sex and HIV status are shown in Appendix Tables A.1 and A.2.

Tuberculosis diagnosis using acid-fast bacilli smear, Xpert and culture

We diagnosed 205 (24%) participants with pulmonary TB, 184 (89%) of whom were AFB-positive, and 134 (74%) were AFB 3+. Xpert detected *M. tuberculosis* DNA in 210 (24%), and 7 (3.3%) were found to be RMP-resistant. Compared to new presumptive TB patients (Table 1), previously treated TB patients were older ($P = 0.02$), had a lower body mass index (BMI) ($P = 0.009$), were less likely to self-report fever ($P = 0.002$), but were more likely to have hemoptysis ($P = 0.02$); they were also more likely to be sputum AFB-negative ($P = 0.008$) and culture-negative ($P < 0.001$), but Xpert-positive ($P = 0.04$).

Effect of previous anti-tuberculosis treatment and sputum quality on the diagnostic accuracy of Xpert

In the overall cohort (Table 2), Xpert correctly identified 188/205 culture-positive TB cases and 633/655 culture-negative presumptive TB patients, resulting in a sensitivity of 91.7% (95%CI 89.7–93.5) and a specificity of 96.6% (95%CI 95.2–97.7). In a stratified analysis by previous anti-tuberculosis treatment status, both the sensitivity (178/194, 91.8%) and the specificity (543/547, 97.5%) of Xpert in the cohort without previous TB ($n = 751$) was similar. However, in the cohort with a previous history of anti-tuberculosis treatment ($n = 109$), whereas the

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000004/art00007

Table 1 Baseline characteristics of 860 presumptive pulmonary TB patients according to TB treatment history in Mbarara, Uganda

Characteristics	Total (n = 860) n (%)	New TB suspected (n = 751) n (%)	Previous anti-tuberculosis treatment (n = 109) n (%)	P value*
Age, years, median [IQR]	38 [29–49]	37 [29–48]	40 [35–49]	0.02
Sex				0.14
Male	433 (51)	371 (49)	62 (57)	
Female	427 (49)	380 (51)	47 (43)	
BMI, kg/m^2, median [IQR]	20.2 [18.1–22.7]	20.3 [18.3–22.9]	19.6 [17.2–21.7]	0.009
HIV-infection				
CD4 cell count, cells/ml	591 (69)	514 (68)	77 (71)	0.64
median [IQR]	300 [106–468]	268 [101–466]	361 [204–499]	0.10
BCG scar†				0.84
Yes	507 (60)	445 (61)	62 (59)	
No/uncertain	332 (40)	289 (39)	43 (41)	
Karnofsky status†				0.67
20–60	354 (41)	311 (42)	43 (39)	
70–100	503 (59)	437 (58)	66 (61)	
Current smoker†				0.10
No	769 (90)	667 (89)	102 (94)	
Yes	86 (10)	80 (11)	6 (6)	
Current alcohol use†				0.59
No	710 (83)	623 (83)	87 (81)	
Yes	144 (17)	124 (17)	20 (19)	
Symptom present (self-report)†				
Fever	608 (71)	544 (73)	64 (59)	0.002
Hemoptysis	159 (19)	130 (17)	29 (27)	0.02
Night sweats	576 (67)	503 (67)	73 (67)	0.97
Loss of appetite	579 (67)	506 (68)	73 (67)	0.90
Dyspnea	544 (64)	480 (64)	64 (60)	0.37
Weight loss	669 (78)	583 (78)	86 (79)	0.80
Chest radiograph findings				
Extent of disease				0.55
Normal/minimal	142 (51)	123 (50)	19 (56)	
Moderate/advanced	136 (49)	121 (50)	15 (44)	
Cavitation				0.51
No	228 (81)	199 (81)	29 (85)	
Yes	53 (19)	48 (19)	5 (15)	
Sputum volume, ml, median [IQR]†				
Maximum volume (out of 3)	5 [4–7]	5 [4–6]	5 [4–7]	0.13
Xpert specimen	3 [2–4]	3 [2–4]	4 [2–5]	0.08
Sputum characteristics†				0.05
Salivary/mucoid	358 (42)	322 (43)	36 (33)	
Purulent/mucopurulent	501 (58)	428 (57)	73 (67)	
AFB smear†				0.008
Negative	675 (79)	575 (77)	100 (92)	
1+	19 (2)	17 (2)	2 (2)	
2+	32 (4)	30 (4)	2 (2)	
3+	133 (15)	128 (17)	5 (4)	
MGIT culture				<0.001
Positive	205 (24)	194 (26)	11 (10)	
Negative	655 (76)	557 (74)	98 (90)	
MGIT, days to positivity, median [IQR]	17 [11–23]	17 [9–23]	21 [13–23]	0.21
Xpert				0.04
Positive	210 (24)	192 (26)	18 (17)	
Negative	650 (76)	559 (74)	91 (83)	

* Comparing new vs. previously treated.
† Missing data: BCG scar = 21, Karnofsky status = 3, current smoker = 5, current alcohol use = 6, fever = 4, hemoptysis = 7, night sweats = 2, loss of appetite = 2, dyspnea = 6, weight loss = 2, sputum volume = 1, sputum characteristics = 1, AFB smear = 1.
TB = tuberculosis; IQR = interquartile range; BMI = body mass index; BCG = bacille Calmette-Guérin; AFB = acid-fast bacilli; MGIT = Mycobacterial Growth Indicator Tube; Xpert = Xpert® MTB/RIF.

sensitivity of Xpert did not change (10/11, 90.9%), the specificity dropped significantly (90/98, 91.8%; P = 0.01). A further stratification by HIV infection status (Table 2) and by sputum appearance (Appendix Table A.3) did not significantly change these specificity results. Furthermore, in an analysis stratified by sputum appearance, Xpert sensitivity in mucosalivary samples was significantly lower than

Table 2 Diagnostic performance of Xpert® MTB/RIF in presumptive pulmonary tuberculosis patients in Mbarara, Uganda by history of anti-tuberculosis treatment and HIV infection status

Study group	Sensitivity* *n/N* (%) (95%CI)	*P* value†	Specificity‡ *n/N* (%) (95%CI)	*P* value†	PPV§ *n/N* (%) (95%CI)	*P* value†	NPV¶ *n/N* (%) (95%CI)¶	*P* value†
Overall cohort ($n = 860$)	188/205 (91.7) (89.7–93.5)	1.0	633/655 (96.6) (95.2–97.7)	0.01	188/210 (89.5) (87.3–91.5)	<0.001	633/650 (97.4) (96.2–98.4)	0.49
No previous anti-tuberculosis treatment ($n = 751$)	178/194 (91.8) (89.5–93.6)		543/557 (97.5) (96.1–98.5)		178/192 (92.7) (90.6–94.4)		543/559 (97.1) (95.6–98.2)	
Previous anti-tuberculosis treatment ($n = 109$)	10/11 (90.9) (83.8–95.5)		90/98 (91.8) (84.9–96.2)		10/18 (55.6) (46.1–65.5)		90/91 (98.9) (95.0–100.0)	
HIV-infected cohort ($n = 591$)	118/130 (90.8) (88.2–93.1)	1.0	446/461 (96.8) (95.0–98.1)	0.06	118/133 (88.7) (85.8,91.1)	0.01	446/458 (97.4) (95.8–98.6)	1.0
No previous anti-tuberculosis treatment ($n = 514$)	110/122 (90.2) (83.6–94.3)		382/392 (97.5) (95.4–98.6)		110/120 (91.7) (85.3–95.4)		389/394 (97.0) (94.8–98.3)	
Previous anti-tuberculosis treatment ($n = 77$)	8/8 (100.0) (67.6–100.0)		64/69 (92.8) (84.1–96.9)		8/13 (61.5) (35.5–82.3)		64/64 (100.0) (94.3–100.0)	
Non-HIV-infected cohort ($n = 269$)	70/75 (93.3) (89.6–96.0)	0.19	187/194 (96.4) (93.3–98.2)	0.07	70/77 (90.9) (87.0–94.2)	0.004	187/192 (97.4) (94.7–98.9)	0.53
No previous anti-tuberculosis treatment ($n = 237$)	68/72 (94.4) (86.6–97.8)		161/165 (97.6) (93.9–99.1)		68/72 (94.4) (86.6–97.8)		161/165 (97.6) (93.9–99.1)	
Previous anti-tuberculosis treatment ($n = 32$)	2/3 (66.7) (20.8–93.9)		26/29 (89.7) (73.6–96.4)		2/5 (40.0) (11.8–76.9)		26/27 (96.3) (81.7–99.3)	

* Xpert and culture-positive/all culture-positive.
† Fisher's exact test; all comparisons are 'salivary' vs. 'purulent' sputum groups; 1 missing value for sputum characteristic.
‡ Xpert and culture-negative/all culture-negative.
§ Xpert and culture-positive/all Xpert-positive.
¶ Xpert and culture-negative/all Xpert-negative.
HIV = human immunodeficiency virus; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

in mucopurulent samples (82.5% vs. 95.8%, $P = 0.004$), independently of previous TB treatment history (Appendix Table A.3).

Factors associated with discordant culture and Xpert results

Of the 210 presumptive TB patients who were Xpert-positive, 22 (10.5%) were culture-negative; of these, 18 (82%) had mucosalivary samples. In an unadjusted analysis comparing patients with discordant culture–, Xpert+ results and those with concordant positive (e.g., culture+, Xpert+) results (Table 3), the former was associated with absence of fever ($P < 0.001$), mucoid/salivary sputum ($P = 0.002$), and previous history of anti-tuberculosis treatment ($P < 0.001$). In an adjusted analysis (Table 4), discordant results remained positively associated with previous anti-tuberculosis treatment (OR 8.3, 95%CI 2.1–32.0; $P = 0.001$), mucosalivary sputum (OR 4.1, 95%CI 1.1–14.6; $P = 0.03$), and absence of self-reported fever (OR 0.23, 95%CI 0.1–0.7; $P = 0.008$) and weakly associated with female sex (OR 2.92, 95%CI 0.96–8.9; $P = 0.06$). Similarly, when we compared discordant culture–, Xpert+ results to those with concordant negative (e.g. culture–, Xpert–) patients with suspected TB (Tables 3 and 4), the most important independent predictor of a discordant positive Xpert result was previous anti-tuberculosis treatment status ($P = 0.01$), followed by mucosalivary sputum ($P = 0.05$) and lower BMI ($P = 0.05$) (Table 4).

DISCUSSION

In this secondary analysis of a large diagnostic study that included mostly HIV-infected out-patients in Southwestern Uganda, presumptive TB patients with a previous history of anti-tuberculosis treatment were more likely to have discordant culture–, Xpert+ results, leading to considerably lower specificity and positive predictive value than presumptive TB patients with no previous treatment history. These results did not significantly change by HIV status, and clinical indicators of discordance included the absence of self-reported fever and expectorating mucosalivary sputum. Furthermore, we found that Xpert sensitivity was significantly lower in mucosalivary samples than in mucopurulent specimens.

Each year, 10–20% of patients with TB in low- and middle-income countries present with previously treated TB after failing, interrupting, or relapsing from previous treatment—totaling an estimated 1 million people in over 90 countries.[17] Previously treated TB patients are key to current WHO treatment algorithms because the prevalence of anti-tuberculosis drug resistance is 5–10 times higher than in 'new' TB patients. Our findings are consistent with the initial case reports[6–8] and two recent studies from

Table 3 Unadjusted analyses of factors associated with concordant and discordant culture and Xpert® MTB/RIF results in 860 presumptive pulmonary TB patients in Mbarara, Uganda

Characteristic	Xpert+/culture+ ($n = 188$) *n* (%)	Xpert+/culture− ($n = 22$) *n* (%)	OR (95%CI)*	*P* value*	Xpert−/culture− ($n = 633$) *n* (%)	OR (95%CI)†	*P* value†
Age, years, median [IQR]	32 [27–41]	39 [30–51]	1.04 (1.0–1.08)	0.06	40 [30–50]	0.99 (0.96–1.02)	0.46
Female sex	59 (31)	11 (50)	2.19 (0.9–5.4)	0.08	285 (45)	1.22 (0.5–2.9)	0.65
BMI, kg/m^2, median [IQR]‡	18.6 [16.6–20.1]	19.4 [17.3–20.9]	1.10 (0.93–1.32)	0.22	21 [18.8–23.3]	0.88 (0.79–0.98)	0.02
BCG scar present‡	105 (58)	15 (68)	1.57 (0.6–4.1)	0.35	379 (61)	1.11 (0.4–2.77)	0.83
Karnofsky >70‡	88 (47)	13 (59)	1.63 (0.7–4.0)	0.29	395 (63)	0.86 (0.4–2.05)	0.74
Current smoker‡	22 (12)	3 (14)	1.18 (0.3–4.3)	0.80	59 (9)	1.53 (0.4–5.31)	0.50
Current alcohol use‡	32 (17)	3 (14)	0.76 (0.21–2.7)	0.67	106 (17)	0.78 (0.23–2.7)	0.69
HIV infection	118 (63)	15 (68)	1.27 (0.49–3.28)	0.61	446 (70)	0.90 (0.36–2.24)	0.82
Fever (self-report)‡	159 (85)	12 (55)	0.21 (0.1–0.6)	<0.001	421 (67)	0.60 (0.3–1.4)	0.23
Hemoptysis‡	32 (17)	6 (27)	1.80 (0.6–5.0)	0.25	119 (19)	1.60 (0.6–4.19)	0.33
Weight loss	175 (93)	18 (82)	0.30 (0.1–1.2)	0.07	464 (74)	1.62 (0.5–4.86)	0.39
Sputum volume, ml, median [IQR]	5 [4–6]	4 [3–5]	1.09 (0.95–1.25)	0.24	5 [4–7]	0.88 (0.76–1.04)	0.14
Mucosalivary sputum	88 (48)	18 (82)	4.91 (1.55–15.5)	0.002	412 (66)	2.34 (0.78–7.1)	0.12
Previous anti-tuberculosis treatment	10 (5)	8 (36)	10.2 (3.2–32.1)	<0.001	90 (14)	3.45 (1.4–8.51)	0.004
TB treatment duration, weeks, median [IQR]‡	34.7 [32.1–44.3]	34.7 [30.4–39]	1.03 [0.94–1.13]	0.54	35.0 [34.6–36.7]	1.02 [0.93–1.13]	0.63
Time since previous treatment, years, median [IQR]‡	5.9 [0.9–7.6]	7.0 [1.4–13.9]	0.91 [0.76–1.09]	0.30	6.45 [1.97–12.0]	0.98 [0.93–1.04]	0.48

* ORs and *P* values estimated for comparison between discordant Xpert+, culture− results with concordant Xpert+, culture+ results.
† ORs and *P* values estimated for comparison between discordant Xpert+, culture− results with concordant Xpert−, culture+ results.
‡ Missing data: BMI ($n = 50$), BCG ($n = 6$), Karnofsky ($n = 1$), smoking history ($n = 1$), drinking history ($n = 1$), fever ($n = 1$), hemoptysis ($n = 2$), TB treatment duration ($n = 1$), time since previous treatment ($n = 1$).
TB = tuberculosis; Xpert = Xpert® MTB/RIF; + = positive; − = negative; OR = odds ratio; CI = confidence interval; IQR = interquartile range; BMI = body mass index; BCG = bacille Calmette-Guérin; HIV = human immunodeficiency virus.

Table 4 Adjusted analyses of factors associated with concordant and discordant culture and Xpert® MTB/RIF results in 860 presumptive pulmonary TB patients in Mbarara, Uganda

Characteristic	Xpert+, culture+ ($n = 188$) n (%)	Xpert+, culture− ($n = 22$) n (%)	aOR (95%CI)*	P value*	Xpert−, culture− ($n = 633$) n (%)	aOR (95%CI)†	P value†
Age, years, median [IQR]	32 [27–41]	39 [30–51]	1.03 (0.98–1.09)	0.17	40 [30–50]		
Female sex	59 (31)	11 (50)	2.92 (0.96–8.9)	0.06	285 (45)		
BMI, kg/m^2, median [IQR]‡	18.6 [16.6–20.1]	19.4 [17.3–20.9]			21 [18.8–23.3]	0.85 (0.73–1.00)	0.05
HIV infection	118 (63)	15 (68)	1.05 (0.3–3.6)	0.94	446 (70)	0.61 (0.23–1.7)	0.35
Fever (self-report)‡	159 (85)	12 (55)	0.23 (0.1–0.7)	0.008	421 (67)		
Weight loss	175 (93)	18 (82)	0.95 (0.21–4.4)	0.95	464 (74)		
Sputum volume, ml, median [IQR]	5 [4–6]	4 [3–5]			5 [4–7]	0.85 (0.68–1.07)	0.17
Mucosalivary sputum	88 (48)	18 (82)	4.1 (1.1–14.6)	0.03	412 (66)	4.68 (1.03–21.3)	0.05
Previous anti-tuberculosis treatment	10 (5)	8 (36)	8.3 (2.1–32.0)	0.002	90 (14)	3.45 (1.3–9.3)	0.01
TB treatment duration, weeks, median [IQR]‡	34.7 [32.1–44.3]	34.7 [30.4–39]			35.0 [34.6–36.7]		
Time since previous treatment, years, median [IQR]‡	5.9 [0.9–7.6]	7.0 [1.4–13.9]			6.45 [1.97–12.0]		

* aORs estimated using logistic regression analysis comparing discordant Xpert+, culture− results with concordant positive Xpert+, culture+ results in presumptive TB patients. The following variables were included in the model: age, sex, HIV infection, weight loss, salivary/mucoid sputum, previous anti-tuberculosis treatment and fever.

† aORs estimated by logistic regression analysis comparing discordant Xpert+, culture− with concordant Xpert−/culture− results. The following variables were included in the model: BMI, HIV infection, sputum volume, salivary/mucoid sputum and previous anti-tuberculosis treatment.

‡ Missing data: BMI ($n = 50$), fever ($n = 1$), hemoptysis ($n = 2$), TB treatment duration ($n = 1$), time since previous treatment ($n = 1$).

TB = tuberculosis; Xpert = Xpert® MTB/RIF; + = positive; − = negative; aOR = adjusted odds ratio; CI = confidence interval; IQR = interquartile range; BMI = body mass index; HIV = human immunodeficiency virus.

Zimbabwe and South Africa, where Xpert specificity was respectively 87% and 92%.[7–9] These results collectively stand in contrast with the initial validation and implementation trials where Xpert achieved an overall specificity of 99%.[1,4,5] We suspect that post-enrollment exclusions of AFB-positive, culture-negative patients and the inclusion of lower proportions of retreatment cases could have led to an overestimation of the specificity of Xpert in the initial trials.[18] Our results add to the growing body of evidence showing that this new molecular test has lower-than-expected specificity in retreatment TB patients, an important clinical group already burdened by poor treatment outcomes and more post-TB residual pulmonary pathology.[19–21]

The lower specificity of Xpert in previously treated TB cases is likely to have a consequential impact in treatment algorithms and public health policy, especially for countries with high retreatment TB rates. Vassall et al. found that using Xpert to replace AFB microscopy is highly cost-effective in diagnosing pulmonary TB, even in high retreatment rate settings, with costs per disability-adjusted life-years (DALYs) averted between US$25 and US$85.[22] The model assumed that Xpert specificity was 99% and that anti-tuberculosis treatment was started after a positive Xpert result without AFB smear microscopy or culture confirmation. If the lower specificity found in retreatment cases is real, the cost of additional diagnostic procedures (i.e., chest radiograph and culture) for those with false-positive Xpert results would translate into higher costs of false-positives and costs per DALYs averted.

Our results also suggest that the diagnostic accuracy of Xpert is largely dependent on the macroscopic or gross appearance of expectorated sputum—a frequently used indicator (together with specimen volume) of the quality or 'representativeness' of the clinical specimen being tested.[11] In this study, Xpert sensitivity was 18–20% lower in mucosalivary than in mucopurulent samples, independently of previous TB treatment status. In previous studies, purulent samples have been shown to increase the yield of sputum AFB smear[12] and culture,[10,11] but data on how sample quality may impact Xpert performance are scarce. Furthermore, because males expectorated larger volumes and more purulent sputum samples than females, the interpretation of the true impact of specimen quality in our study was further confounded. While these findings are consistent with evidence from multiple settings demonstrating a sex gap in TB diagnosis that is thought to be primarily due to differences in specimen quality,[23,24] the association between female sex and discordant culture and Xpert results in our study was independent of sputum characteristics, suggesting that other factors, apart from the quality of sputum,

may play a role in the greater frequency of discordant results among females.

The biological and clinical significance of detecting *M. tuberculosis* DNA in presumptive TB patients who are culture-negative is currently not well understood. The most widely held opinion is that it represents remnant, non-viable bacilli from previously treated culture-positive TB, as suggested by studies evaluating DNA-based assays to monitor response to anti-tuberculosis treatment.[25] Theron et al. reported that approximately one of six Xpert-positive results in retreatment patients are false-positives due to non-viable *M. tuberculosis* DNA.[7] However, although mycobacterial cultures remain the most sensitive method of detection, the sample decontamination process prior to culture is inherently detrimental to mycobacterial viability, and, as a result, the overall sensitivity of culture is only 85%, and much lower in paucibacillary disease.[26,27] Furthermore, shortly after the initiation of anti-tuberculosis treatment, *M. tuberculosis* bacilli enter into a persister-like phenotype that renders them non-culturable in standard culture media, yet their viability is restored with enriched media.[28] Finally, a recent study that used advanced imaging techniques found that persistent Xpert positivity at end of treatment, even when clinical and microbiological cure was achieved, was a risk factor for TB relapse.[29] In this study, 82% of presumptive TB patients with discordant culture–, Xpert+ results had mucosalivary samples, suggesting that these sample types may be negatively impacting the yield of MGIT culture. If this finding is reproduced in other studies, discordant results might be better explained by inter- and intra-sample variability in sensitivity between culture and Xpert rather than non-viable bacillary populations, as they would be expected to be uniformly present in all samples, regardless of rheological characteristics.

Our study has limitations. First, we excluded 187 patients with unavailable microbiologic or retreatment history data, and our study population was conveniently sampled to include more HIV-infected individuals. Selection bias could have implications on the estimated Xpert specificity if excluded presumptive TB patients had differential performance on this test; we tried to minimize this by comparing the excluded and study groups in terms of demographics and clinical variables and found no differences. Second, we used liquid culture as reference; although liquid media is considered faster and more sensitive, discordance between solid and liquid media is known to occur.[30] Third, as radiographic information was not available for 67% of patients, we were unable to properly analyze disease severity. Finally, the parent study did not follow up presumptive TB patients with discordant results for clinical outcomes.

In conclusion, we report a lower specificity of Xpert in diagnosing culture-proven pulmonary TB among presumptive TB out-patients in Southwestern Uganda. Our findings suggest that Xpert is not as specific as initially reported. Furthermore, the sensitivity of Xpert may be lower in non-purulent samples. Clinicians should be aware that false-positive results can occur, especially among retreatment TB cases, and future studies should address the clinical and biological significance of discordant culture/Xpert results, and the role of additional diagnostic procedures, to confirm Xpert results in this population.

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APPENDIX

Table A.1 Sputum volume and characteristics by sex

	Total Median [IQR]	Male Median [IQR]	Female Median [IQR]	*P* value
Sputum volume, ml, maximum	5 [4–7]	5 [4–7]	5 [4–6]	0.02
Sputum volume, ml, Xpert sample	3 [2–4]	3 [2–5]	3 [2–4]	0.05
Sputum characteristics, *n* (%)				0.01
Salivary/mucoid	358 (42)	163 (38)	194 (46)	
Purulent/mucopurulent	501 (58)	270 (72)	231 (54)	

IQR = interquartile value.

Table A.2 Baseline characteristics of 860 presumptive pulmonary tuberculosis patients according to HIV status in Mbarara, Uganda

Characteristics	Total ($n = 860$)	HIV-infected ($n = 591$)	Non-HIV-infected ($n = 269$)	*P* value*
Age, years, median [IQR]	38 [29–49]	36 [29–44]	44 [30–58]	<0.000
Sex				0.05
Male	433 (51)	284 (48)	149 (55)	
Female	427 (49)	307 (52)	120 (45)	
BMI, kg/m^2, median [IQR]	20.2 [18.1–22.7]	20.3 [18.3–22.8]	20.1 [17.9–22.5]	0.29
Previous anti-tuberculosis treatment				0.64
Yes	109 (13)	77 (13)	32 (12)	
No	751 (87)	514 (87)	237 (88)	
BCG scar†				0.12
Yes	507 (60)	358 (62)	149 (56)	
No/uncertain	332 (40)	217 (38)	115 (44)	
Karnofsky status†				0.87
20–60	354 (41)	244 (42)	110 (41)	
70–100	503 (59)	344 (58)	159 (59)	
Current smoker†				0.22
No	769 (90)	533 (91)	236 (88)	
Yes	86 (10)	54 (9)	32 (12)	
Current alcohol use†				0.43
No	710 (83)	492 (84)	218 (82)	
Yes	144 (17)	95 (16)	49 (18)	
Fever (self-report)†				0.03
No	248 (29)	157 (27)	91 (34)	
Yes	608 (71)	431 (73)	177 (66)	
Hemoptysis†				0.001
No	694 (81)	492 (84)	202 (75)	
Yes	159 (19)	92 (16)	67 (25)	
Night sweats†				0.10
No	282 (33)	204 (35)	78 (29)	
Yes	576 (67)	385 (65)	191 (71)	
Loss of appetite†				0.82
No	279 (33)	193 (33)	86 (32)	
Yes	579 (67)	396 (67)	186 (68)	
Dyspnea†				0.84
No	310 (36)	211 (36)	99 (37)	
Yes	544 (64)	374 (64)	170 (63)	
Weight loss†				0.96
No	189 (22)	130 (22)	59 (22)	
Yes	669 (78)	459 (78)	210 (68)	
Chest radiograph findings				
Extent of disease				0.68
Normal/minimal	142 (51)	97 (50)	45 (53)	
Moderate/advanced	136 (49)	96 (50)	40 (40)	
Cavitation				0.51
No	228 (81)	161 (82)	67 (79)	
Yes	53 (19)	35 (18)	18 (21)	
Maximum sputum volume, ml, median [IQR]†	5 [4–7]	5 [4–6]	5 [4–7]	0.02
Xpert sample sputum volume, ml, median [IQR]†	3 [2–4]	3 [2–4]	3 [3–5]	0.0008
Sputum characteristics†				<0.000
Salivary/mucoid	358 (42)	274 (46)	84 (31)	
Purulent/mucopurulent	501 (58)	317 (54)	184 (69)	
AFB smear†				<0.000
Negative	675 (79)	478 (81)	197 (73)	
1+	19 (2)	17 (3)	2 (1)	
2+	32 (4)	24 (4)	8 (3)	
3+	133 (15)	71 (12)	62 (23)	
MGIT culture				0.06
Positive	205 (24)	130 (22)	75 (28)	
Negative	655 (76)	461 (78)	194 (72)	
MGIT, days to positivity, median [IQR]	17 [11–23]	19 [13–25]	11 [7–19]	<0.000
Xpert				0.05
Positive	210 (24)	133 (23)	77 (29)	
Negative	650 (76)	458 (77)	192 (71)	

* Comparing new vs. previously treated.
† Missing data: BCG scar = 21, Karnofsky status = 3, current smoker = 5, current alcohol use = 6, fever = 4, hemoptysis = 7, night sweats = 2, loss of appetite = 2, dyspnea = 6, weight loss = 2, sputum volume = 1, sputum characteristics = 1, AFB smear = 1.
HIV = human immunodeficiency virus; IQR = interquartile range; BMI = body mass index; BCG = bacille Calmette-Guérin; AFB = acid-fast bacilli; MGIT = Mycobacterial Growth Indicator Tube; Xpert = Xpert® MTB/RIF.

Table A.3 Diagnostic performance of Xpert® MTB/RIF in different subgroups of presumptive tuberculosis patients in Mbarara, Uganda*

Study group	Sensitivity† *n/N* (%) (95%CI)	*P* value	Specificity‡ *n/N* (%) (95%CI)	*P* value	PPV§ *n/N* (%) (95%CI)	*P* value	NPV¶ *n/N* (%) (95%CI)	*P* value
Overall cohort ($n = 860$)	188/205 (91.7) (89.7–93.5)	0.01	633/655 (96.6) (95.2–97.7)	0.20	188/210 (89.5) (87.3–91.5)	0.01	633/650 (97.4) (96.2–98.4)	0.14
Salivary sputum ($n = 358$)	52/63 (82.5) (70.5–90.6)		282/295 (95.6) (92.4–97.5)		52/65 (80.0) (67.9–88.5)		282/293 (96.2) (93.2–98.0)	
Purulent sputum ($n = 501$)	136/142 (95.8) (90.6–98.3)		350/359 (97.5) (95.1–98.8)		136/145 (93.8) (88.2–96.9)		350/396 (88.3) (84.7–91.3)	
No previous anti-tuberculosis treatment ($n = 751$)	178/194 (91.8) (89.5–93.6)	0.01	543/557 (97.5) (96.1–98.5)	0.10	178/192 (92.7) (90.6–94.4)	0.001	543/559 (97.1) (95.6–98.2)	0.31
Salivary sputum ($n = 322$)	48/58 (82.8) (70.1–91.0)		254/264 (96.2) (92.9–98.1)		48/58 (82.8) (70.1–91.0)		254/264 (96.2) (92.9–98.1)	
Purulent sputum ($n = 428$)	130/136 (95.6) (90.2–98.2)		288/292 (98.6) (96.3–99.6)		130/134 (97.0) (92.1–99.0)		288/294 (98.0) (95.4–99.2)	
Previous anti-tuberculosis treatment ($n = 109$)	10/11 (90.9) (83.8–95.5)	0.45	90/98 (91.8) (84.9–96.2)	0.71	10/18 (55.6) (46.1–65.5)	1	90/91 (98.9) (95.0–100.0)	0.32
Salivary sputum ($n = 36$)	4/5 (80.0) (28.4–99.5)		28/31 (90.3) (73.1–97.5)		4/7 (57.1) (18.4–90.1)		28/29 (96.6) (82.2–99.9)	
Purulent sputum ($n = 73$)	6/6 (100.0) (54.1–100.0)		62/67 (92.5) (82.7–97.2)		6/11 (54.6) (23.4–83.2)		62/62 (100.0) (94.2–100.0)	

* *P* value = Fisher's exact test; all comparisons are 'salivary' vs. 'purulent' sputum groups; 1 missing value for sputum characteristic.
† Xpert and culture-positive/all culture-positive.
‡ Xpert and culture-negative/all culture-negative.
§ Xpert and culture-positive/all Xpert-positive.
¶ Xpert and culture-negative/all Xpert-negative.
CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

Table A.4 Diagnostic performance of Xpert® MTB/RIF in different subgroups of presumptive tuberculosis patients in Mbarara, Uganda, using only the spot Xpert sample*

Study group	Sensitivity† *n/N* (%) (95%CI)	*P* value	Specificity‡ *n/N* (%) (95%CI)	*P* value	PPV§ *n/N* (%) (95%CI)	*P* value	NPV *n/N* (%) (95%CI)¶	*P* value
Overall cohort ($n = 832$)	186/202 (92.1) (87.5–95.4)	0.01	608/630 (96.5) (94.8–97.8)	0.20	186/208 (89.4) (84.4–93.3)	0.01	608/624 (97.4) (95.9–98.5)	0.55
Salivary sputum ($n = 347$)	51/61 (83.6) (71.9–91.8)		273/286 (95.4) (92.4–97.6)		51/64 (79.7) (67.8–88.7)		273/283 (96.5) (93.6–98.3)	
Purulent sputum ($n = 484$)	135/141 (95.7) (91.0–98.4)		334/343 (97.4) (95.1–98.8)		135/144 (93.8) (88.5–97.1)		334/340 (98.2) (96.2–99.3)	
No previous anti-tuberculosis treatment ($n = 727$)	176/191 (92.2) (87.4–95.5)	0.01	522/536 (97.4) (95.7–98.6)	0.10	176/190 (92.2) (87.9–95.9)	0.001	522/537 (97.4) (95.4–98.4)	0.1
Salivary sputum ($n = 312$)	47/56 (83.9 (71.7–92.4)		246/256 (96.1) (92.9–98.1)		47/57 (82.5) (70.1–91.3)		246/255 (96.5) (93.4–98.4)	
Purulent sputum ($n = 414$)	129/135 (95.6 (90.6–98.4)		275/279 (98.6) (96.4–99.6)		129/133 (97.0) (92.5–99.2)		275/281 (97.9) (95.4–99.2)	
Previous anti-tuberculosis treatment ($n = 105$)	10/11 (90.9 (58.7–99.8)	0.45	86/94 (91.5) (83.9–96.3)	0.71	10/18 (55.6) (46.1–65.5)	1	86/87 (98.9 (93.8–100.0)	0.32
Salivary sputum ($n = 35$)	4/5 (80.0 (28.3–99.5)		27/30 (90.0) (73.5–97.9)		4/7 (57.1) (18.4–90.1)		27/28 (96.4) (81.7–99.9)	
Purulent sputum ($n = 70$)	6/6 (100.0 (54.1–100.0)		59/64 (92.2) (82.7–97.4)		6/11 (54.6) (23.4–83.2)		59/59 (100.0) (94.2–100.0)	

* Fisher's exact test; all comparisons are 'salivary' vs. 'purulent' sputum groups; 1 missing value for sputum characteristic.
† Xpert and culture-positive/all culture-positive.
‡ Xpert and culture-negative/all culture-negative.
§ Xpert and culture-positive/all Xpert-positive.
¶ Xpert and culture-negative/all Xpert-negative.
CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

RESUME

CONTEXTE : Dans des études précoces, l'Xpert® MTB/RIF a détecté avec précision la tuberculose (TB) pulmonaire prouvée par la culture. Des données récentes ont cependant fait état d'une spécificité inférieure à ce que l'on attendait chez des patients TB déjà traités.

OBJECTIF : Investiguer la précision diagnostique de l'Xpert chez des patients présumés de TB pulmonaire dans le Sud-Ouest de l'Ouganda.

SCHÉMA : Nous avons obtenu des renseignements démographiques et cliniques et recueilli trois échantillons de crachats de chaque patient pour une microscopie de frottis, un Xpert et une culture. Nous avons estimé la sensibilité et la spécificité de l'Xpert contre la culture et stratifié l'analyse en fonction du traitement préalable et de la qualité des crachats.

RÉSULTATS : Nous avons analysé 860 patients présumés de TB, dont 109 (13%) ayant déjà été traités pour TB ; 205 (24%) ont eu une culture positive. La spécificité de l'Xpert a été plus basse (91,8% ; IC95% 84,9–96,2) dans les cas déjà traités comparés aux nouveaux patients TB (97,5% ; IC95% 96,1–98,5 ; $P = 0,01$). Dans une analyse ajustée, les patients ayant comme résultat culture–, Xpert+ ont été plus susceptibles d'avoir été traités préalablement pour TB (OR 8,3 ; IC95% 2,1–32,0 ; $P = 0,002$), d'avoir des crachats mucosalivaires (OR 4,1 ; 1,1–14,6 ; $P = 0,03$) mais moins susceptibles de déclarer de la fièvre (OR 0,23 ; 0,1–0,7 ; $P = 0,008$) quand ils ont été comparés aux patients ayant des résultats concordants.

CONCLUSION : La spécificité de l'Xpert a été plus faible chez les sujets déjà traités pour TB. L'impact clinique et programmatique des résultats culture–, Xpert+ requiert une évaluation dans d'autres études.

RESUMEN

MARCO DE REFERENCIA: En los estudios iniciales, la prueba Xpert® MTB/RIF detectaba con precisión los casos de tuberculosis (TB) pulmonar confirmados por cultivo. En estudios recientes se ha observado una especificidad inferior a la prevista en los pacientes con antecedente de tratamiento antituberculoso.

OBJETIVO: Investigar la precisión diagnóstica de la prueba Xpert en pacientes con presunción clínica de TB pulmonar en la región suroccidental de Uganda.

MÉTODO: Se obtuvieron los datos demográficos y la información clínica de los pacientes y se recogieron tres muestras de esputo para el estudio microscópico, la prueba Xpert y el cultivo. Se estimó la sensibilidad y la especificidad de la prueba Xpert con respecto al cultivo y el análisis se estratificó en función del antecedente de tratamiento y la calidad de la muestra de esputo.

RESULTADOS: Se analizaron 860 casos con presunción clínica de TB, incluidos 109 con antecedente de tratamiento antituberculoso (13%); en 205 casos se obtuvo un cultivo positivo (24%). La especificidad de la prueba Xpert fue inferior en los pacientes tratados previamente (91,8%; IC95% de 84,9 a 96,2) que en los casos nuevos de TB (97,5%; IC95% de 96,1 a 98,5; $P = 0,01$). En un análisis ajustado, los pacientes con cultivo negativo y prueba Xpert positiva exhibieron una mayor probabilidad de haber recibido tratamiento antituberculoso previo (OR 8,3; IC95% de 2,1 a 32,0; $P = 0,002$) y haber aportado muestras de esputo de tipo mucosalival (OR 4,1; IC95% de 1,1 a 14,6; $P = 0,03$), pero fue menos probable que refiriesen la presencia de fiebre (OR 0,23; IC95% de 0,1 a 0,7; $P = 0,008$), cuando se compararon con los pacientes que presentaron resultados positivos concordantes.

CONCLUSIÓN: La especificidad de la prueba Xpert fue menor en los pacientes con presunción clínica de TB cuando presentaban un antecedente de tratamiento antituberculoso. Se precisan nuevos estudios que evalúen las repercusiones clínicas y programáticas de la obtención de resultados discordantes con cultivo negativo y prueba Xpert positiva.