



# Screening for active TB in children: a systematic review

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## BACKGROUND

- Globally, ~225,000 children <15 years died from TB in 2019
- Given challenges in case finding, the large majority of children that die from TB are never even diagnosed
- Effective screening could **enhance case finding** to improve:
  - Outcomes for individuals
  - TB control in populations
- Screening that effectively rules out active TB could be leveraged to **expand access to TB preventive treatment**
- The WHO's End-TB strategy emphasizes systematic screening of high-risk groups of children:
  - TB close contacts
  - Children living with HIV
  - Children with wasting or edematous malnutrition
  - Children with pneumonia

## METHODS

**Objective:** Estimate accuracy of screening tests for pulmonary tuberculosis (TB) in high-risk groups of children and those accessing healthcare

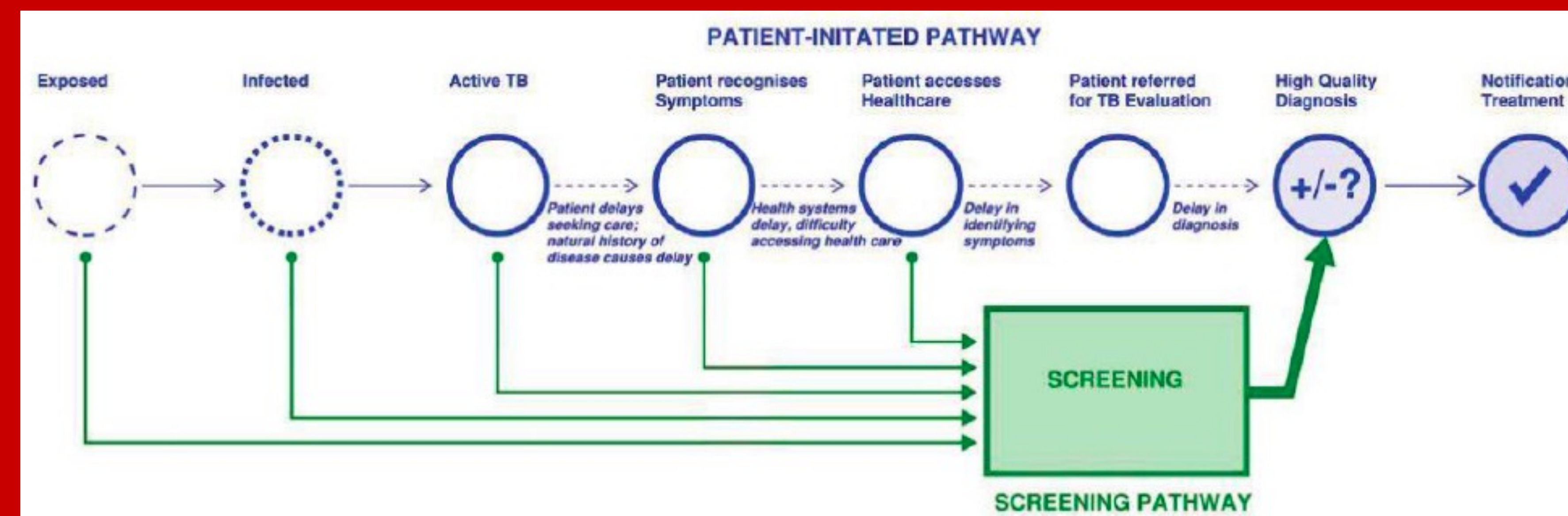
**Study Design:** Systematic review & meta-analysis

**Study Selection Criteria:**

- Cross-sectional and cohort studies
- >75% of children under 15 years of age
- Index tests done for screening rather than diagnosis
- Included index tests:
  - symptom(s) screening,
  - chest radiography (CXR), or
  - Xpert MTB/RIF or Ultra
- Included reference standards:
  - Composite—clinical or microbiologic diagnosis
  - Microbiologic diagnosis

**Data Collection and Analysis:**

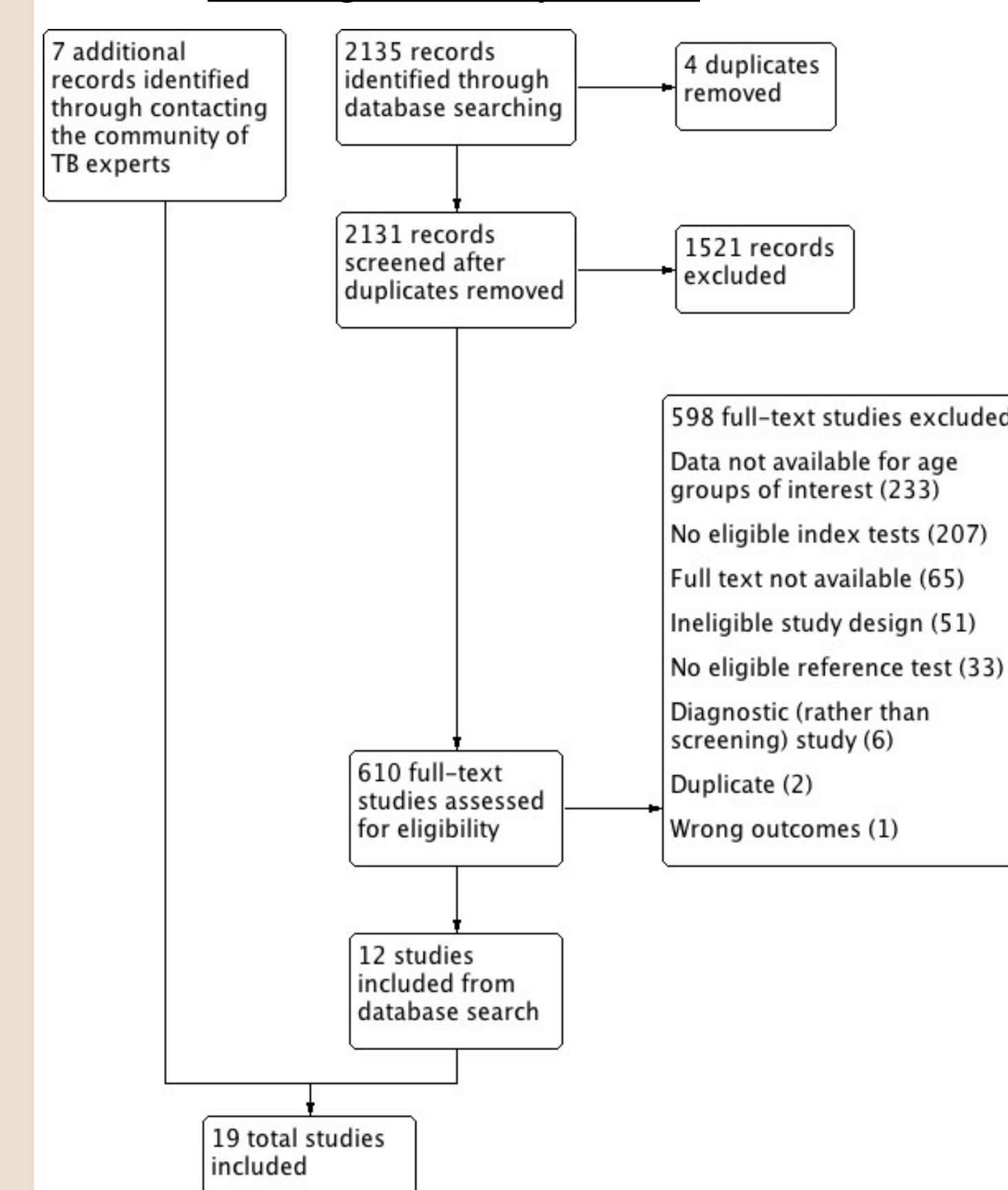
- At least two review authors—
  - Independently selected studies for inclusion
  - Independently extracted data
  - Assessed study quality using QUADAS-2
- Consolidated symptom screens into groups that used similar combinations of symptoms
- Performed analyses separately by reference standard
- Estimated pooled sensitivity and specificity with 95% confidence intervals using a bivariate model
- Assessed certainty of evidence using GRADE



- Overall, there is a **striking lack of quality evidence** describing strategies to screen for TB in high-risk populations of children.
- Limited evidence demonstrates **symptom screening & CXR may be useful in high-risk children** (TB contacts & those living w/ HIV).

## RESULTS

### Flow Diagram of Study Selection



### Summary of Findings for Selected Analyses

Population of Children and Adolescents	Index Test	Reference Standard	Studies	TB Prevalence	Number of Children (TB cases)	Sensitivity (95% CI)	Specificity (95% CI)
Close TB contacts	One or more of cough, fever, or poor weight gain	CRS	4	2% to 13%	2695 (113)	89% (52 to 98)	69% (51 to 83)
Inpatient or outpatient settings, < 5 years	One or more of cough, fever, or decreased playfulness	CRS	3	2% to 13%	2445 (106)	64% to 76%*	37% to 77%*
Outpatients living with HIV	One or more of cough, fever, poor weight gain, or TB close contact (WHO four-symptom screen) done at each healthcare visit	CRS	2	3% and 8%	203,135 (1219)**	61% (58 to 64)	94% (86 to 98)
Close TB contacts	Undernutrition	CRS	3	10% to 13%	1399 (162)	21% (11 to 38)	85% (71 to 93)
Inpatient or outpatient settings	Undernutrition	CRS	5	10% to 34%	1723 (233)	32% (18 to 50)	75% (56 to 88)
Inpatient or outpatient settings	Undernutrition	MRS	2	4% to 16%	561 (39)	48% to 67%*	62% to 72%*
Close TB contacts	Abnormal CXR	CRS	8	2% to 25%	3513 (232)	87% (75 to 93)	99% (68 to 100)
Close TB contacts	Suggestive CXR	CRS	4	2% to 13%	2550 (113)	84% (70 to 92)	91% (90 to 92)
Inpatient or outpatient settings, < 5 years	Suggestive CXR	CRS	3	2% to 13%	2388 (110)	87% (66 to 96)	89% (88 to 90)
Inpatients with pneumonia, < 5 years	Abnormal CXR	MRS	1	1%	3540 (28)	86% (67 to 96)	56% (54 to 58)
Inpatient or outpatient settings	Xpert MTB/RIF	MRS	2	1% and 4%	787 (16)	43% to 100%*	98% to 99%*
Inpatient or outpatient settings	Xpert MTB/RIF	CRS	2	7% and 13%	787 (84)	9% to 19%*	100% to 100%*

Abbreviations: CI: confidence interval; CRS: composite reference standard; CXR: chest radiography; ICF: WHO-recommended intensified case finding four-symptom screen; MRS: microbiological reference standard; TB: tuberculosis

\*Reported as range from studies as meta-analysis did not converge and pooled estimates could not be obtained

\*\*Reported as: number of screens (cases)

## CONCLUSIONS

- Symptom screens:**
  - One or more of cough, fever, or poor weight gain in TB contacts had the highest sensitivity; though specificity was low
  - The WHO four-symptom screen in children living w/ HIV had the highest specificity
- CXR** screening against the composite reference standard had high accuracy, though there was strong concern for incorporation bias
- Xpert MTB/RIF** demonstrated high specificity; estimation of sensitivity was limited by few cases
- Accurate and feasible screening tests for active TB in children are lacking and urgently needed

## ADDITIONAL RESULTS

### Symptom Screening: selected forest plots

One or more of cough, fever, or poor weight gain, close TB contacts, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Birungi 2018	4	33	0	173	1.00 [0.40, 1.00]	0.84 [0.79, 0.89]
Triasih 2015a	21	77	0	171	1.00 [0.84, 1.00]	0.69 [0.63, 0.75]
Kruk 2008	25	51	8	168	0.76 [0.58, 0.89]	0.77 [0.71, 0.82]
Schwoebel 2020	35	1150	20	753	0.64 [0.50, 0.76]	0.40 [0.37, 0.42]

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kruk 2008	25	51	8	168	0.76 [0.58, 0.89]	0.77 [0.71, 0.82]
Aggerbeck 2018	12	136	6	81	0.67 [0.41, 0.87]	0.37 [0.31, 0.44]
Schwoebel 2020	35	1150	20	753	0.64 [0.50, 0.76]	0.40 [0.37, 0.42]

WHO four-symptom screen, outpatients living with HIV, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Vonasek 2021	742	22481	470	178099	0.61 [0.58, 0.64]	0.89 [0.89, 0.89]
Sawry 2018	4	41	3	1295	0.57 [0.18, 0.90]	0.97 [0.96, 0.98]

### CXR Screening: selected forest plots

CXR abnormal, close TB contacts, composite

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	1553	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]

CXR abnormal, < 5 y/o hospitalised with pneumonia, microbiological

Study	TP	FP	FN	TN	High TB burden	Sensitivity (95% CI)	Specificity (95% CI)
PERCH 2019	24	1547	4	1965	Majority	0.86 [0.67, 0.96]	0.56 [0.54, 0.58]

### Xpert MTB/RIF Screening: selected forest plots

Xpert MTB/RIF, inpatient or outpatient, microbiological

Study	TP	FP	FN	TN	High TB burden	Sensitivity (95% CI)	Specificity (95% CI)
LaCourse 2014	2	1	0	297	No	1.00 [0.16, 1.00]	1.00 [0.99, 1.00]
Togun 2015	6	6	8	467	No	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]

Xpert MTB/RIF, inpatient or outpatient, composite

Study	TP	FP	FN	TN	High TB burden	Sensitivity (95% CI)	Specificity (95% CI)
Togun 2015	12	0	50	425	No	0.19 [0.10, 0.31]	1.00 [0.99, 1.00]
LaCourse 2014	2	1	20	277	No	0.09 [0.01, 0.29]	1.00 [0.98, 1.00]

### Summary of risk of bias and applicability concerns as assessed using QUADAS-2.

