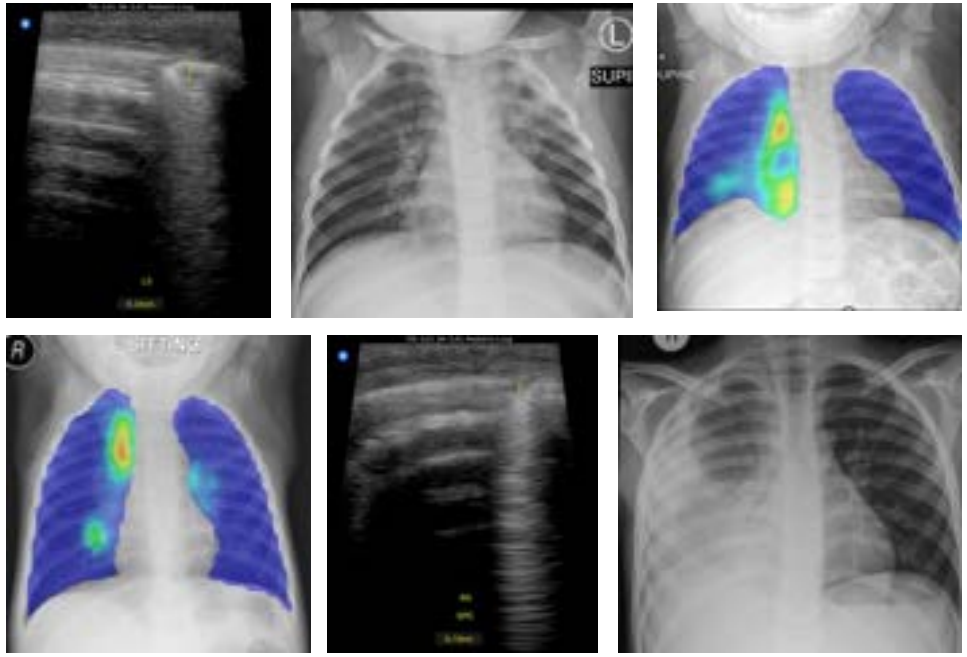
NOVEL APPROACHES TO IMAGING IN PAEDIATRIC TB: APPLICATION TO CLINICAL TRIALS



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Overview

- First line imaging
  - **Chest x-ray**
  - Lung ultrasound
- CXR CAD
- Advanced imaging
  - CT, MRI, PET
  - Bronchoscopy, EBUS

Focus on CXR and CXR CAD & use in the clinical trial context

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CHEST X-RAY: context

- Most widely used and available global imaging modality for TB

- Recognised limitations
  - 2D representation of 3D space
  - Sensitivity and specificity are suboptimal
  - Lack of standard terminology and definitions
  - Intra- and inter-reader variability

- Accessible, available and useful tool within clinical trials globally

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CHEST X-RAY: context

- Traditional role with new applications:
  - CXR as a **diagnostic tool** in symptomatic children
  - CXR as a **screening tool** in children with TB exposure and/or TB infection
  - CXR for **disease severity stratification**
  - (CXR for treatment response monitoring)

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CXR on paediatric TB trials

Entry points

End points

Enrolment → **Outcome**

CXR as a **diagnostic** tool

CXR as a **screening** tool

CXR for **disease severity stratification**

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CXR on paediatric TB trials

Entry points	End points
Diagnostic studies, TB Rx trials • Screen ‘in’ active TB disease	IMPAACT P1108, 2005, 2034
TB prevention trial • Screen ‘out’ active TB disease	A5300/P2003 (Phoenix)
TB Rx shortening trials • Screen ‘out’ severe TB disease	SHINE SMILE 4: SMART4TB

Enrolment → **Outcome**

CXR as a **diagnostic** tool

CXR as a **screening** tool

CXR for **disease severity stratification**

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CXR on paediatric TB trials

Entry points		End points
Diagnostic studies, TB Rx trials • Screen ‘in’ active TB disease	IMPAACT P1108, 2005, 2034	Diagnostic studies, TB Rx trials • ‘Treatment response marker’
TB prevention trial • Screen ‘out’ active TB disease	A5300/P2003 (Phoenix)	
TB Rx shortening trials • Screen ‘out’ severe TB disease	SHINE SMILE 4: SMART4TB	TB prevention trials, vaccine trials, TB Rx shortening trials • Incident TB

Enrolment → **Outcome**

CXR as a **diagnostic** tool

CXR as a **screening** tool

CXR for **disease severity stratification**

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Utility of CXR on paediatric TB trials

- Real-time interpretation by on-site clinicians
  - Eligibility
  - Investigating end-points
  - Clinical care (treatment response, alternative diagnoses)

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Utility of CXR on paediatric TB trials

- Real-time interpretation
  - Eligibility
  - Investigating end-points
  - Clinical care
- Retrospective interpretation
  - Characterizing trial cohort
  - Classifying end-points
  - Analysis

Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update

Stephen M. Graham, Luis E. Cuevas, Patrick Jean-Philippe, Renee Browning, Martina Casenghi, Anne K. Detjen, Devasena Gnanashanmugam, Anneke C. Hesseling, Beate Kampmann, Anna Mandalakas, Ben J. Marais, Marco Schito, Hans M. L. Spiegel, Jeffrey R. Starke, Carol Worrell, and Heather J. Zar

Unconfirmed tuberculosis	Bacteriological confirmation NOT obtained AND at least 2 of the following:
	• Symptoms/signs suggestive of tuberculosis (as defined)
	• Chest radiograph consistent with tuberculosis
	• ~~Close tuberculosis exposure or immunologic~~ evidence of *M. tuberculosis* infection
	• Positive response to tuberculosis treatment (requires documented positive clinical response on tuberculosis treatment—no time duration specified)
	- With *M. tuberculosis* infection
	  • Immunological evidence of *M. tuberculosis* infection (TST and/or IGRA positive)
	- Without *M. tuberculosis* infection
	  • No immunological evidence of *M. tuberculosis* infection

CHEST X-RAY: diagnostic tool

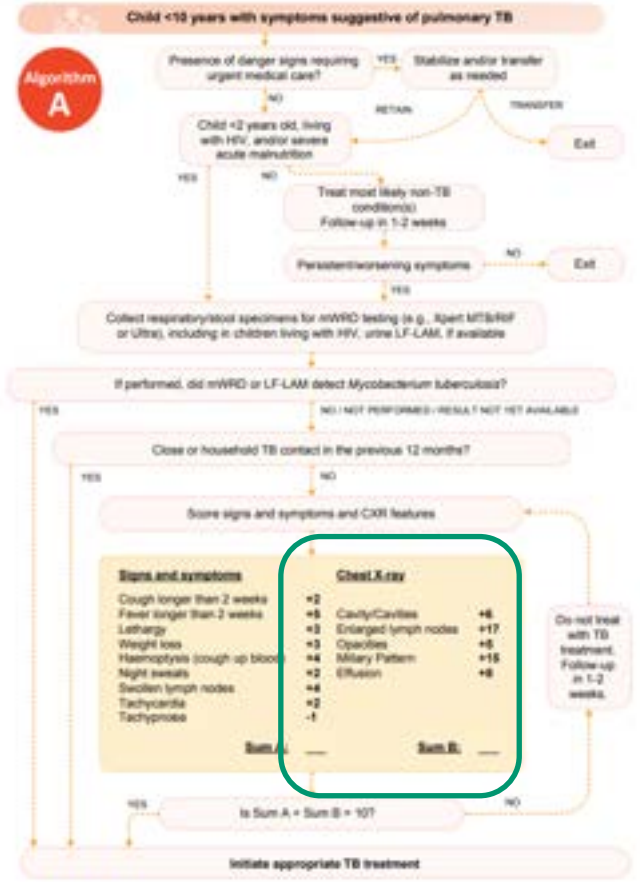
WHO consolidated guidelines on tuberculosis

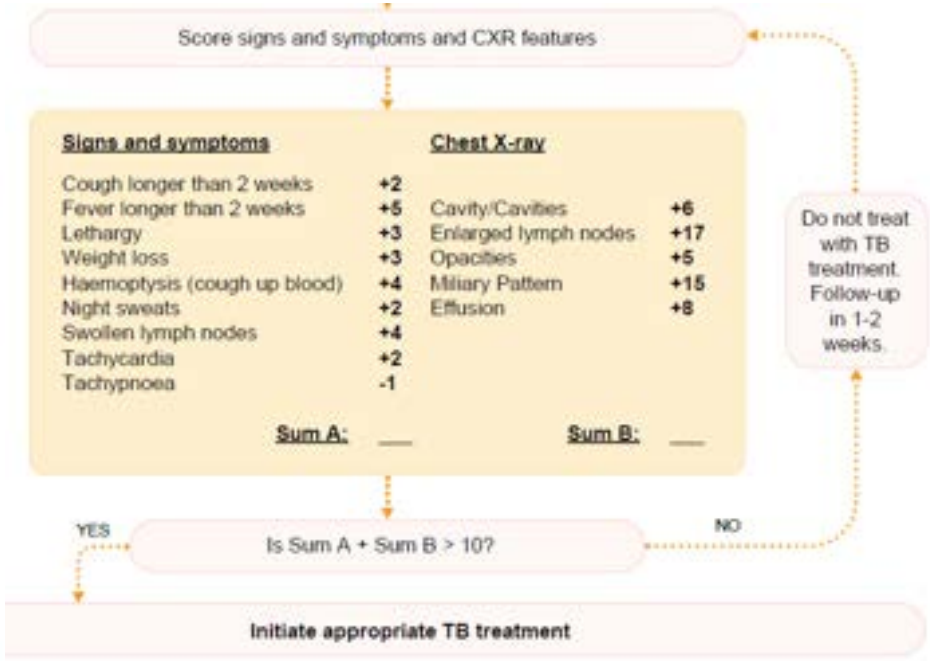
Module 5: Management of tuberculosis in children and adolescents

WHO operational handbook on tuberculosis

Module 5: Management of tuberculosis in children and adolescents

Figure A5.1. Algorithm A (for settings with chest X-ray) and Algorithm B (for settings without chest X-ray)





- Treatment Decision Algorithms include CXR features in the scoring step

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Value of chest X-ray in TB diagnosis in HIV-infected children living in resource-limited countries: the ANRS 12229-PAANTHER 01 study

L. Berteloot,* O. Marcy,†‡ B. Nguyen,§ V. Ung,¶# M. Tejiokem,** B. Nacro,†† S. Goyet,† B. Dim,† S. Blanche,‡‡ L. Borand,† P. Msellati,§§ C. Delacourt,¶¶ for the ANRS 12229 PAANTHER 01 Study Group

Table 3 Diagnostic accuracy of CXR features as determined by final consensus (case-control subanalysis)

	Sensitivity* *n/N* (%) (95%CI)	Specificity* *n/N* (%) (95%CI)	ODA %	*P* value
CXR consistent with TB	35/49 (71.4) (58.8–84.1)	74/148 (50.0) (41.9–58.1)	55.3	0.0089
Agreement on presence and site of:*				
Ghon focus	0/51 (0) (0.0–7.0)	150/151 (99.3) (98.0–100.0)	74.3	1.0000
Alveolar opacities	21/50 (42.0) (28.3–55.7)	97/150 (64.7) (57.0–72.3)	59.0	0.3978
Miliary	6/51 (11.8) (2.9–20.6)	149/151 (98.7) (96.9–100.0)	76.7	0.0037
Nodular opacities	9/51 (17.6) (7.2–28.1)	143/151 (94.7) (91.1–98.3)	75.2	0.0155
Excavation	2/51 (3.9) (0.0–9.2)	150/151 (99.3) (98.0–100.0)	75.2	0.1576
Paratracheal lymph nodes	3/51 (5.9) (0.0–12.3)	145/151 (96.0) (92.9–99.1)	73.3	0.6947
Peri-hilar lymph nodes	19/50 (38.0) (24.5–51.5)	106/151 (70.2) (62.9–77.5)	62.2	0.2808
Tracheal compression	1/51 (2.0) (0.0–5.8)	150/150 (100) (97.6–100.0)	75.1	0.2537
Bronchial compression	0/51 (0) (0.0–7.0)	147/150 (98.0) (95.8–100.0)	73.1	0.5725
Pleural effusion	3/51 (5.9) (0.0–12.3)	145/151 (96.0) (92.9–99.1)	73.3	0.6947
Gibbus	0/51 (0) (0.0–7.0)	151/151 (100) (97.6–100.0)	74.8	NA

Cochrane Library

Cochrane Database of Systematic Reviews

CHEST X-RAY: screening tool

Screening tests for active pulmonary tuberculosis in children (Review)

Vonasek B, Ness T, Takwoingi Y, Kay AW, van Wyk SS, Ouellette L, Marais BJ, Steingart KR, Mandalakas AM

Setting: inpatient and outpatient

Patients/population: children with close tuberculosis contacts

Index test: abnormal chest radiography

Role: an initial test

Threshold for index tests: author defined and implicit as utilized by the chest radiography reader

Reference standard: composite

Estimation (95% CI)	Number of participants (studies); % with pulmonary TB	Test result	Number of results per 1000 participants tested (95% CI)			Certainty of the evidence (GRADE)
			Prevalence 0.5%	Prevalence 5%	Prevalence 10%	
Pooled sensitivity 87% (75% to 93%)	232 (8); 2% to 25%	True positives	4 (4 to 5)	44 (38 to 47)	87 (75 to 93)	⊕⊕⊖⊖ **Low** [a,b,c]
		False negatives	1 (0 to 1)	6 (3 to 12)	13 (7 to 25)	
Pooled specificity 99% (68% to 100%)	3281 (8)	True negatives	975 (677 to 985)	931 (646 to 941)	882 (612 to 891)	⊕⊕⊖⊖ **Low** [a,d,e]
		False positives	20 (10 to 318)	19 (9 to 304)	18 (9 to 288)	

CI: confidence interval; **TB:** tuberculosis.

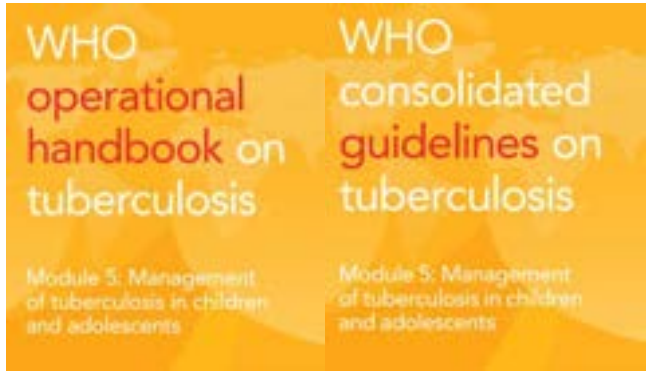
CHEST X-RAY: disease severity stratification

- Treatment shortening

- In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

NEW: Strong recommendation, moderate certainty of evidence

- *Relevance for treatment shortening trials*



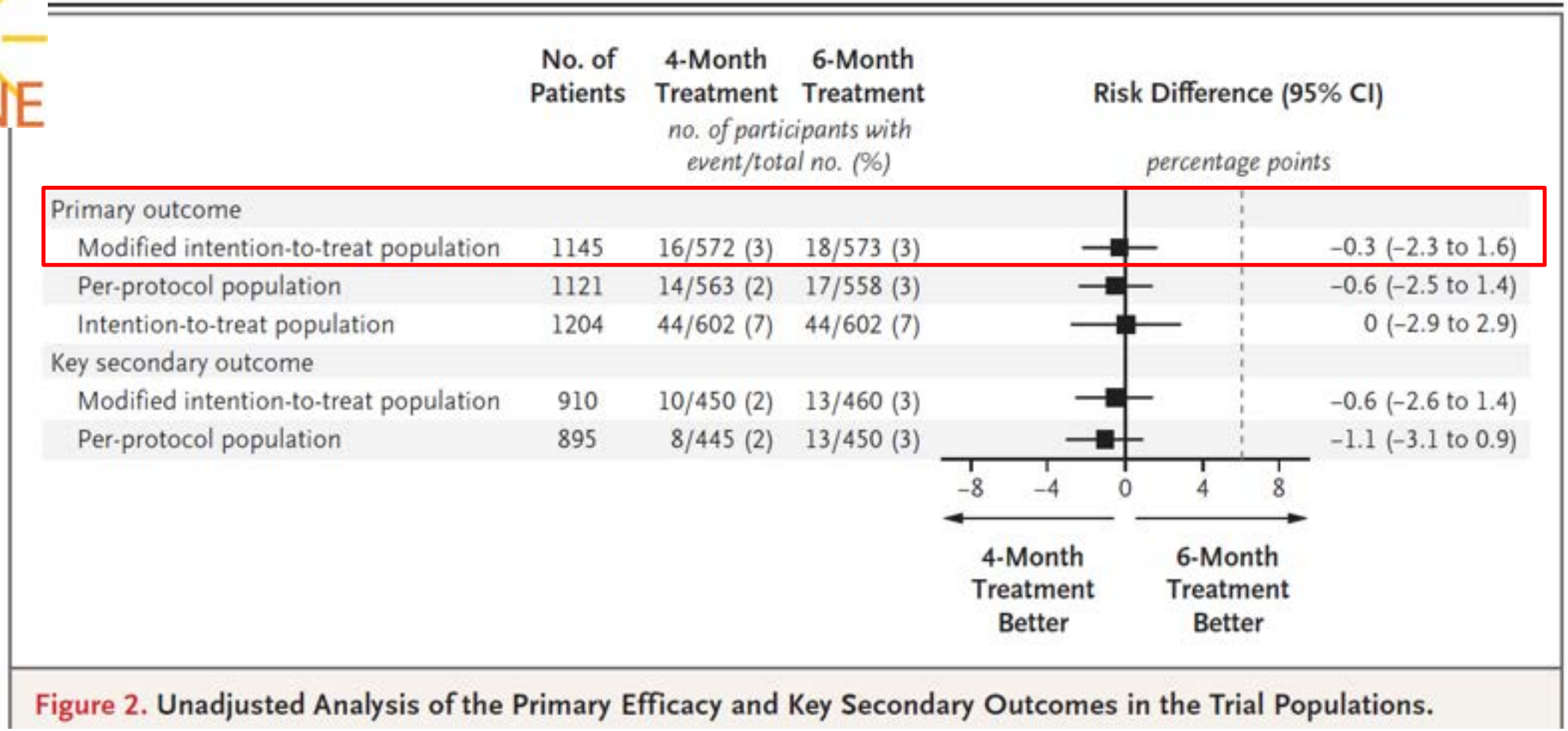


Figure 2. Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

- Definition of non-severe pulmonary TB based largely on CXR findings

The NEW ENGLAND JOURNAL of MEDICINE
MARCH 10, 2022

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

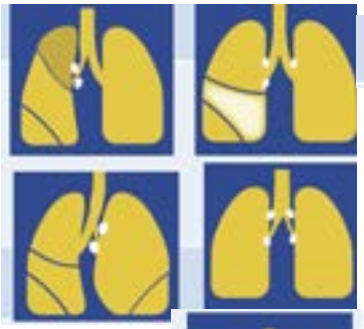
Non-severe

Uncomplicated lymph node disease

Consolidation <1 lobe

Simple pleural effusion

Severe



Complicated lymph node disease

Any consolidation ≥1 lobe

Complicated pleural effusion

Miliary infiltrates

Cavities

Lessons from SHINE

- On-site clinicians interpreted CXRs from all 1204 children enrolled in real time
- 1174 (98%) available for expert review

Table. Inter-reader agreement (2 expert readers):

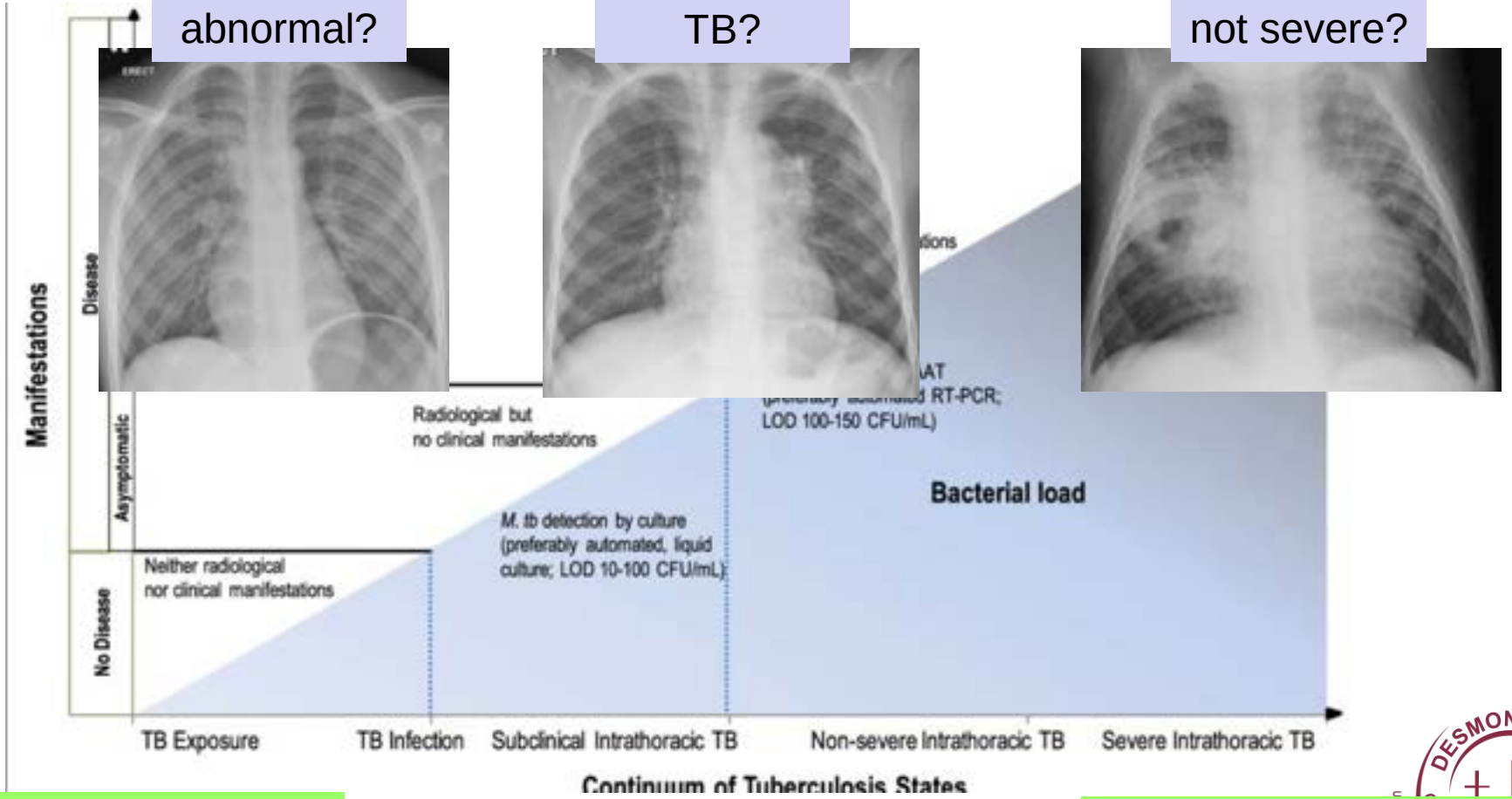
Palmer, in progress

More nuanced approach to CXR classification

Normal vs abnormal?

TB vs not TB?

Severe vs not severe?



TB prevention trial
- Screen ‘out’ active TB disease

Diagnostic studies, TB Rx trials
- Screen ‘in’ active TB disease

TB Rx shortening trials
- Screen ‘out’ severe TB disease

AI: CXR computer aided detection “CAD”

- Potential benefits
  - Eliminates inter-reader variability
  - Access to ‘expert’ read when a human expert is not available
  - Immediate result
  - Can choose your CAD threshold
  - Particularly useful for clinical trials?

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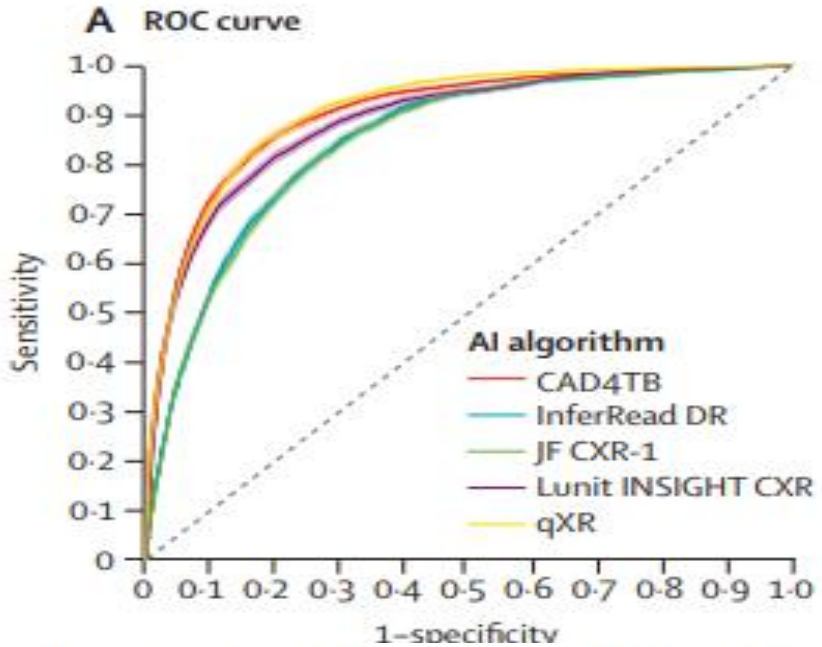
AI: CXR computer aided detection "CAD"

- CAD recommended for use for screening and triage in persons >15 years, WHO 2021

	Threshold abnormality score*	Sensitivity*	Specificity	PPV	NPV	Absolute difference between AI and radiologists reading†		
						Specificity	PPV	NPV
Binary classification A								
Radiologists	..	38·9% (37·3 to 40·5)	88·9% (88·5 to 89·4)	39·1% (37·5 to 40·7)	89·0% (88·5 to 89·4)	..	..	..
AI algorithm								
CAD4TB‡	0·98	..	97·8% (97·6 to 98·0)	76·2% (74·2 to 78·1)	89·8% (89·4 to 90·2)	8·9% (8·4 to 9·4)	37·1% (36·2 to 38·0)	0·8% (0·2 to 1·4)
InferRead DR	0·79	..	94·2% (93·8 to 94·5)	54·9% (52·9 to 56·8)	89·4% (89·0 to 89·8)	5·2% (4·7 to 5·8)	15·7% (14·8 to 16·7)	0·4% (−0·2 to 1·0)
JF CXR-1	1·00	..	93·5% (93·1 to 93·8)	54·2% (52·4 to 56·0)	89·9% (89·5 to 90·3)	4·6% (4·0 to 5·1)	15·1% (14·1 to 16·0)	1·0% (0·4 to 1·6)
Lunit INSIGHT CXR	0·96	..	98·0% (97·8 to 98·1)	75·5% (73·3 to 77·5)	89·1% (88·7 to 89·5)	9·0% (8·5 to 9·5)	36·3% (35·4 to 37·2)	0·2% (−0·5 to 0·8)
qXR	0·91	..	97·9% (97·7 to 98·1)	75·9% (73·8 to 77·8)	89·5% (89·1 to 89·9)	8·9% (8·5 to 9·4)	36·8% (35·9 to 37·7)	0·5% (−0·1 to 1·1)



Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms

Zhi Zhen Qin, Shahnoor Ahmed, Mohammad Shahnewaz Sarker, Kishor Paul, Ahammad Shofiq Sikder Adel, Tasneem Naheyan, Rachael Barrett, Sayera Banu*, Jacob Creswell*

CAD for paediatric TB

- Not yet recommended by WHO
- Few CAD software solutions are marketed for children
  - None for children <2 years
- No data published on diagnostic performance in children

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http://www.ai4hlth.org/

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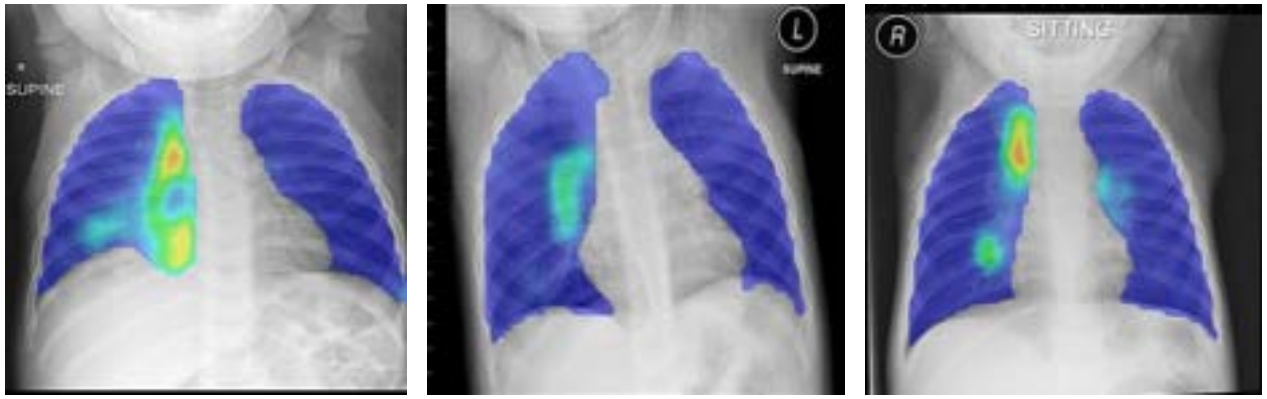
CAD for paediatric TB

- Specific challenges in paediatrics
  - Access to CXR image datasets
  - Appropriate reference standards
  - Diverse radiological disease spectrum



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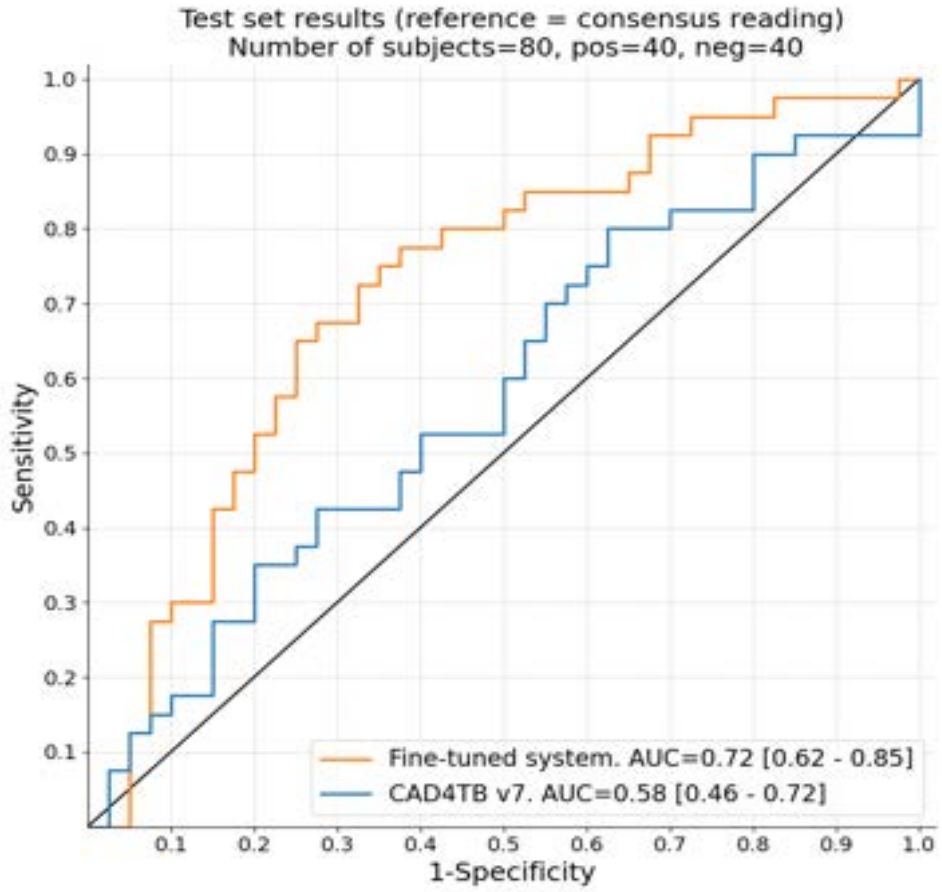
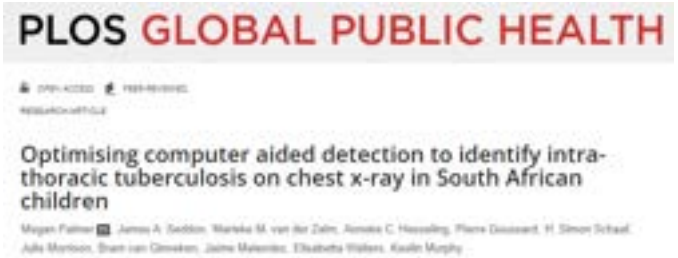
CAD for paediatric TB

- Re-trained ‘adult’ CAD4TB v7 algorithm with 445 paediatric CXRs
  - AUC increased from 0.58 (0.46-0.72) to 0.72 (0.62-0.85, **p=0.0016**) after fine-tuning
  - Reference standard: human expert read




PLOS GLOBAL PUBLIC HEALTH

Optimising computer aided detection to identify intra-thoracic tuberculosis on chest x-ray in South African children

Capture consortium

- **CAPTURE: Catalyzing Artificial intelligence for Paediatric Tuberculosis Research**
- Stellenbosch University, UCSF and FIND
- Aims:
  - Develop a cloud-based CXR repository of images from children with presumptive TB
  - Assess the performance of current CAD models for TB detection in children
  - Develop a CAD algorithm that can analyse CXRs for paediatric pulmonary TB

Every breath counts

Capture consortium

- Partners across 21 countries
- CXRs from South America Sub-Saharan Africa and South and Southeast Asia
- ≈8 000/10 000 CXRs

  - ≈ 48% TB
  - ≈ 12% confirmed TB
  - Median age: 3 years

Invitation to collaborate

Conclusions and future directions

- Imaging remains important for clinical care and research in paediatric TB:
  - Diagnosis: identify key radiological features
  - Screening: normal vs abnormal
  - Disease severity classification
- CAD: software with acceptable performance in children in the next year?
  - ?potential use in clinical trials

- LUS and advanced imaging not addressed

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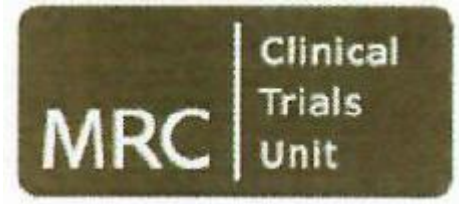

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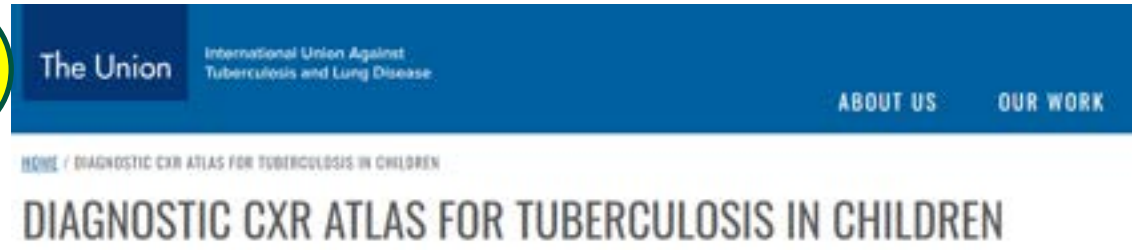
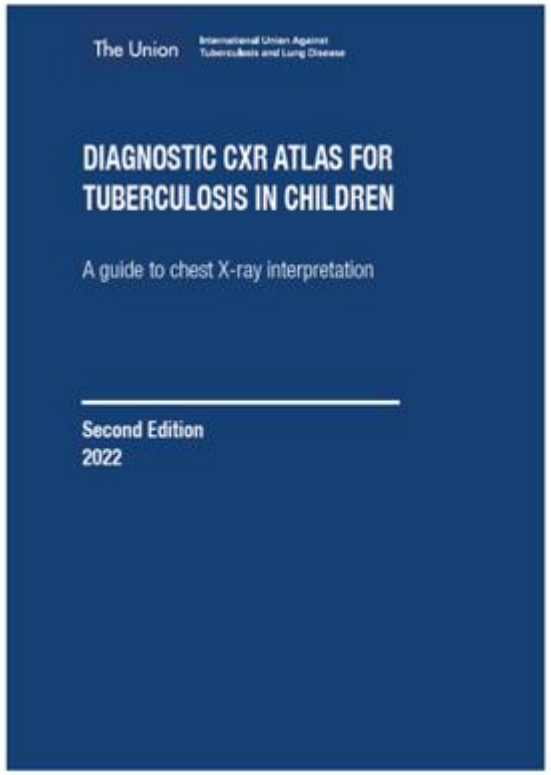
CHEST X-RAY: interpretation resources

1





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3