Xpert MTB/RIF Ultra assay for active pulmonary tuberculosis and rifampicin resistance in children younger than 10 years of age, systematic review update

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Background

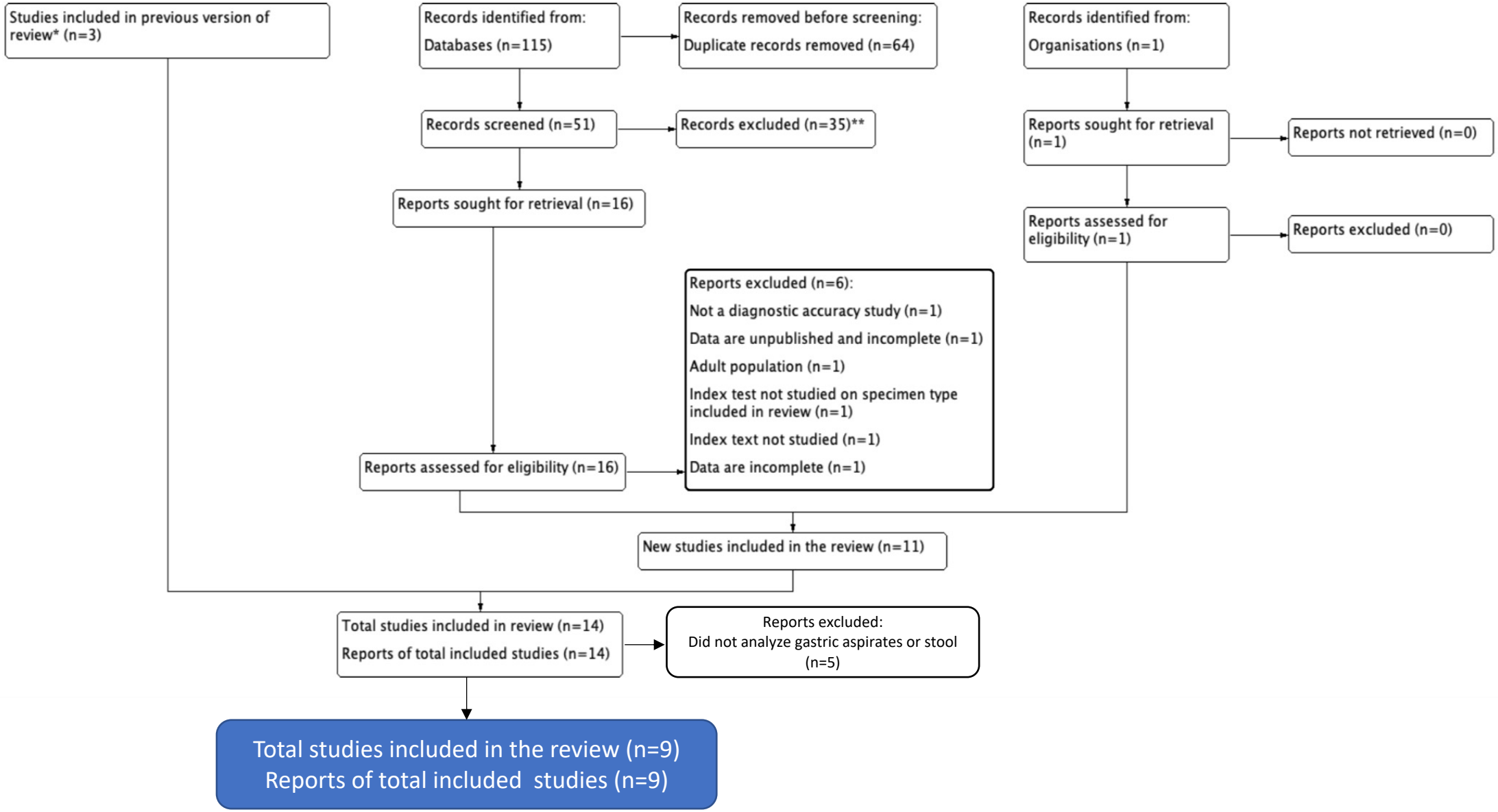
- Child TB accounts for 12% of the 10 million global cases and a disproportionate share of TB mortality (over 16%)
- It is estimated that 56% of all child TB cases and 65% in children < 5 years are not diagnosed, in part due to challenging specimen collection
- A Cochrane Review informed the WHO 'Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children: Policy update 2020'.
- Xpert Ultra diagnostic accuracy for child PTB using sputum and nasopharyngeal specimens
  - Sputum (3 studies, 697 participants): Pooled sensitivity 73% (95% CI 65% to 80%), Pooled specificity 97% (95%CI 96% to 98%)
  - Nasopharyngeal (1 study, 195 participants): Sensitivity 46% (95% CI: 29% to 63%), Specificity 98% (95% CI: 94% to 99%)

- **We performed a systematic review update as additional Xpert Ultra studies have been published on important specimens not included in the original review**

PICO 2b: What is the diagnostic accuracy of Xpert Ultra in gastric aspirate and stool specimens for pulmonary TB in children aged below 10 years, as compared with microbiologic reference standard (MRS) and composite reference standard (CRS)?

- Population: Children 0 to 9 years
  - Age stratification:
    - Less than 1 year
    - 1 to 4 years
    - 5 to 9 years
  - Sub-populations:
    - Children with severe acute malnutrition
    - Children living with HIV
    - Children with severe acute pneumonia

PRISMA Diagram



Identification of studies, data collection and analysis

- We searched multiple databases to 27 January 2021 without language restriction
- Two review authors independently screened titles and abstract and full-text publications
- We systematically contacted all **primary study** authors of identified articles for stratified data and study characteristics
- We identified unpublished data outside of our search results through conversations with child TB experts
- We accepted unpublished data if it was cleaned and considered final by the **primary study authors**
- Meta-analyses were performed using a bivariate random-effects model

Characteristics of Included Studies

- Xpert Ultra Gastric Aspirate or Lavage Specimens
  - 6 studies
  - 50% took place in a high TB burden country and 83% in a high TB/HIV burden country
  - Median prevalence of confirmed TB was 7%
  - One study limited enrollment to HIV+ children and one to children with severe acute malnutrition

- Xpert Ultra Stool Specimens
  - 6 studies
  - 100% took place in a high TB burden country and 83% in a high TB/HIV burden country
  - Median prevalence of confirmed TB was 5%
  - One study limited enrollment to HIV+ children and one to children with severe acute malnutrition

Characteristics of Included Studies

Study	Countries	High TB burden/high TB/HIV burden	Clinical setting	Type of specimen	Study design	Patient selection	Number of cultures	Composite reference standard
FIND 2021	India, Uganda, South Africa	Yes/Yes	Inpatient and outpatient	Stool	Prospective cohort	Consecutive and referral	Multiple	No
Jaganath 2021	Uganda	No/Yes	Inpatient and outpatient	Gastric aspirate	Prospective cohort	Consecutive	Multiple	Yes
Kabir 2020	Bangladesh	Yes/No	Inpatient	Stool	Cross-sectional	Consecutive	Single	Yes
Liu 2020	China	Yes/Yes	Inpatient and outpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	Yes
NCT04121026 2021	Côte d'Ivoire, Mozambique, Uganda, Zambia	Yes/Yes	Inpatient and outpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	No
NCT04203628 2020	Uganda and Zambia	Yes/Yes	Inpatient and outpatient	Stool	Prospective cohort	Consecutive	Multiple	No
NCT04240990 2021	Uganda and Zambia	Yes/Yes	Inpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	No
Parigi 2021	Italy	No/No	Inpatient	Gastric aspirate	Prospective cohort	Unclear	Multiple	Yes
Ssengooba 2020	Uganda	No/Yes	Outpatient	Gastric aspirate and lavage	Prospective cohort	Consecutive	Multiple	Yes

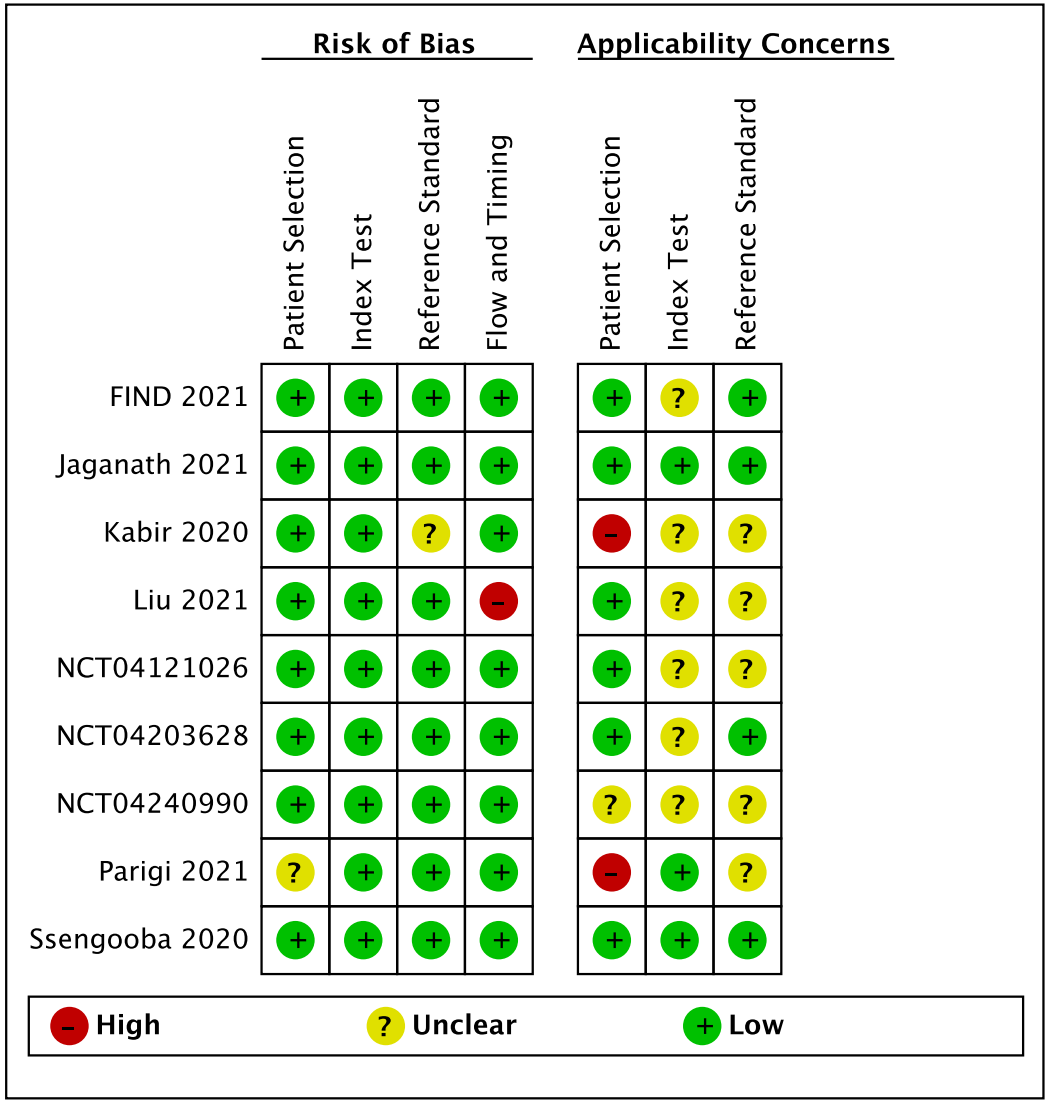
QUADAS-2 Assessment of Methodological Quality

Risk of Bias

- Enrolment strategy: prospective, consecutive
- Multiple cultures as compared to a single culture

Applicability

- Enrolment site
- Index test procedure
- Was cultured mycobacteria confirmed as MTB

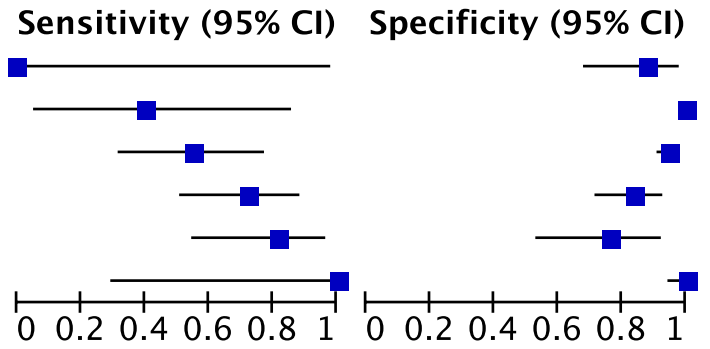


PICO Sub-questions; Gastric Aspirate/Lavage Specimens

Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS?

6 studies, 659 participants
Reference standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage
(Median TB prevalence 7%)
Pooled sensitivity: 63.6% (47.7 to 77.0) **| Pooled specificity:** 94.9% (83.8 to 98.5)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaganath 2021	0	3	1	21	0.00 [0.00, 0.97]	0.88 [0.68, 0.97]
NCT04240990	2	1	3	215	0.40 [0.05, 0.85]	1.00 [0.97, 1.00]
Ssengooba 2020	11	12	9	203	0.55 [0.32, 0.77]	0.94 [0.90, 0.97]
Liu 2021	18	9	7	46	0.72 [0.51, 0.88]	0.84 [0.71, 0.92]
Parigi 2021	13	5	3	16	0.81 [0.54, 0.96]	0.76 [0.53, 0.92]
NCT04121026	3	0	0	58	1.00 [0.29, 1.00]	1.00 [0.94, 1.00]



Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS?

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Reference standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage
(Median TB prevalence 7%)
Pooled sensitivity: 63.6% (47.7 to 77.0) **| Pooled specificity:** 94.9% (83.8 to 98.5)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1%	Prevalence 10%	Prevalence 20%		
True positives	6 (5 to 8)	64 (48 to 77)	128 (96 to 154)	70 (6)	⨁⨁⨁◯ MODERATE [a]
False negatives	4 (2 to 5)	36 (23 to 52)	72 (46 to 104)		
True negatives	941 (832 to 980)	855 (756 to 891)	760 (672 to 792)	589 (6)	⨁⨁⨁◯ MODERATE [b,c]
False positives	49 (10 to 158)	45 (9 to 144)	40 (8 to 128)		

Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a CRS?

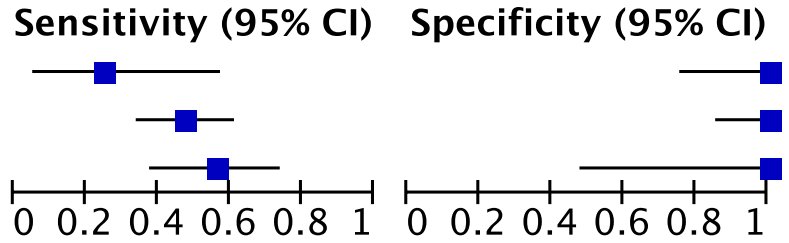
3 studies, 142 participants

Reference Standard: A positive culture on a respiratory specimen *OR* a clinical decision to treat for tuberculosis *OR* TB as defined by a research definition

(Median TB prevalence 71%)

Pooled sensitivity: 47.5% (38.0 to 57.2) | **Pooled specificity:** 100% (91.4 to 100)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaganath 2021	3	0	9	13	0.25 [0.05, 0.57]	1.00 [0.75, 1.00]
Liu 2021	27	0	30	23	0.47 [0.34, 0.61]	1.00 [0.85, 1.00]
Parigi 2021	18	0	14	5	0.56 [0.38, 0.74]	1.00 [0.48, 1.00]



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3 studies, 142 participants
Reference standard: A positive culture on a respiratory specimen *OR* a clinical decision to treat for tuberculosis *OR* TB as defined by a research definition
(Median TB prevalence 71%)
Pooled sensitivity: 47.5% (38.0 to 57.2) | **Pooled specificity:** 100% (91.4 to 100)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1%	Prevalence 10%	Prevalence 20%		
True positives	5 (4 to 6)	48 (38 to 57)	96 (76 to 114)	101 (3)	⨁⨁◯◯ LOW [a,b]
False negatives	5 (4 to 6)	52 (43 to 62)	104 (86 to 124)		
True negatives	990 (901 to 990)	900 (819 to 900)	800 (728 to 800)	41 (3)	⨁⨁◯◯ LOW [b,c]
False positives	0 (0 to 89)	0 (0 to 81)	0 (0 to 72)		

PICO Sub-questions; Stool Specimens

Stool Study Processing Methods and Non-Determinates

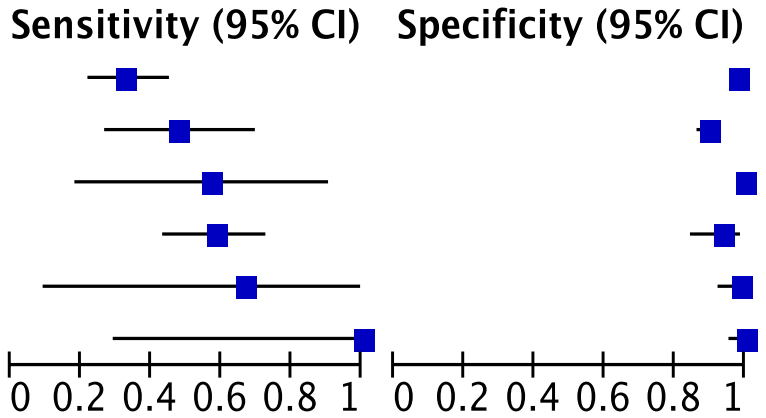
Study	Method	Reference standard	Proportion of non-determinate results*
FIND 2021	Stool processing kit	Respiratory specimen culture(s) and Xpert Ultra	10% (42/434)
Kabir 2020	Centrifuge based method	Respiratory specimen culture (solid), Xpert Ultra, and Xpert MTB/RIF	< 1% (1/446)
NCT 04240990	Optimized sucrose floatation	Respiratory specimen culture(s) and Xpert Ultra	1% (2/237)
Liu 2021	Sedimentation and filtration	Respiratory specimen culture(s) and Xpert Ultra and Xpert MTB/RIF	Not reported
NCT 04121026	Optimized sucrose floatation	Respiratory specimen culture(s) and Xpert Ultra	4% (5/114)
NCT 04203628	Optimized sucrose floatation	Respiratory specimen culture(s) and Xpert Ultra	3% (2/76)

*Proportion is reported as a percentage.
A non-determinate Xpert Ultra test result is one that results in an Error, Invalid, or No Result and may be due to an operator error, instrument, or cartridge issue.
Non-determinate results were < 1% for gastric aspirates when reported

Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS?

6 studies, 1278 participants
Reference Standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median TB prevalence 5%)
Pooled sensitivity: 52.8 (35.0 to 69.9) **| Pooled specificity:** 98.0 (93.4 to 99.4)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
FIND 2021	23	8	47	313	0.33 [0.22, 0.45]	0.98 [0.95, 0.99]
Kabir 2020	11	40	12	339	0.48 [0.27, 0.69]	0.89 [0.86, 0.92]
NCT04240990	4	1	3	226	0.57 [0.18, 0.90]	1.00 [0.98, 1.00]
Liu 2021	28	4	20	57	0.58 [0.43, 0.72]	0.93 [0.84, 0.98]
NCT04121026	2	1	1	65	0.67 [0.09, 0.99]	0.98 [0.92, 1.00]
NCT 04203628	3	0	0	71	1.00 [0.29, 1.00]	1.00 [0.95, 1.00]



Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS?

6 studies, 1278 participants
Reference standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median Prevalence 5%)
Pooled sensitivity: 52.8% (35.0 to 69.9) **| Pooled specificity:** 98.0% (93.4 to 99.4)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1%	Prevalence 10%	Prevalence 20%		
True positives	5 (3 to 7)	53 (35 to 70)	106 (70 to 140)	153 (6)	⨁⨁⨁◯ MODERATE [a]
False negatives	5 (3 to 7)	47 (30 to 65)	94 (60 to 130)		
True negatives	970 (921 to 980)	882 (837 to 891)	784 (744 to 792)	1125 (6)	⨁⨁⨁◯ MODERATE [b]
False positives	20 (10 to 69)	18 (9 to 63)	16 (8 to 56)		

Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a CRS?

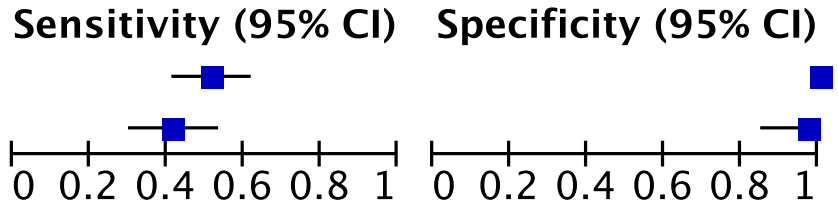
2 studies, 511 participants

Reference Standard: Liquid or solid culture or Xpert on a respiratory specimen *OR* a clinical decision to treat for tuberculosis *OR* TB as defined by a research definition

(TB prevalence 9.0% and 70%)

Pooled sensitivity: 47.1% (39.8 to 54.6) | **Pooled specificity:** 99.7% (97.9 to 100)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kabir 2020	51	0	48	303	0.52 [0.41, 0.62]	1.00 [0.99, 1.00]
Liu 2021	31	1	44	33	0.41 [0.30, 0.53]	0.97 [0.85, 1.00]



Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a CRS?

2 studies, 511 participants
Reference standard: Liquid or solid culture or Xpert on a respiratory specimen *OR* a clinical decision to treat for tuberculosis *OR* TB as defined by a research definition
(TB prevalence 9.0% and 70%)
Pooled sensitivity: 47.1% (39.8 to 54.6) | **Pooled specificity:** 99.7% (97.9 to 100)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1%	Prevalence 10%	Prevalence 20%		
True positives	5 (4 to 6)	47 (40 to 55)	94 (80 to 110)	174 (2)	⨁⨁◯◯ LOW [a,b]
False negatives	5 (4 to 6)	53 (45 to 60)	106 (90 to 120)		
True negatives	990 (970 to 990)	900 (882 to 900)	800 (784 to 800)	337 (2)	⨁⨁◯◯ LOW [b,c]
False positives	0 (0 to 20)	0 (0 to 18)	0 (0 to 16)		

Xpert Ultra Trace Results

Trace Results: Gastric Aspirates

- Of the total nine studies, eight (89%) reported the number of Xpert Ultra positive results that were trace results.
- The percentage of Ultra trace results, of the total Xpert Ultra positive results, ranged from 0% to 67% (median 52%) in studies evaluating gastric specimens

Study	Total (TB cases)	Number of trace results	Number of test positives	Trace % (95% CI)*
Jaganath 2021	25 (1)	2	3	66.7 (20.8 to 93.9)
Liu 2021	80 (25)	8	27	29.6 (15.9 to 48.5)
NCT04121026	61 (3)	0	3	0.00 (0.00 to 56.1)
NCT04240990	221 (5)	1	3	33.3 (6.15 to 79.2)
Parigi 2021	37 (16)	NA	18	NA
Ssengooba 2020	235 (20)	13	23	56.5 (36.8 to 74.4)

NA = not available

Trace Results: Stool Specimens

- The percentage of Ultra trace results, of the total Xpert Ultra positive results, ranged from 0% to 84% (median 52%) in studies evaluating stool specimens.

Study	Total (TB cases)	Number of trace results	Number of test positives	Trace % (95% CI)*
FIND 2021	391 (70)	12	31	38.7 (23.7 to 56.2)
Kabir 2020	402 (23)	43	51	84.3 (72.0 to 91.8)
Liu 2021	109 (48)	14	32	43.8 (28.2 to 60.7)
NCT04121026	69 (3)	0	3	0.00 (0.00 to 56.1)
NCT 04203628	74 (3)	2	3	66.7 (20.8 to 93.9)
NCT04240990	234 (7)	3	5	60.0 (23.1 to 88.2)

Summary estimates with and without trace results

Test, specimen, age group, reference standard	Studies	Total (TB cases)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
Xpert Ultra, gastric aspirate, 0 to 9 years, MRS	6	659 (70)	63.6 (47.7 to 77.0)	94.9 (83.8 to 98.5)
Xpert Ultra, gastric aspirate, 0 to 9 years, MRS (trace results excluded)	6	635 (63)	59.4 (41.1 to 75.5)	97.6 (91.1 to 99.4)
Xpert Ultra, stool, 0 to 9 years, MRS	6	1279 (154)	52.8 (35.0 to 69.9)	98.0 (93.4 to 99.4)
Xpert Ultra, stool, 0 to 9 years, MRS (trace results excluded)	6	1206 (130)	38.1 (27.2 to 50.4)	99.7 (98.9 to 99.9)

Rifampicin resistance and sub-populations

- We did not identify any studies that evaluated the diagnostic accuracy of Xpert Ultra for rifampicin resistance.
- We identified four studies (259 participants, 9 with tuberculosis) in children with severe malnutrition and four studies (99 participants, 8 with tuberculosis) in children living with HIV testing gastric aspirates.
- We identified three studies (428 participants, 19 with tuberculosis) in children with severe malnutrition and two studies (100 participants, 3 with tuberculosis) in children living with HIV testing stool.
- The paucity of data meant we could not perform meta-analyses in children living with HIV and children with severe malnutrition*. No studies were identified evaluating gastric aspirate or stool specimens in children with severe pneumonia.

*meta-analysis performed on stool specimens in children with severe malnutrition

Summary of Main Results

- For gastric aspirate, Xpert Ultra sensitivity was 64% in children 0 to 9 years, against MRS. Sensitivity was similar (67%) in children < 1 year and slightly higher (72%) in children 1 to 4 years. Specificity was 94% to 95% in these analyses.
- For stool, Xpert Ultra sensitivity was 53% in children 0 to 9 years, against MRS. Sensitivity was higher (65%) in children < 1 year and lower (43%) in children 1 to 4 years. Specificity was 96% to 98% in these analyses.
- Sensitivity estimates against a composite reference standard were lower for both specimen types.
- Xpert Ultra trace results were common in both gastric aspirate and stool specimens.
- *Authors' conclusions: Overall, Xpert Ultra sensitivity appeared to be slightly higher in gastric aspirate than stool (indirect comparison). Xpert Ultra specificity in both specimens was > 94%. The small numbers of children < 1 and 1 to 4 years in the analyses, limits our confidence in the precision of the estimates for these age groups.*

Summary Table

Test, specimen, age group, reference standard	Studies	Total (cases)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Xpert Ultra, gastric aspirate, 0 to 9 years, MRS	6	659 (70)	63.6 (47.7 to 77.0)	94.9 (83.8 to 98.5)	57.9 (31.0 to 80.9)	95.9 (94.1 to 97.2)
Xpert Ultra, gastric aspirate, 0 to 9 years, CRS	3	142 (101)	47.5 (38.0 to 57.2)	100 (91.4 to 100)*	100 (32.9 to 100)	94.5 (93.0 to 95.5)
Xpert Ultra, gastric aspirate, < 1 year, MRS	5	182 (26)	67.3 (43.5 to 84.6)	94.0 (84.7 to 97.8)	55.4 (31.5 to 77.1)	96.3 (93.1 to 98.0)
Xpert Ultra, gastric aspirate, 1 to 4 years, MRS	4	327 (30)	71.5 (40.0 to 90.4)	94.0 (73.8 to 98.9)	57.1 (25.1 to 84.1)	96.8 (92.5 to 98.6)
Xpert Ultra, stool, 0 to 9 years, MRS	6	1279 (154)	52.8 (35.0 to 69.9)	98.0 (93.4 to 99.4)	74.1 (55.2 to 96.6)	94.9 (92.7 to 96.6)
Xpert Ultra, stool, 0 to 9 years, CRS	2	511 (174)	47.1 (39.8 to 54.6)	99.7 (97.9 to 100)	94.6 (71.2 to 99.2)	94.4 (93.7 to 95.1)
Xpert Ultra, stool, < 1 year, MRS	4	295 (31)	65.2 (33.7 to 87.3)	96.2 (88.9 to 98.7)	65.3 (40.2 to 84.0)	96.2 (91.5 to 98.3)
Xpert Ultra, stool, 1 to 4 years, MRS	3	331 (30)	43.3 (27.1 to 61.2)	97.1 (74.8 to 99.7)	62.7 (13.2 to 94.9)	93.9 (91.8 to 95.5)
Xpert Ultra, stool, severe malnutrition, 0 to 9, MRS	3	428 (19)	63.2 (40.3 to 81.3)	98.5 (84.1 to 99.9)	82.3 (27.7 to 98.3)	96.1 (93.1 to 97.7)

Questions?

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- The Cochrane Review team: Lucia González Fernández, Michael Eisenhut, Anne Detjen and Anna Mandalakas
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- The FIND stool diagnostic study for sharing unpublished data
- The TB SPEED study consortium for sharing unpublished data
- All study authors who kindly provided stratified data of their study results

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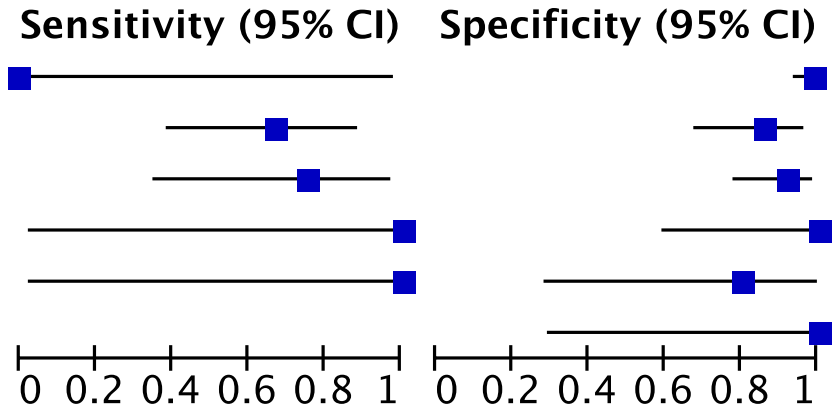
Additional Age Stratified Analyses for Gastric Aspirates and Stool Specimens

Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 1 year, against a MRS?

5 studies, 182 participants
Reference Standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage (Median TB prevalence 9%)
Pooled sensitivity: 67.3% (43.5 to 84.6) **| Pooled specificity:** 94.0% (84.7 to 97.8)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
NCT04240990	0	1	1	79	0.00 [0.00, 0.97]	0.99 [0.93, 1.00]
Liu 2021	10	4	5	24	0.67 [0.38, 0.88]	0.86 [0.67, 0.96]
Ssengooba 2020	6	3	2	33	0.75 [0.35, 0.97]	0.92 [0.78, 0.98]
NCT04121026	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
Parigi 2021	1	1	0	4	1.00 [0.03, 1.00]	0.80 [0.28, 0.99]
Jaganath 2021	0	0	0	3	Not estimable	1.00 [0.29, 1.00]



Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 1 year, against a MRS?

5 studies, 182 participants
Reference standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage (Median TB prevalence 9%)
Pooled sensitivity: 67.3% (43.5 to 84.6) **| Pooled specificity:** 94.0% (84.7 to 97.8)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1% Typically seen in	Prevalence 10% Typically seen in	Prevalence 20% Typically seen in		
True positives	7 (4 to 9)	67 (44 to 85)	134 (88 to 170)	26 (5)	⨁⨁◯◯ LOW [a]
False negatives	3 (1 to 6)	33 (15 to 56)	66 (30 to 112)		
True negatives	931 (842 to 970)	846 (765 to 882)	752 (680 to 784)	156 (5)	⨁⨁⨁◯ MODERATE [b]
False positives	59 (20 to 148)	54 (18 to 135)	48 (16 to 120)		

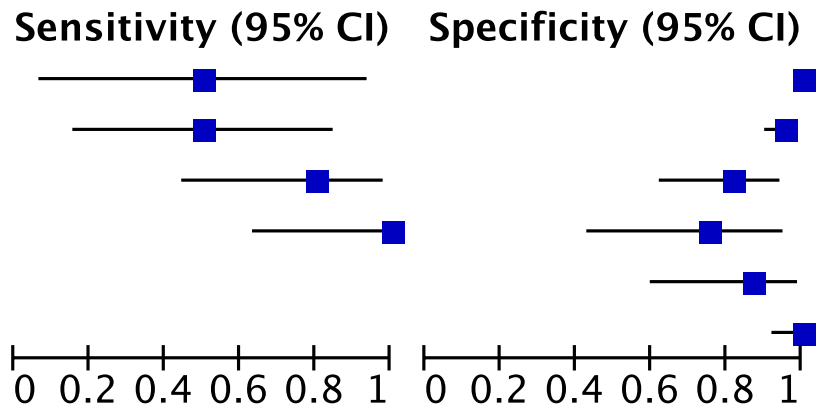
Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged 1 to 4 years against a MRS?

4 studies, 327 participants

Reference Standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage (Median TB prevalence 20%)

Pooled sensitivity: 71.5% (40.0 to 90.4) **| Pooled specificity:** 94.0% (73.8 to 98.9)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
NCT04240990	2	0	2	135	0.50 [0.07, 0.93]	1.00 [0.97, 1.00]
Ssengooba 2020	4	6	4	117	0.50 [0.16, 0.84]	0.95 [0.90, 0.98]
Liu 2021	8	5	2	22	0.80 [0.44, 0.97]	0.81 [0.62, 0.94]
Parigi 2021	8	3	0	9	1.00 [0.63, 1.00]	0.75 [0.43, 0.95]
Jaganath 2021	0	2	0	13	Not estimable	0.87 [0.60, 0.98]
NCT04121026	0	0	0	42	Not estimable	1.00 [0.92, 1.00]



Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged 1 to 4 years against a MRS?

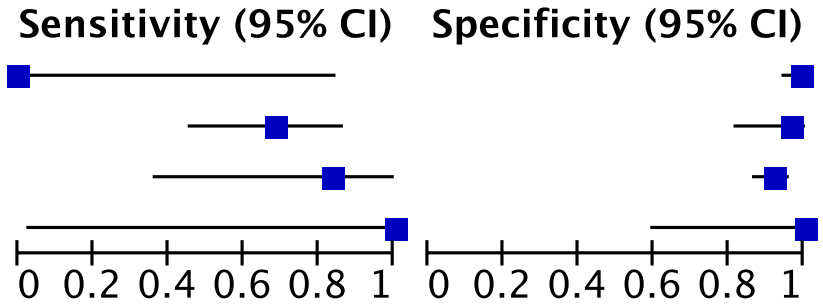
4 studies, 327 participants
Reference standard: Liquid or solid culture on a sputum specimen collected through gastric aspiration or lavage (Median TB prevalence 20%)
Pooled sensitivity: 71.5% (40.0 to 90.4) **| Pooled specificity:** 94.0% (73.8 to 98.9)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1% Typically seen in	Prevalence 10% Typically seen in	Prevalence 20% Typically seen in		
True positives	7 (4 to 9)	72 (40 to 90)	144 (80 to 180)	30 (4)	⨁⨁◯◯ LOW [a]
False negatives	3 (1 to 6)	28 (10 to 60)	56 (20 to 120)		
True negatives	931 (733 to 980)	846 (666 to 891)	752 (592 to 792)	297 (4)	⨁⨁◯◯ LOW [b,c]
False positives	59 (10 to 257)	54 (9 to 234)	48 (8 to 208)		

Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 1 year, against a MRS?

4 studies, 295 participants
Reference Standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median TB prevalence 5%)
Pooled sensitivity: 65.2% (33.7 to 87.3) **| Pooled specificity:** 96.2% (88.9 to 98.7)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
NCT04240990	0	1	2	85	0.00 [0.00, 0.84]	0.99 [0.94, 1.00]
Liu 2021	15	1	7	26	0.68 [0.45, 0.86]	0.96 [0.81, 1.00]
Kabir 2020	5	12	1	132	0.83 [0.36, 1.00]	0.92 [0.86, 0.96]
NCT04121026	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]



Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 1 year, against a MRS?

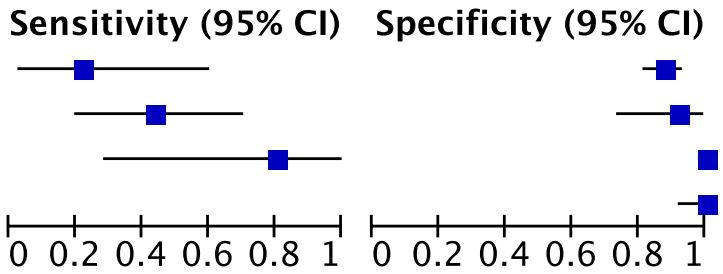
4 studies, 295 participants
Reference standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median TB prevalence 5%)
Pooled sensitivity: 65.2% (33.7 to 87.3) **| Pooled specificity:** 96.2% (88.9 to 98.7)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1% Typically seen in	Prevalence 10% Typically seen in	Prevalence 20% Typically seen in		
True positives	7 (3 to 9)	65 (34 to 87)	130 (68 to 174)	31 (4)	⨁◯◯◯ VERY LOW [a,b]
False negatives	3 (1 to 7)	35 (13 to 66)	70 (26 to 132)		
True negatives	950 (881 to 980)	864 (801 to 891)	768 (712 to 792)	264 (4)	⨁⨁⨁◯ MODERATE [c]
False positives	40 (10 to 109)	36 (9 to 99)	32 (8 to 88)		

Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged 1 to 4 years, against a MRS?

3 studies, 331 participants
Reference Standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median Prevalence 5%)
Pooled sensitivity: 43.3% (27.1 to 61.2) | **Pooled specificity:** 97.1% (74.8 to 99.7)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kabir 2020	2	17	7	120	0.22 [0.03, 0.60]	0.88 [0.81, 0.93]
Liu 2021	7	2	9	22	0.44 [0.20, 0.70]	0.92 [0.73, 0.99]
NCT04240990	4	0	1	140	0.80 [0.28, 0.99]	1.00 [0.97, 1.00]
NCT04121026	0	0	0	41	Not estimable	1.00 [0.91, 1.00]



Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged 1 to 4 years, against a MRS?

3 studies, 331 participants
Reference standard: Liquid or solid culture or Xpert on a respiratory specimen
(Median TB prevalence 5%)
Pooled sensitivity: 43.3% (27.1 to 61.2) | **Pooled specificity:** 97.1% (74.8 to 99.7)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 1% Typically seen in	Prevalence 10% Typically seen in	Prevalence 20% Typically seen in		
True positives	4 (3 to 6)	43 (27 to 61)	86 (54 to 122)	30 (3)	⨁◯◯◯ VERY LOW [a,b]
False negatives	6 (4 to 7)	57 (39 to 73)	114 (78 to 146)		
True negatives	960 (742 to 990)	873 (675 to 900)	776 (600 to 800)	301 (3)	⨁⨁◯◯ LOW [c,d]
False positives	30 (0 to 248)	27 (0 to 225)	24 (0 to 200)		