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20–24 OCTOBER 2020
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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

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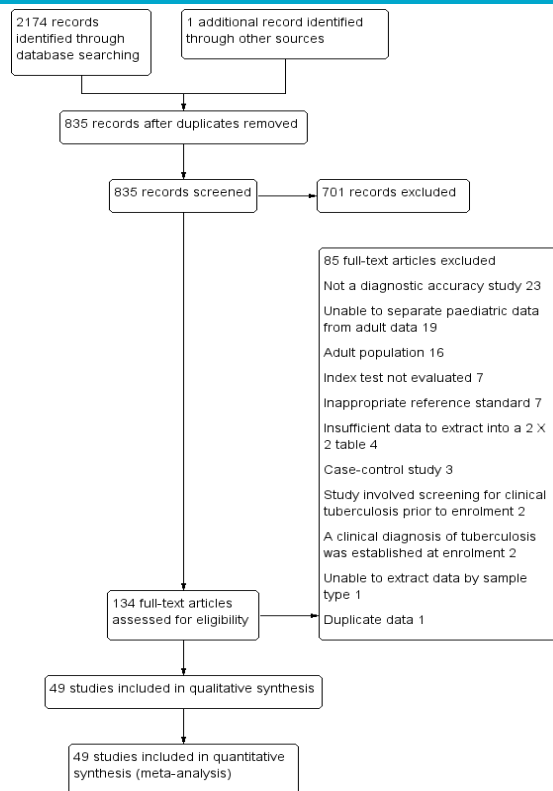
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BACKGROUND

- 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)

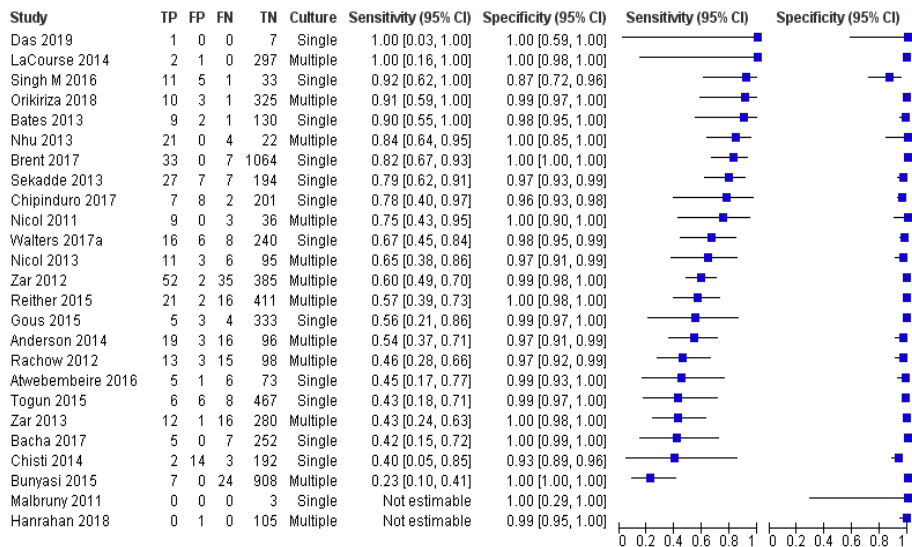
- Sensitivity: 19.7% (95% CI 12.1 to 30.4)
- Specificity: 100% (95% CI 100 to 100)

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)



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)

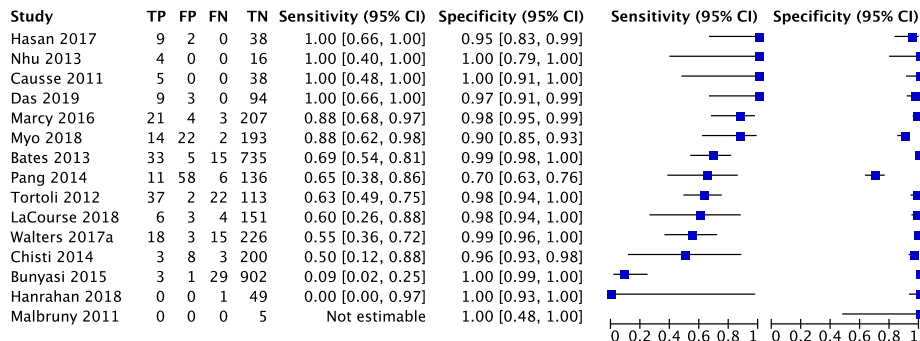
Xpert MTB/RIF against Composite

(6 studies, 933 participants):

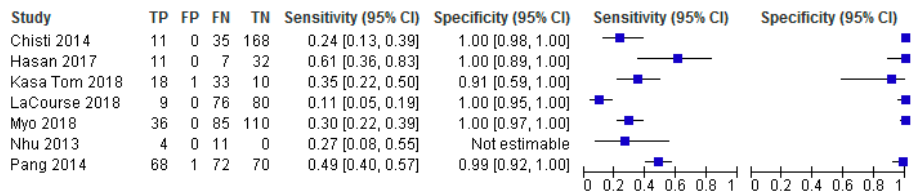
- Sensitivity: 31.7% (95% CI 20.2 to 46.0)
- Specificity: 99.7% (95% CI 97.1 to 100)

* No studies evaluated Xpert Ultra on gastric aspiration

Xpert MTB/RIF, gastric aspirate specimen, culture



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



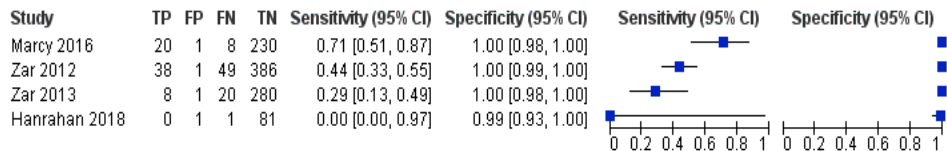
RESULTS: NASOPHARYNGEAL ASPIRATION

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



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):

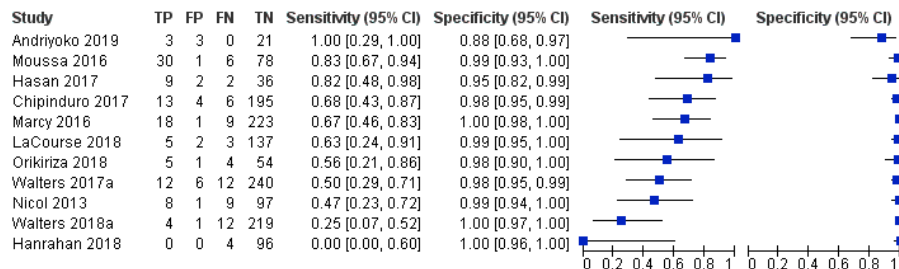
- Sensitivity: 61.5% (95% CI 44.1 to 76.4)
- Specificity: 98.5% (95% CI 97.0 to 99.2)

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

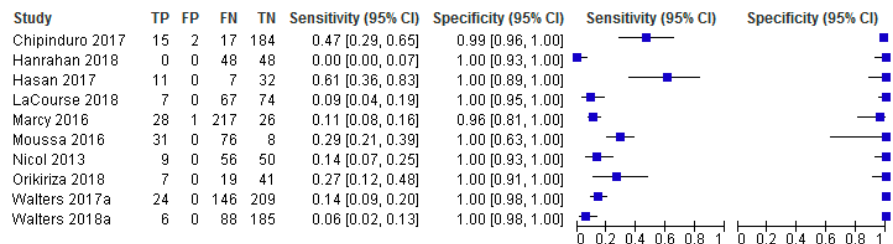
- Sensitivity: 16.3% (95% CI 8.4 to 29.2)
- Specificity: 99.7% (95% CI 97.8 to 100)

**No studies evaluated Xpert Ultra on stool*

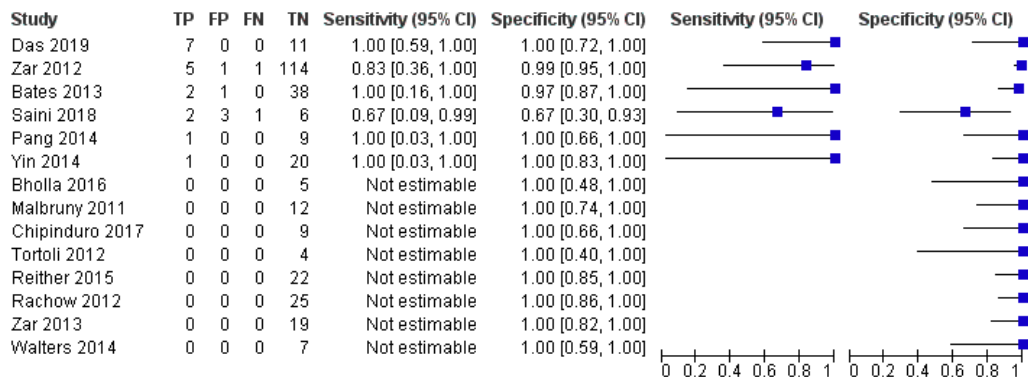
Xpert MTB/RIF, stool, culture



Xpert MTB/RIF, stool, composite reference standard



RESULTS: RIFAMPICIN RESISTANCE



- 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.

ACKNOWLEDGEMENTS

- **Vittoria Lutje** (CIDG) for developing the search strategy.
- **Ryan Vu** (Rice University) who contributed to development of the protocol
- **Mikashmi Kohli** (McGill University) for providing technical expertise
- **Emily Maclean** (McGill University) for providing data on stool analysis
- **Andrew DiNardo** (Baylor College of Medicine) for technical assistance
- **Gemma Villanueva and Hanna Bergman** (Cochrane Response) for assisting with data entry
- **Aakshi Kalra** (FIND), provided data from a large-scale Xpert MTB/RIF demonstration project conducted in India

Thank you

