







Typert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in

Alexander Kay, MD

Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children

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CONFLICT OF INTEREST DISCLOSURE

X I have no Conflict of Interest to report.

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	□ Receipt of grants/research supports:
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	□ Participation in a company sponsored speaker's bureau:
	☐ Tobacco-industry and tobacco corporate affiliate:
	□ Stock shareholder:
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	□ Other:

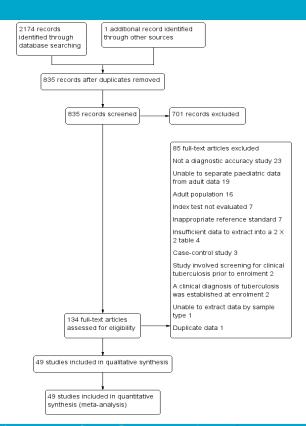
BACKGROUND

- Child TB accounts for 11% of the 10 million global cases
- Children shoulder a disproportionate share of TB mortality (14%)
- 96% of child TB deaths occur in the undiagnosed (Dodd et al, Lancet Global Health, 2017)
- Previous Xpert MTB/RIF Review (Detjen et al, Lancet Resp Med, 2015)
 - sensitivity (62% sputum, 66% gastric specimen)
 - specificity (98% sputum and gastric specimens)
- Updated the systematic review as additional Xpert MTB/RIF studies have been published and Xpert Ultra was introduced in order to inform 2020 WHO TB molecular diagnostic guidelines



METHODS: SEARCH

- Searched multiple databases without language restriction to 29 Apr 2019
- Covidence systematic review software to manage selection of studies
- Reviewed reference lists of articles and review articles
- Reviewed included studies from prior review
- Data obtained directly from manuscripts and through author inquiries



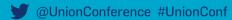






METHODS: APPROACH

- Types of Studies: Diagnostic accuracy cross-sectional studies, cohort studies, and randomized controlled trials from all settings
- Participants: Studies that evaluated the index tests for pulmonary TB in HIV-positive and HIV-negative children aged 0 to 14 years with presumptive TB
- Index Test: Xpert MTB/RIF and Xpert Ultra
- **Specimens:** sputum, gastric aspirate, stool or nasopharyngeal specimens
- Target Condition: Pulmonary TB



METHODS: REFERENCE STANDARDS

- Microbiologic Reference Standard: A positive culture on liquid or solid media from the same specimen type as the index test
 - The reference test for stool was a positive culture or Xpert test on a respiratory specimen
- Composite Reference Standard: A positive culture or a clinical decision to treat for TB based on clinical features
 - If treatment decisions could not be abstracted then study specific definitions were used



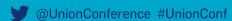
METHODS: ANALYSIS

- Methodological quality assessed by QUADAS-2: patient selection, index test, reference standard, and flow & timing domains
- Performed meta-analyses using bivariate random-effects models when data were sufficient to estimate pooled results
- Investigated sources of heterogeneity by subgroup analysis: age groups, smear status, HIV status
- Sensitivity analyses were based on methodological quality



RESULTS

- 49 studies, which provided 299 data sets (68,544 participants) for pulmonary TB
- 80% of studies were performed in TB high-burden settings
- Median TB prevalence in the included studies was similar across specimen types ranging from 7-11%



RESULTS: SPUTUM

Xpert MTB/RIF against Culture (23 studies, 6612 participants)

- Sensitivity: 64.6% (95% CI 55.3 to 72.9)
- Specificity: 99.0% (95% CI 98.1 to 99.5)

Xpert MTB/RIF against Composite (16 studies, 4379 participants)

- Sensitivity: 19.7% (95% CI 12.1 to 30.4)
- Specificity: 100% (95% CI 100 to 100)

Xpert Ultra against Culture (3 studies, 697 participants)

- Sensitivity: 72.8%(95% CI 64.7 to 79.6)
- Specificity: 97.5% (95% CI 95.8 to 98.5)

Xpert Ultra against Composite (3 studies, 753 participants)

- Sensitivity: 23.5% (95% CI 20.0 to 27.4)
- Specificity: 99.2% (95% CI 96.9 to 99.8)

Study	TP	FP	FN	TN	Culture	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Das 2019	1	0	0	7	Single	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]		
LaCourse 2014	2	1	ō	297	Multiple	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]		
Singh M 2016	11	5	1	33	Single	0.92 [0.62, 1.00]	0.87 [0.72, 0.96]		-
Orikiriza 2018	10	3	1	325	Multiple	0.91 [0.59, 1.00]	0.99 [0.97, 1.00]		
Bates 2013	9	2	1	130	Single	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]		•
Nhu 2013	21	0	4	22	Multiple	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]		-
Brent 2017	33	0	- 7	1064	Single	0.82 [0.67, 0.93]	1.00 [1.00, 1.00]	-	
Sekadde 2013	27	7	- 7	194	Single	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]		•
Chipinduro 2017	7	8	2	201	Single	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]		•
Nicol 2011	9	0	3	36	Multiple	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]		-
Walters 2017a	16	6	8	240	Single	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]		•
Nicol 2013	11	3	6	95	Multiple	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]		-
Zar 2012	52	2	35	385	Multiple	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]	-	•
Reither 2015	21	2	16	411	Multiple	0.57 [0.39, 0.73]	1.00 [0.98, 1.00]	_	•
Gous 2015	- 5	3	4	333	Single	0.56 [0.21, 0.86]	0.99 [0.97, 1.00]		•
Anderson 2014	19	3	16	96	Multiple	0.54 [0.37, 0.71]	0.97 [0.91, 0.99]		-
Rachow 2012	13	3	15	98	Multiple	0.46 [0.28, 0.66]	0.97 [0.92, 0.99]		-
Atwebembeire 2016	- 5	1	6	73	Single	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]		-
Togun 2015	6	6	8	467	Single	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]		•
Zar 2013	12	1	16	280	Multiple	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]		•
Bacha 2017	- 5	0	- 7	252	Single	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]		•
Chisti 2014	2	14	3	192	Single	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]		-
Bunyasi 2015	7	0	24	908	Multiple	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]	-	•
Malbruny 2011	0	0	0	3	Single	Not estimable	1.00 [0.29, 1.00]		
Hanrahan 2018	0	1	0	105	Multiple	Not estimable	0.99 [0.95, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1









RESULTS: GASTRIC ASPIRATION

Xpert MTB/RIF against Culture

(14 studies, 3482 participants):

• Sensitivity: 73.0% (95% CI 52.9 to 86.7)

• Specificity: 98.1% (95% CI 95.5 to 99.2)

Xpert MTB/RIF against Composite

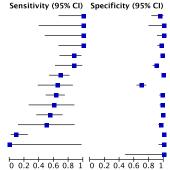
(6 studies, 933 participants):

• Sensitivity: 31.7% (95% CI 20.2 to 46.0)

• Specificity: 99.7% (95% CI 97.1 to 100)

Xpert MTB/RIF, gastric aspirate specimen, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hasan 2017	9	2	0	38	1.00 [0.66, 1.00]	0.95 [0.83, 0.99]
Nhu 2013	4	0	0	16	1.00 [0.40, 1.00]	1.00 [0.79, 1.00]
Causse 2011	5	0	0	38	1.00 [0.48, 1.00]	1.00 [0.91, 1.00]
Das 2019	9	3	0	94	1.00 [0.66, 1.00]	0.97 [0.91, 0.99]
Marcy 2016	21	4	3	207	0.88 [0.68, 0.97]	0.98 [0.95, 0.99]
Myo 2018	14	22	2	193	0.88 [0.62, 0.98]	0.90 [0.85, 0.93]
Bates 2013	33	5	15	735	0.69 [0.54, 0.81]	0.99 [0.98, 1.00]
Pang 2014	11	58	6	136	0.65 [0.38, 0.86]	0.70 [0.63, 0.76]
Tortoli 2012	37	2	22	113	0.63 [0.49, 0.75]	0.98 [0.94, 1.00]
LaCourse 2018	6	3	4	151	0.60 [0.26, 0.88]	0.98 [0.94, 1.00]
Walters 2017a	18	3	15	226	0.55 [0.36, 0.72]	0.99 [0.96, 1.00]
Chisti 2014	3	8	3	200	0.50 [0.12, 0.88]	0.96 [0.93, 0.98]
Bunyasi 2015	3	1	29	902	0.09 [0.02, 0.25]	1.00 [0.99, 1.00]
Hanrahan 2018	0	0	1	49	0.00 [0.00, 0.97]	1.00 [0.93, 1.00]
Malbruny 2011	0	0	0	5	Not estimable	1.00 [0.48, 1.00]



Xpert MTB/RIF, gastric aspirate specimen, composite reference standard

tudy	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95%
histi 2014	11	0	35	168	0.24 [0.13, 0.39]	1.00 [0.98, 1.00]	-	
lasan 2017	11	0	- 7	32	0.61 [0.36, 0.83]	1.00 [0.89, 1.00]		
asa Tom 2018	18	1	33	10	0.35 [0.22, 0.50]	0.91 [0.59, 1.00]	-	
aCourse 2018	9	0	76	80	0.11 [0.05, 0.19]	1.00 [0.95, 1.00]	-	
tyo 2018	36	0	85	110	0.30 [0.22, 0.39]	1.00 [0.97, 1.00]	-	
lhu 2013	4	0	11	0	0.27 [0.08, 0.55]	Not estimable		
ang 2014	68	1	72	70	0.49 [0.40, 0.57]	0.99 [0.92, 1.00]		
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^{*} No studies evaluated Xpert Ultra on gastric aspiration



RESULTS: NASOPHARYNGEAL ASPIRATION

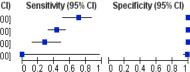
Xpert MTB/RIF against Culture

(4 studies, 1125 participants):

- Sensitivity 45.7% (95% CI 27.6% to 65.1%)
- Specificity: (4 studies, 981 participants): 99.6% (95% CI 98.9 to 99.8)

Xpert MTB/RIF, nasopharyngeal aspirate, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Marcy 2016	20	1	8	230	0.71 [0.51, 0.87]	1.00 [0.98, 1.00]
Zar 2012	38	1	49	386	0.44 [0.33, 0.55]	1.00 [0.99, 1.00]
Zar 2013	8	1	20	280	0.29 [0.13, 0.49]	1.00 [0.98, 1.00]
Hanrahan 2018	0	1	1	81	0.00 [0.00, 0.97]	0.99 [0.93, 1.00]



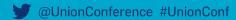
Xpert Ultra against Culture

(1 study, 195 participants):

- Sensitivity 45.7% (95% CI 28.9 to 63.3)
- Specificity 97.5% (95% CI 93.7 to 99.3)



^{*}Composite reference standard was not assessed due to limited data



RESULTS: STOOL

Xpert MTB/RIF against Culture (11 studies, 1512 participants):

- Sensitivity: 61.5% (95% CI 44.1 to 76.4)
- Specificity: 98.5% (95% CI 97.0 to 99.2)

Xpert MTB/RIF against Composite (10 studies, 1739 participants):

- Sensitivity: 16.3% (95% CI 8.4 to 29.2)
- Specificity: 99.7% (95% CI 97.8 to 100)

Xpert MTB/RIF, stool, culture

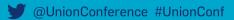
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI) Specificity (95% CI)
Andriyoko 2019	3	3	0	21	1.00 [0.29, 1.00]	0.88 [0.68, 0.97]	
Moussa 2016	30	1	6	78	0.83 [0.67, 0.94]	0.99 [0.93, 1.00]	
Hasan 2017	9	2	2	36	0.82 [0.48, 0.98]	0.95 [0.82, 0.99]	
Chipinduro 2017	13	4	6	195	0.68 [0.43, 0.87]	0.98 [0.95, 0.99]	
Marcy 2016	18	1	9	223	0.67 [0.46, 0.83]	1.00 [0.98, 1.00]	
LaCourse 2018	- 5	2	3	137	0.63 [0.24, 0.91]	0.99 [0.95, 1.00]	
Orikiriza 2018	- 5	1	4	54	0.56 [0.21, 0.86]	0.98 [0.90, 1.00]	
Walters 2017a	12	6	12	240	0.50 [0.29, 0.71]	0.98 [0.95, 0.99]	
Nicol 2013	8	1	9	97	0.47 [0.23, 0.72]	0.99 [0.94, 1.00]	
Walters 2018a	4	1	12	219	0.25 [0.07, 0.52]	1.00 [0.97, 1.00]	
Hanrahan 2018	0	0	4	96	0.00 [0.00, 0.60]	1.00 [0.96, 1.00]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Xpert MTB/RIF, stool, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	15	2	17	184	0.47 [0.29, 0.65]	0.99 [0.96, 1.00]		•
Hanrahan 2018	0	0	48	48	0.00 [0.00, 0.07]	1.00 [0.93, 1.00]	-	-
Hasan 2017	11	0	7	32	0.61 [0.36, 0.83]	1.00 [0.89, 1.00]		-
LaCourse 2018	7	0	67	74	0.09 [0.04, 0.19]	1.00 [0.95, 1.00]	-	-
Marcy 2016	28	1	217	26	0.11 [0.08, 0.16]	0.96 [0.81, 1.00]	•	-
Moussa 2016	31	0	76	8	0.29 [0.21, 0.39]	1.00 [0.63, 1.00]		
Nicol 2013	9	0	56	50	0.14 [0.07, 0.25]	1.00 [0.93, 1.00]		-
Orikiriza 2018	7	0	19	41	0.27 [0.12, 0.48]	1.00 [0.91, 1.00]		-
Walters 2017a	24	0	146	209	0.14 [0.09, 0.20]	1.00 [0.98, 1.00]	-	
Walters 2018a	6	0	88	185	0.06 [0.02, 0.13]	1.00 [0.98, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1



^{*}No studies evaluated Xpert Ultra on stool



RESULTS: RIFAMPICIN RESISTANCE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Das 2019	- 7	0	0	11	1.00 [0.59, 1.00]	1.00 [0.72, 1.00]		
Zar 2012	5	1	1	114	0.83 [0.36, 1.00]	0.99 [0.95, 1.00]		•
Bates 2013	2	1	0	38	1.00 [0.16, 1.00]	0.97 [0.87, 1.00]		-
Saini 2018	2	3	1	6	0.67 [0.09, 0.99]	0.67 [0.30, 0.93]		
Pang 2014	1	0	0	9	1.00 [0.03, 1.00]	1.00 [0.66, 1.00]		
Yin 2014	1	0	0	20	1.00 [0.03, 1.00]	1.00 [0.83, 1.00]		-
Bholla 2016	0	0	0	5	Not estimable	1.00 [0.48, 1.00]		
Malbruny 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]		
Chipinduro 2017	0	0	0	9	Not estimable	1.00 [0.66, 1.00]		
Tortoli 2012	0	0	0	4	Not estimable	1.00 [0.40, 1.00]		
Reither 2015	0	0	0	22	Not estimable	1.00 [0.85, 1.00]		-
Rachow 2012	0	0	0	25	Not estimable	1.00 [0.86, 1.00]		-
Zar 2013	0	0	0	19	Not estimable	1.00 [0.82, 1.00]		-
Walters 2014	0	0	0	7	Not estimable	1.00 [0.59, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

 Xpert MTB/RIF pooled sensitivity against culture or LPA DST was: 90.0% (95% CI 67.6% to 97.5%) and specificity was 98.3% (95% CI 87.7% to 99.8%)

*No studies evaluated Xpert Ultra rifampicin resistance detection



CONCLUSIONS

- Xpert MTB/RIF sensitivity varied by specimen type but 95% CIs overlapped
 - Gastric aspirate specimens had the highest sensitivity followed by sputum and stool, and nasopharyngeal specimens the lowest; specificity in all specimens was > 98%
- Compared with Xpert MTB/RIF, Xpert Ultra sensitivity in sputum was higher (overlapping 95% CIs) and specificity was slightly lower
- The small number of studies and reliance on stored specimens limits our confidence in the precision of the accuracy estimates for Xpert Ultra
- Test sensitivity remains poor against a composite reference standard. Treatment decisions should be based on the entirety of clinical information and treatment not withheld based solely on an Xpert MTB/RIF or Xpert Ultra result.



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Thank you