Screening tests for active pulmonary tuberculosis in children & adolescents: a systematic review

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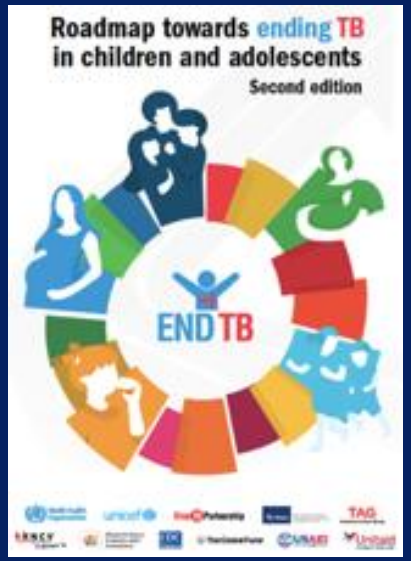
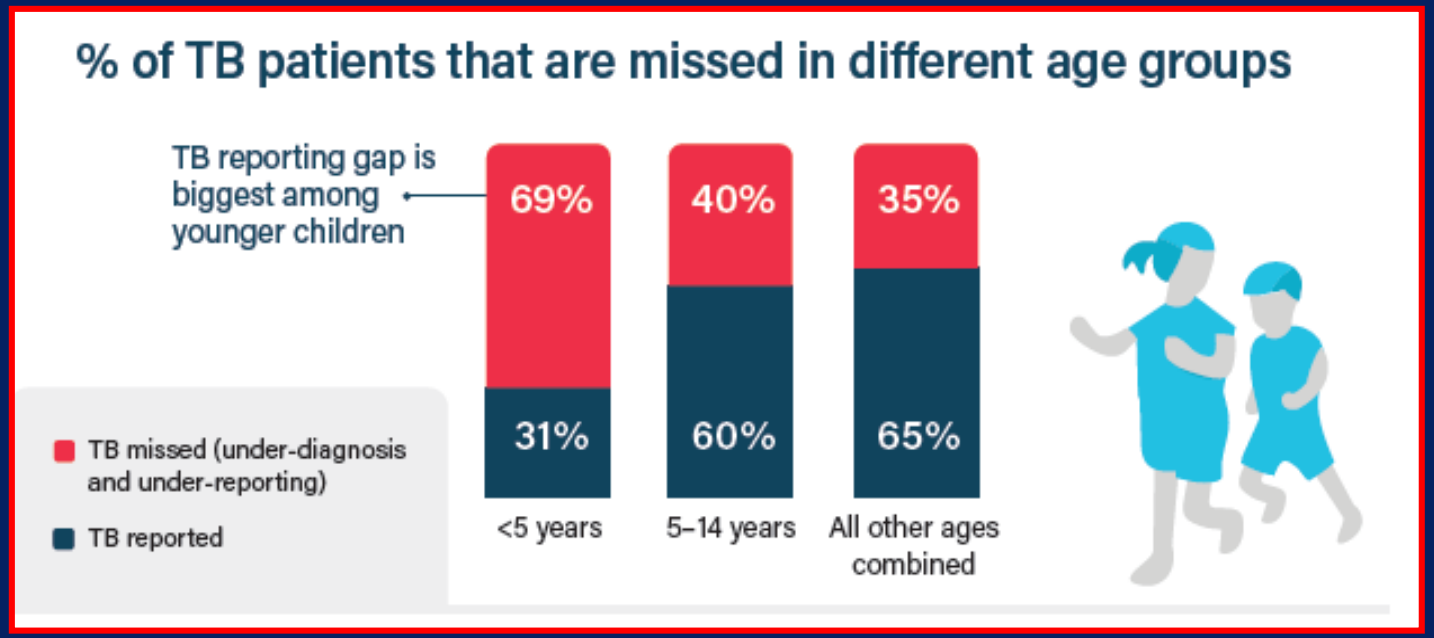
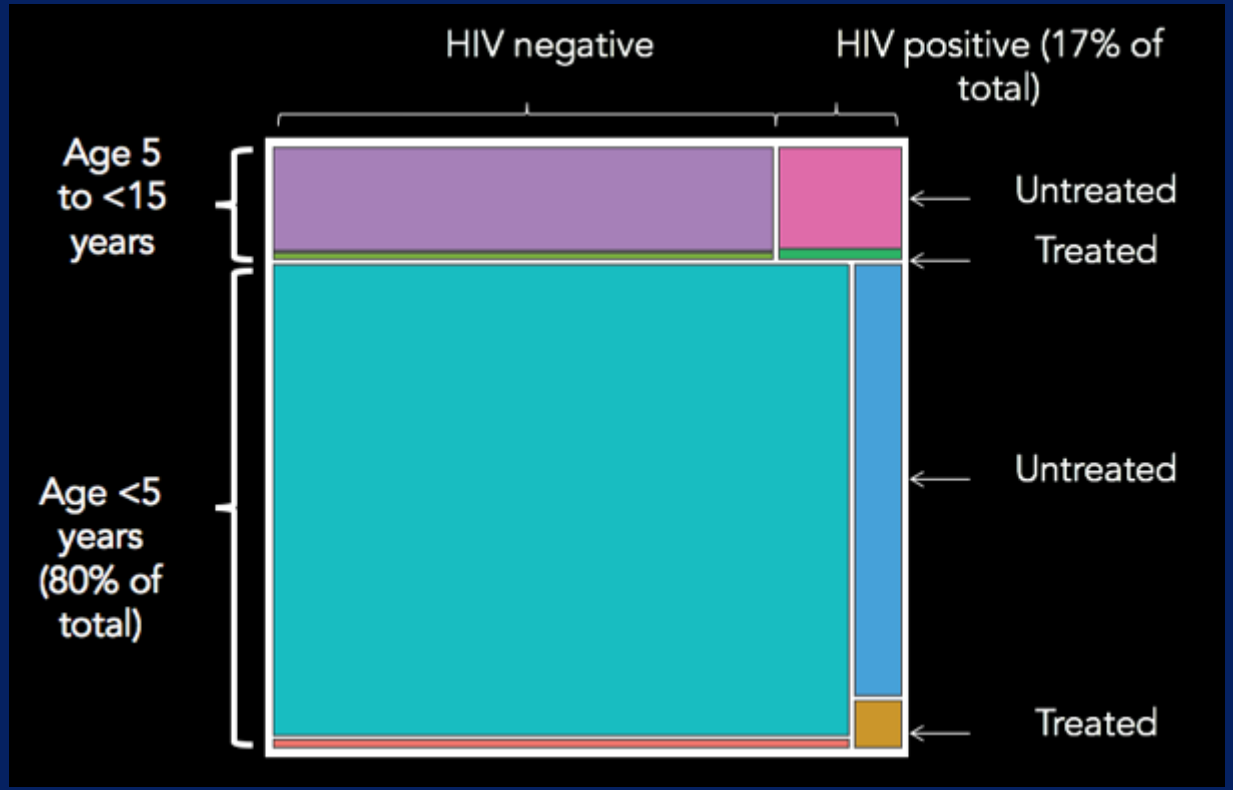

Roadmap towards ending TB
in children and adolescents
Second edition
END TB

Background


% of TB patients that are missed in different age groups
TB reporting gap is biggest among younger children
69%
40%
35%
31%
60%
65%
TB missed (under-diagnosis and under-reporting)
TB reported
<5 years
5–14 years
All other ages combined

Background



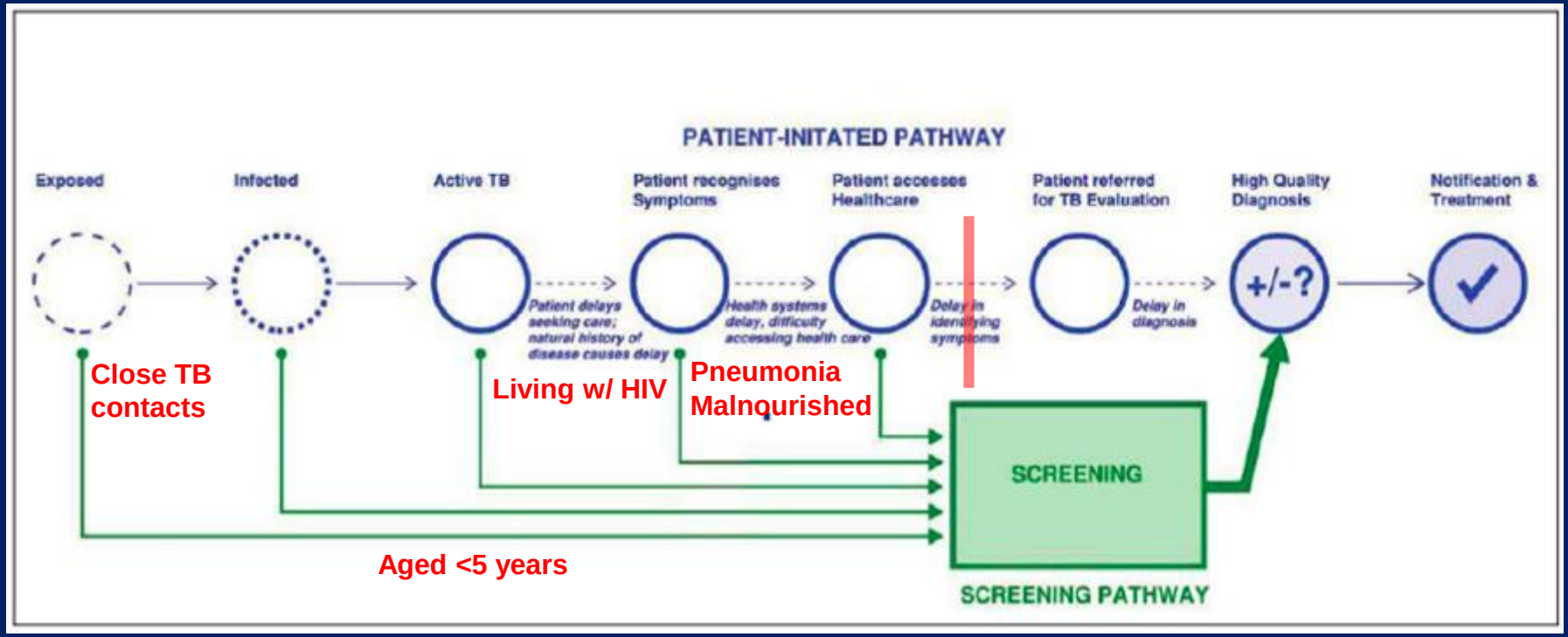
Proportions of estimated 239,000 TB deaths in children aged <15 year in 2015

Dodd PJ, et al. *Lancet Glob Health* 2017;5:e898

Primary Objective:

Determine the accuracy of screening tests for pulmonary tuberculosis in children & adolescents in high-risk groups

Differentiating Screening from Diagnosis



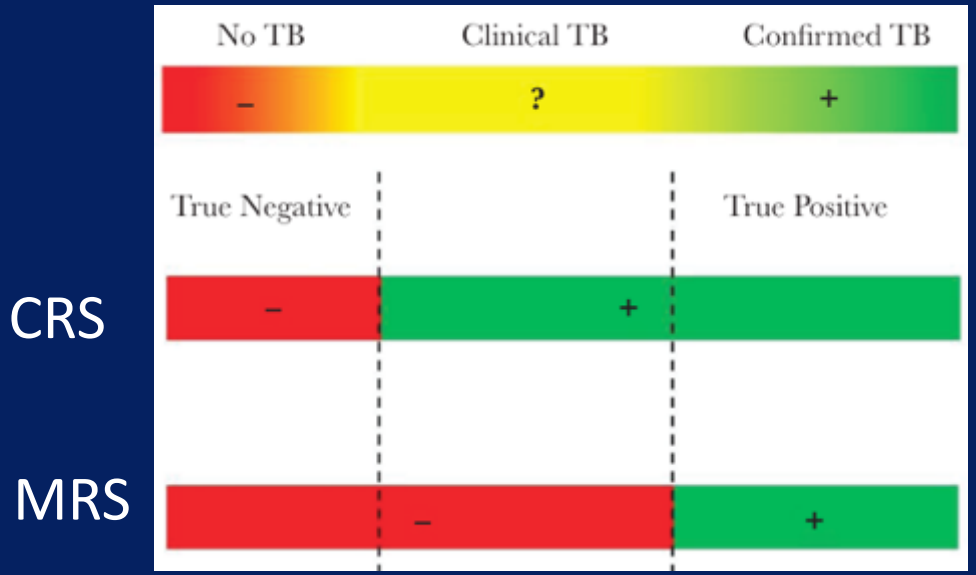
Index Tests

1. **One of multiple symptoms (symptom 'clusters')**
2. **Chest Radiography**
   - Any abnormality
   - Abnormality suggestive of TB
3. **Xpert MTB/RIF**

Reference Standards

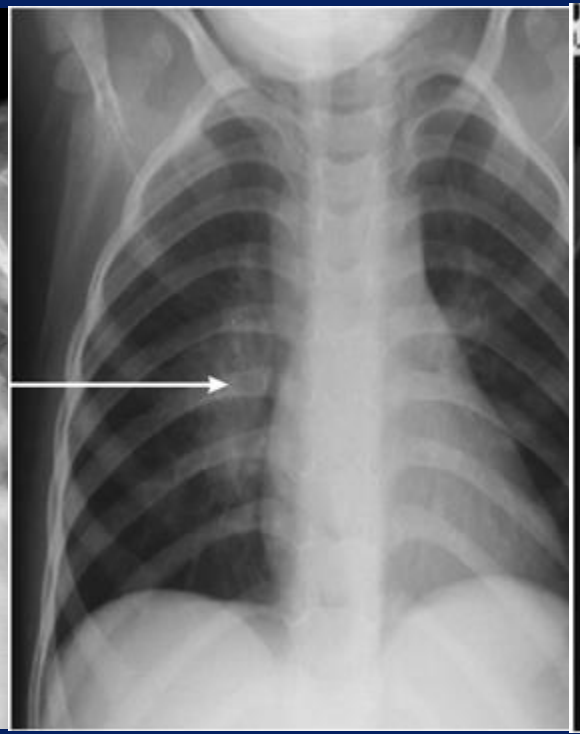
1. **Microbiological (MRS): solid or liquid culture, Xpert MTB/RIF, or Xpert Ultra on a respiratory specimen**
2. **Composite (CRS):**
   - **Microbiological confirmation OR**
   - **Clinically diagnosed pulmonary TB**

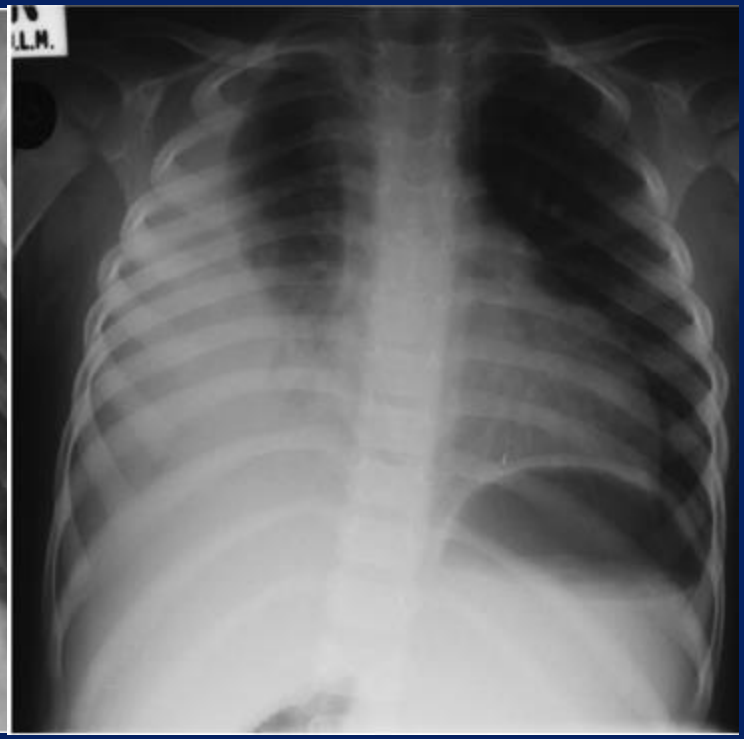
Reference Standards



Adapted from Drain PK, et al. 2019

TB in Children: Chest Radiography





TB in Children: Challenges in Diagnosis

- Respiratory infections in children are common
  - Much overlap with signs, symptoms, and radiographic findings of TB
- Many settings lack CXR or expertise for interpreting CXR
- Microbiological confirmation is complicated by:
  1. Young children can't expectorate sputum
     - Typically rely on gastric lavage or induced sputum
  2. Paucibacillary disease: number of bacilli causing disease in children tends to be low
     - Even when culturing multiple specimens, typically less than half of child TB cases have microbiologic confirmation

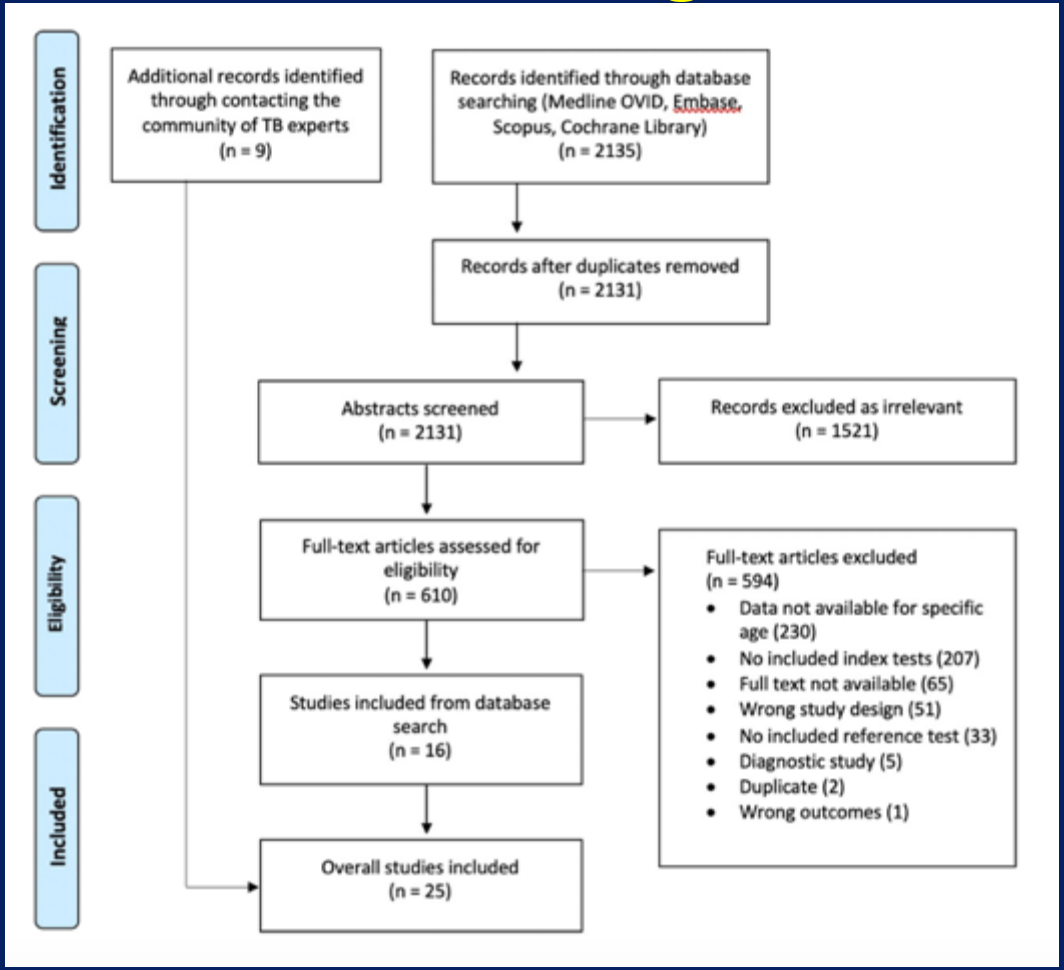
Diagnosis of child TB:

Clinical >> Microbiological

Study Inclusion Criteria

- Study designs: cross-sectional, cohort (retrospective or prospective), RCTs
- Data available for individuals <20 years
- Index test(s) applied with screening, rather than diagnostic, intent
- Index test(s) reported against qualifying MRS or CRS
- If extrapulmonary TB described, must be <20% of cases
- With required reference standards implying pulmonary disease, studies not specifying “pulmonary” TB were included

PRISMA Diagram



Characteristics of 25 Included Studies

First Author	Publication Year	Country or Countries of Sampling	Sampling in High Burden TB Country?
Aggerbeck	2018	South Africa	Yes
Arscott-Mills	2014	Botswana	No
Birungi	2018	Rwanda	No
Chiappini	2019	Italy	No
Clemente	2017	Italy	No
Dorjee	2018	India	Yes
Dreesman	2017	Belgium	No
Jaganath	2013	Uganda	No
Kruk	2008	South Africa	Yes
LaCourse	2014	Malawi	No
Mahomed	2013	South Africa	Yes
Malik	2018	Pakistan	Yes
Marais	2006	South Africa	Yes
Portevin	2014	Tanzania	Yes
PERCH	2019	Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, and Zambia	Majority
Rose	2012	Tanzania	Yes
Sawry	2018	South Africa	No
Schwoebel	2020	Benin, Burkina Faso, Cameroon, & CAR	Only one of four (CAR)
Tieu	2014	Thailand	Yes
Togun	2016	The Gambia	No
Togun	2015	The Gambia	No
Triasih	2015a	Indonesia	Yes
Triasih	2015b	Indonesia	Yes
Ustero	2017	Eswatini (Swaziland)	Yes
Vonasek	2019	Botswana, Eswatini, Lesotho, Malawi, Tanzania, & Uganda	Two of six
	Range: 2006 to 2020	**Sub-Saharan Africa: 17 studies** **Asia: 5 studies** **Europe: 3 studies**	**High-Burden Countries: 15 studies**

PICO Questions Assessed

Population	Index Test/Screen	Reference Standard
General population	TB close contact	Composite
General population	Cough	Composite
All risk groups	Nutrition status	Composite
Accessing healthcare	Xpert MTB/RIF	Microbiological
Accessing healthcare	Nutrition status	Microbiological
Accessing healthcare & < 5 y/o	Suggestive CXR	Composite
Accessing healthcare & < 5 y/o	Cough, fever, or decreased playfulness	Composite
TB close contacts	Abnormal CXR	Composite
TB close contacts	Suggestive CXR	Composite
TB close contacts	Nutrition status	Composite
TB close contacts	Cough, fever, or poor weight gain	Composite
HIV outpatients	ICF symptom screen	Composite
Active pneumonia & <5 y/o	Abnormal CXR	Microbiological

Index Test: Chest radiography with any abnormality

Reference Standard: composite

Population: children and adolescent close TB contacts

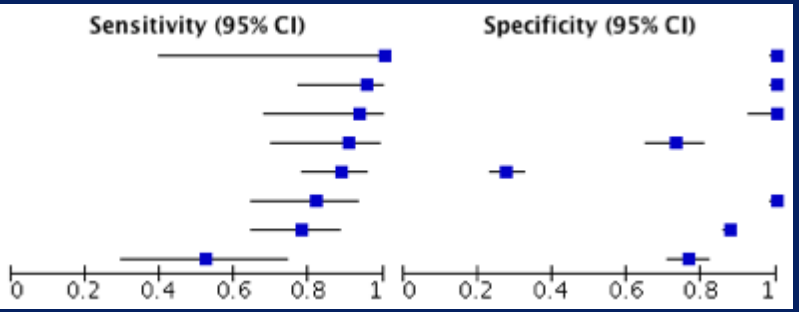
8 studies, 3513 individuals

Prevalences: 2% to 25%

Pooled sensitivity: 0.87 (0.75 to 0.93)

Pooled specificity: 0.98 (0.68 to 1.00)

Study	TP	FP	FN	TN	High TB burden	Sensitivity (95% CI)	Specificity (95% CI)
Birungi 2018	4	0	0	212	No	1.00 [0.40, 1.00]	1.00 [0.98, 1.00]
Clemente 2017	21	0	1	224	No	0.95 [0.77, 1.00]	1.00 [0.98, 1.00]
Dreesman 2017	14	0	1	46	No	0.93 [0.68, 1.00]	1.00 [0.92, 1.00]
Tieu 2014	19	36	2	98	Yes	0.90 [0.70, 0.99]	0.73 [0.65, 0.80]
Togun 2016	55	303	7	117	No	0.89 [0.78, 0.95]	0.28 [0.24, 0.32]
Kruk 2008	27	0	6	219	Yes	0.82 [0.65, 0.93]	1.00 [0.98, 1.00]
Schwoebel 2020	42	223	12	1559	Partially	0.78 [0.64, 0.88]	0.87 [0.86, 0.89]
Triasih 2015b	11	57	10	187	Yes	0.52 [0.30, 0.74]	0.77 [0.71, 0.82]



Index Test: WHO-recommended four-symptom screen

Reference Standard: composite

Population: children and adolescents living with HIV

Adults and adolescents living with HIV and screened for TB with a clinical algorithm and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

Strong recommendation, moderate quality of evidence

Children living with HIV who have any one of the following symptoms – poor weight gain*, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and

Strong recommendations, low quality of evidence

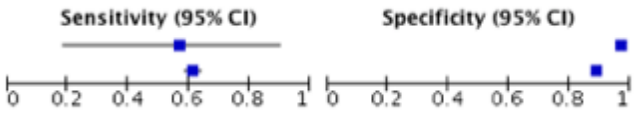
2 studies; 20,926 individuals; 203,135 screens

Prevalences: 3% and 7%

Pooled sensitivity: 0.61 (0.58 to 0.64)

Pooled specificity: 0.94 (0.86 to 0.98)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sawry 2018	4	41	3	1295	0.57 [0.18, 0.90]	0.97 [0.96, 0.98]
Vonasek 2020	742	22481	470	178099	0.61 [0.58, 0.64]	0.89 [0.89, 0.89]



Going Forward

- **Ongoing dissemination of findings**
- **WHO TB Screening guideline update**
- **Systematic review of TST & IGRA to screen for active TB**
- **Overall limited research evaluating TB screening in children; future studies should:**
  - **Use both composite & microbiologic reference standards**
  - **Apply the reference standard to all, not just those with positive screens**
  - **Assess sequential and parallel strategies utilizing complementary strategies (eg. symptom screen→CXR)**

Acknowledgements

- Support from:
  - Liverpool School of Tropical Medicine
  - Department for International Development (DFID)
  - WHO Global TB Programme
- Vittoria Lutje of the Cochrane Infectious Disease Group
- Annemieke Brands, Dennis Falzon, Tamara Kredo, Cecily Miller, and Sabine Verkuijl of the WHO
- Child and Adolescent TB Working Group