



Improving Pediatric TB Outcomes: Practical Approaches Across the Care Continuum

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Prevention and Health Promotion Administration

1 October 2026

Mission and Vision

MISSION

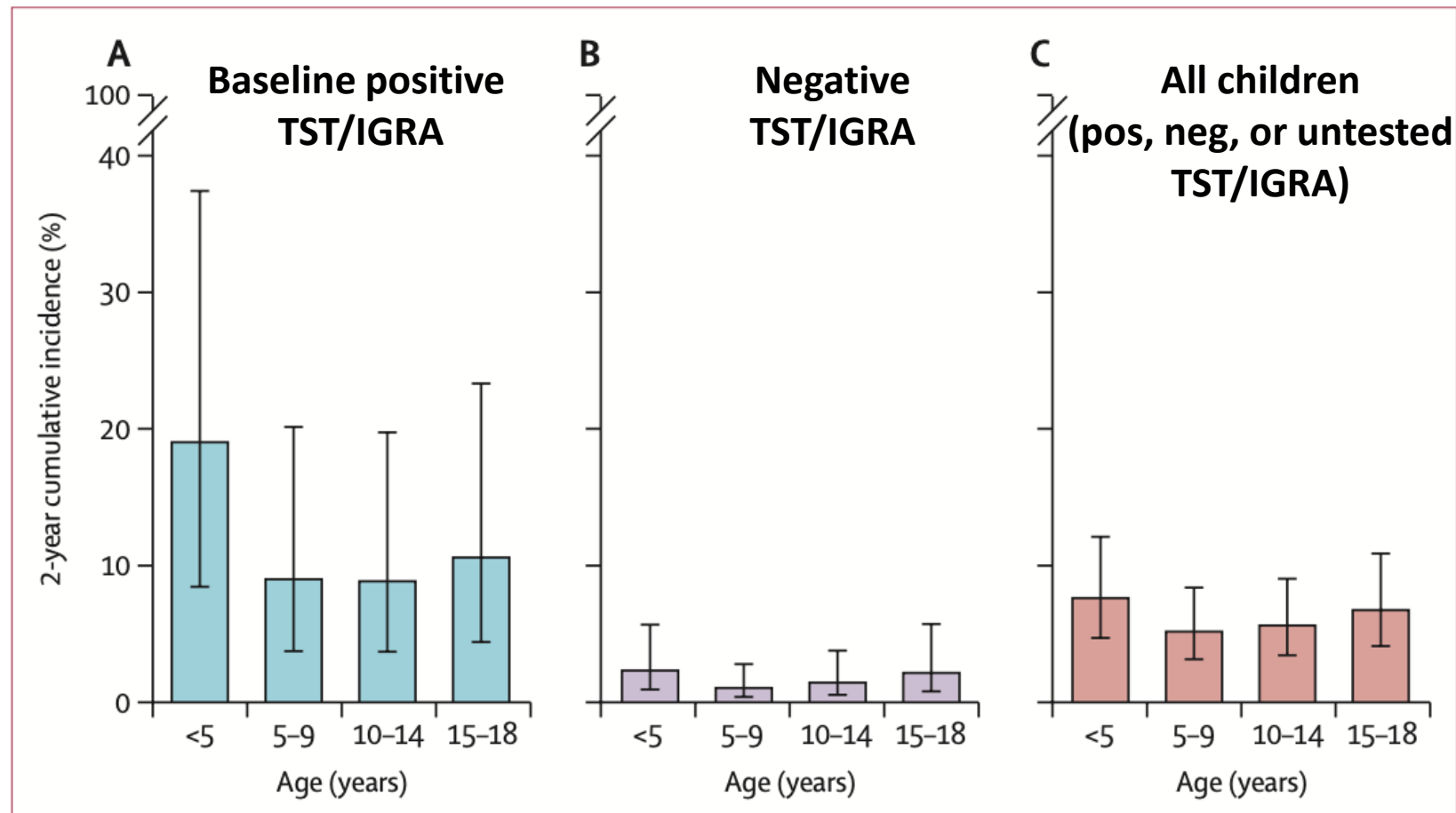
The mission of the Prevention and Health Promotion Administration is to protect, promote and improve the health and well-being of all Marylanders and their families through provision of public health leadership and through community-based public health efforts in partnership with local health departments, providers, community based organizations, and public and private sector agencies, giving special attention to at-risk and vulnerable populations.

VISION

The Prevention and Health Promotion Administration envisions a future in which all Marylanders and their families enjoy optimal health and well-being.

Risk of Tuberculosis Disease in Children by Age

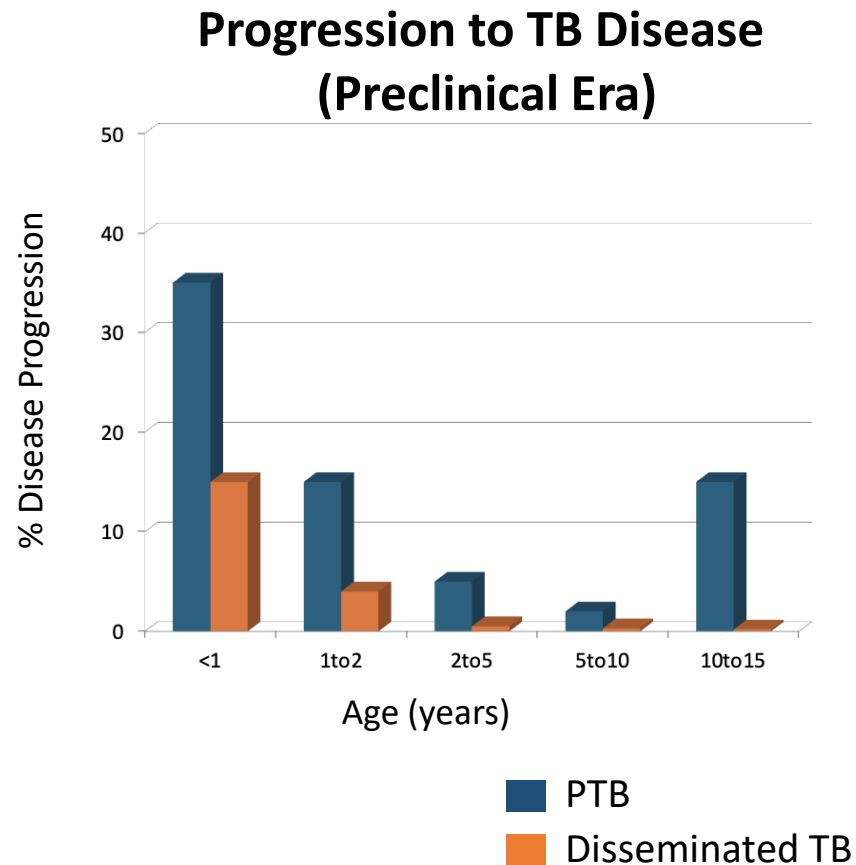
2-year cumulative incidence of TB among children not receiving preventive treatment



**Children < 5 years:
83% diagnosed within
90 days of baseline visit**

**TPT had 91%
effectiveness among
those with infection**

Importance of Preventing Progression to TB Disease in Young Children



- Young children at highest risk **severe** outcomes from disseminated TB
 - 10-20% mortality
 - 20-50% with permanent neurologic or developmental sequelae
- Poor diagnosis leading to increased morbidity and mortality globally

Importance of Preventing Progression to TB Disease in Adolescents

Vulnerable Population:

1. Increased risk of progression to TB disease
2. Capable of transmission
 - Household, school, community
3. Poor Treatment Outcomes
 - Higher Mortality
 - Increased LTFU

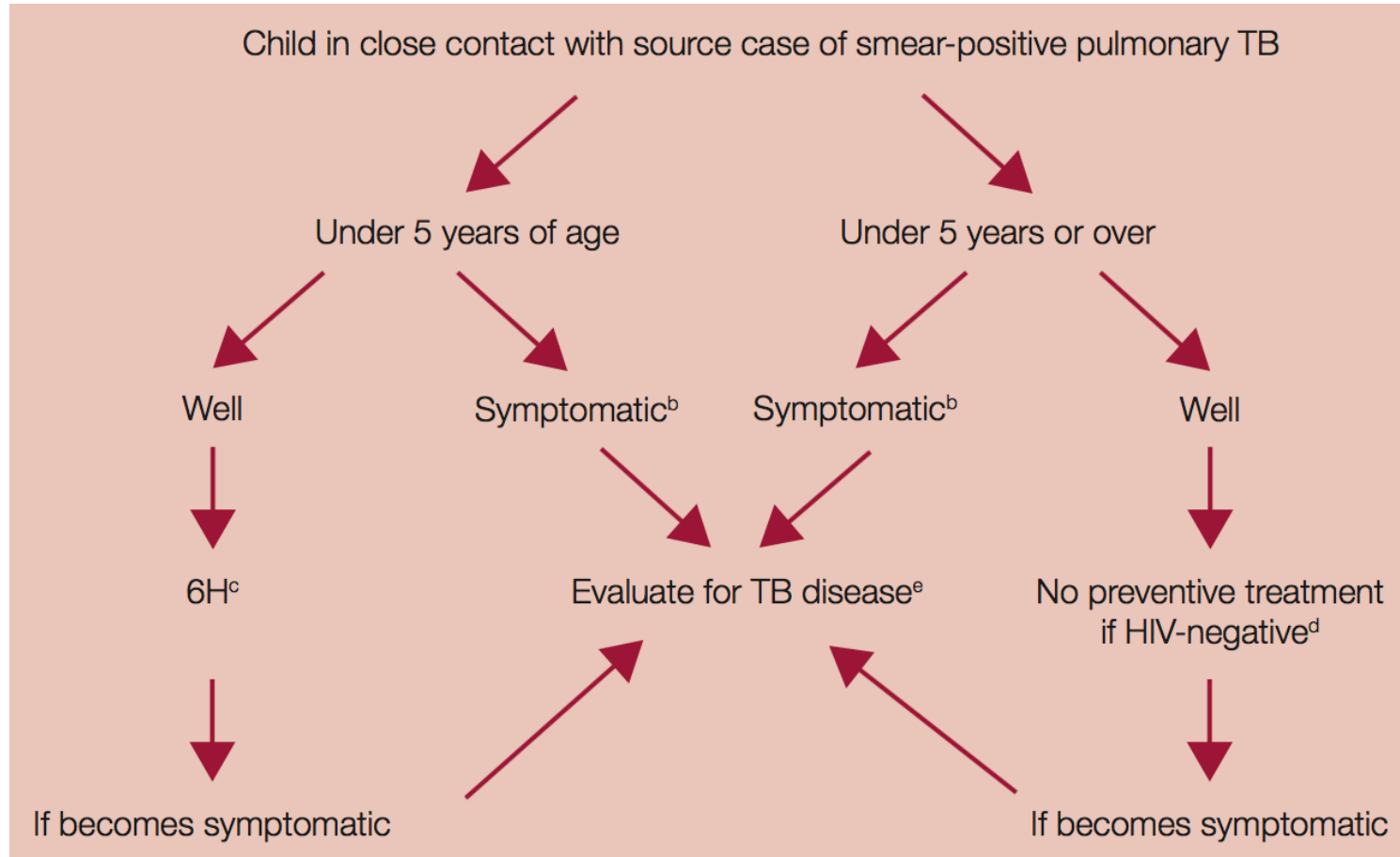


Diagnosing TB in Children

TB is a **CLINICAL** Diagnosis in Children

Step 1: History and Physical Exam

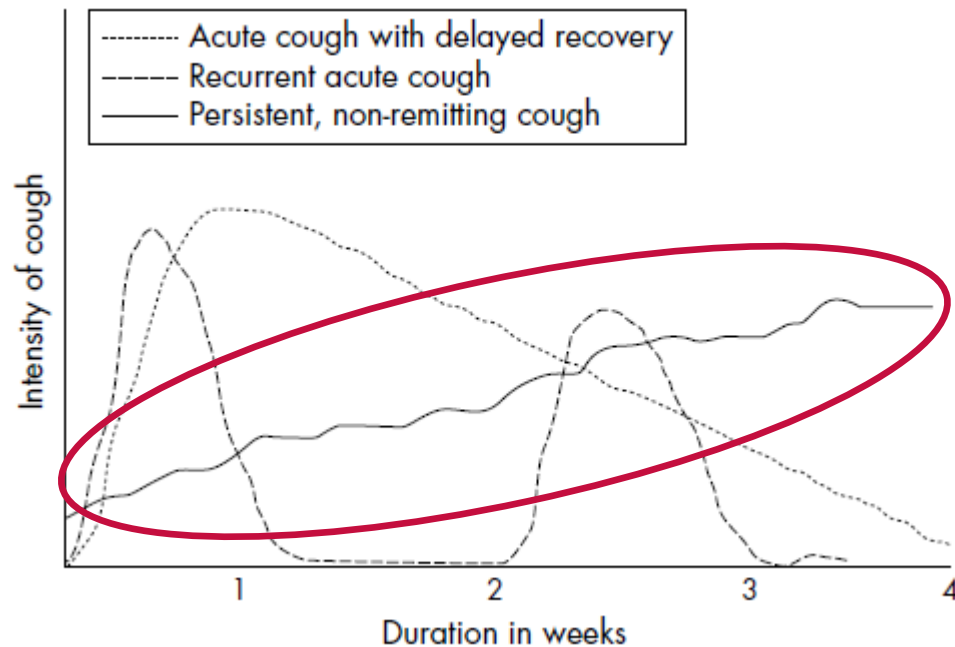
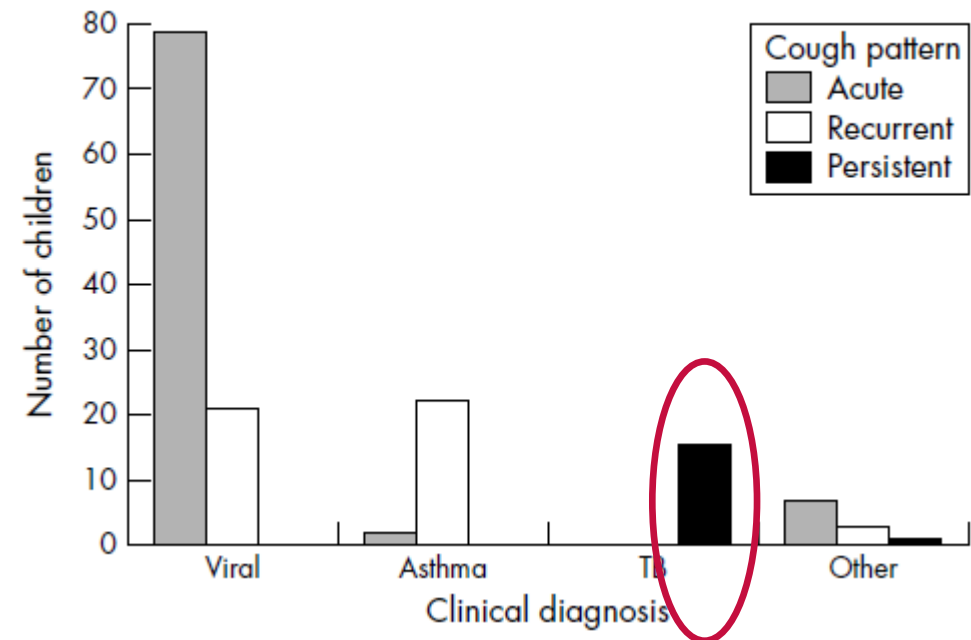
Symptom-Based Screening



Symptom Screen:

Fever
Cough
Wheeze
Reduced Playfulness
Unusual fatigue
Visible neck mass
Weight loss or Failure to Thrive

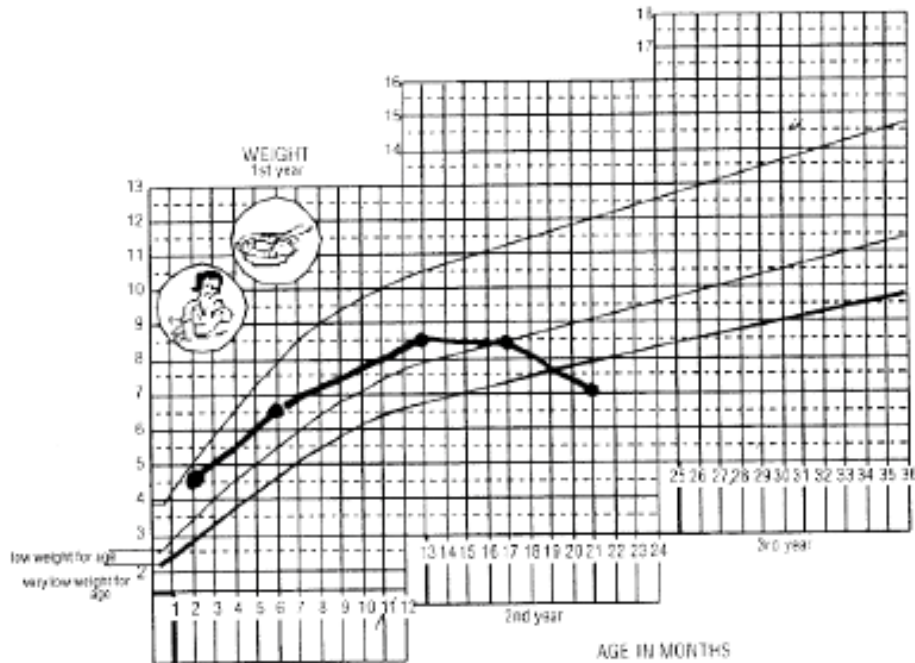
Pediatric TB: Persistent, Non-Remitting Cough



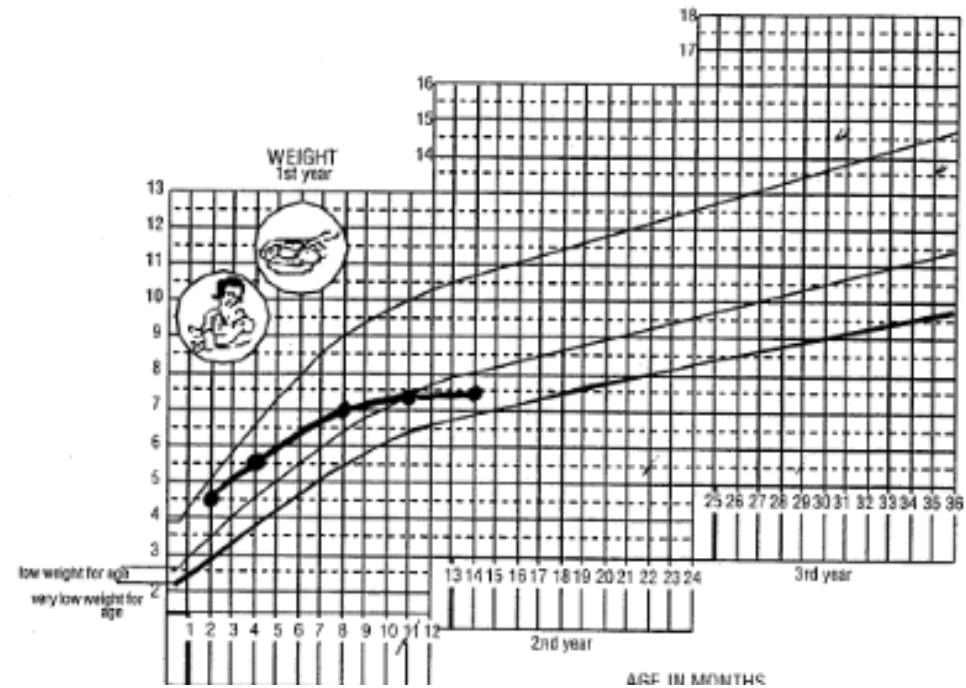
Needs to be distinguished from coughs associated with asthma and upper respiratory tract infection

Assess Child's Growth Over Time

Obtain the child's growth chart – growth is a vital sign in children!



Weight Loss



Failure to Thrive

Ugandan Child Contact Investigation

- 761 Child Contacts <15 years
- 10% had TB Disease (79)
 - 16.4% of children <5
- 71% were biologically confirmed
- Risk Factors for Active TB:
 - Age <5 (OR 5.89)
 - HIV+ (OR 7.9)
 - Baseline positive TST (OR 2.2)

Table 2. Frequency of Diagnostic Findings in Active Tuberculosis Cases

Finding	No. (%)		
	Age ≤5 y	Age >5 y	All Children
Signs and symptoms			
Loss of appetite	14 (23)	0	14 (18)
Cough	42 (70)	9 (50)	51 (65)
Dyspnea	1 (2)	0	1 (1)
Fever	26 (43)	4 (22)	30 (38)
Weight loss	19 (32)	0	19 (24)
Productive sputum	14 (23)	7 (39)	21 (27)
Purulent sputum	1 (2)	0	1 (1)
Sweating	6 (10)	3 (17)	9 (11)
Lymphadenopathy	20 (33)	2 (11)	22 (28)
Abnormal respiratory exam	26 (43)	4 (22)	30 (38)

Sensitivity and Specificity of Individual Symptoms among high and low risk groups

Individual Variables at Presentation ^a	Low Risk HIV Uninfected ≥ 3 y			High Risk					
				HIV Uninfected < 3 y			HIV Infected		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Cough > 3 wk	90.7	65.7	33.8	80.9	58.1	33.5	100	45.0	60.7
Cough > 4 wk	73.3	90.1	58.9	59.6	89.9	60.2	88.2	65.0	68.2
Chest pain	9.3	96.9	36.4	3.2	99.7	75.0	0	95.0	0
Hemoptysis	5.8	98.1	38.4	1.1	100	100	0	95.0	0
Respiratory distress	4.7	99.1	50.0	8.5	94.9	30.8	35.3	60.6	42.8
Fever	37.2	92.4	48.5	43.6	89.9	52.6	52.9	30.0	39.1
Night sweats	57.0	93.9	64.5	40.4	95.2	70.3	41.2	60.0	46.7
Fatigue	94.2	87.0	58.3	68.1	95.5	78.0	94.1	30.0	53.3
Weight loss subjective	70.9	84.8	47.3	60.6	91.9	65.5	88.2	30.0	51.7
Weight loss objective	82.4	84.4	75.0	75.3	79.1	82.1	82.3	35.0	51.9
TST positive	89.3	62.9	59.1	81.9	70.1	77.7	17.6	85.0	50.0
Household contact	48.8	72.3	52.5	69.1	53.6	67.0	52.9	60.0	52.9

Symptoms of Diagnostic Value by Multivariable Logistic Regression

Combined Variables at Presentation ^a	Value		
	Sensitivity	Specificity	PPV
Low-risk children			
≥3 years and HIV uninfected	82.3	90.2	82.3
High-risk children			
<3 years and HIV uninfected	51.8	92.5	90.1
HIV infected (irrespective of age)	56.2	61.8	61.9

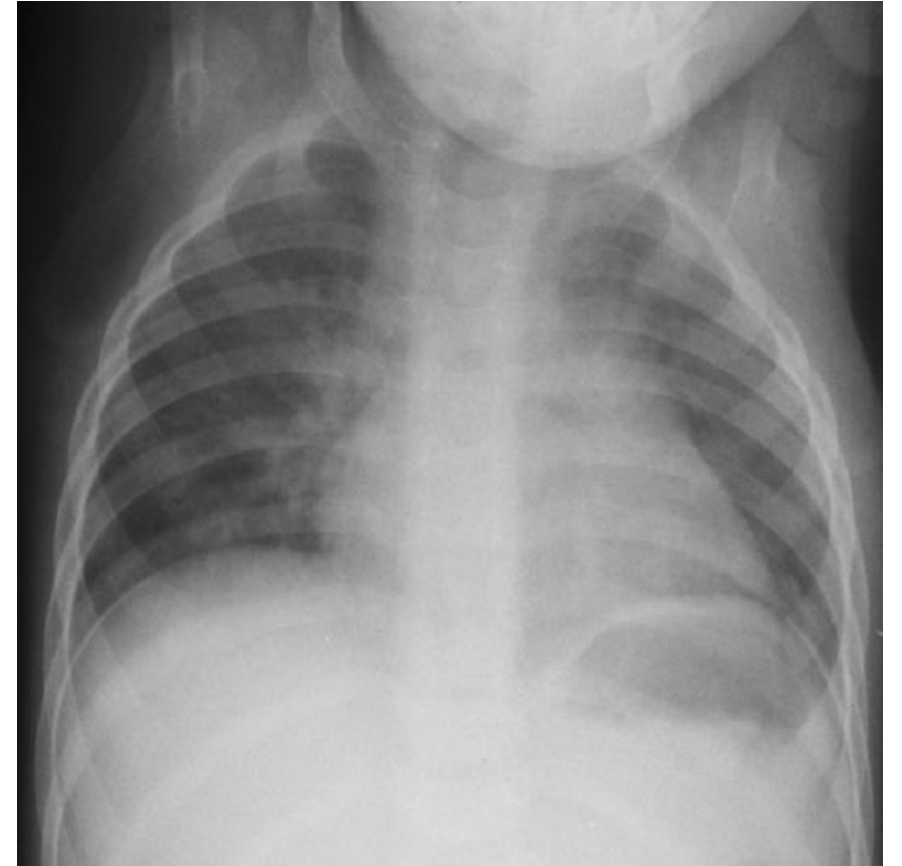
1. Persistent, non-remitting cough for > 2 weeks
2. Documented weight loss or FTT
3. Reported fatigue (perceived decrease in playfulness/activity)

TB is a **CLINICAL** Diagnosis in Children

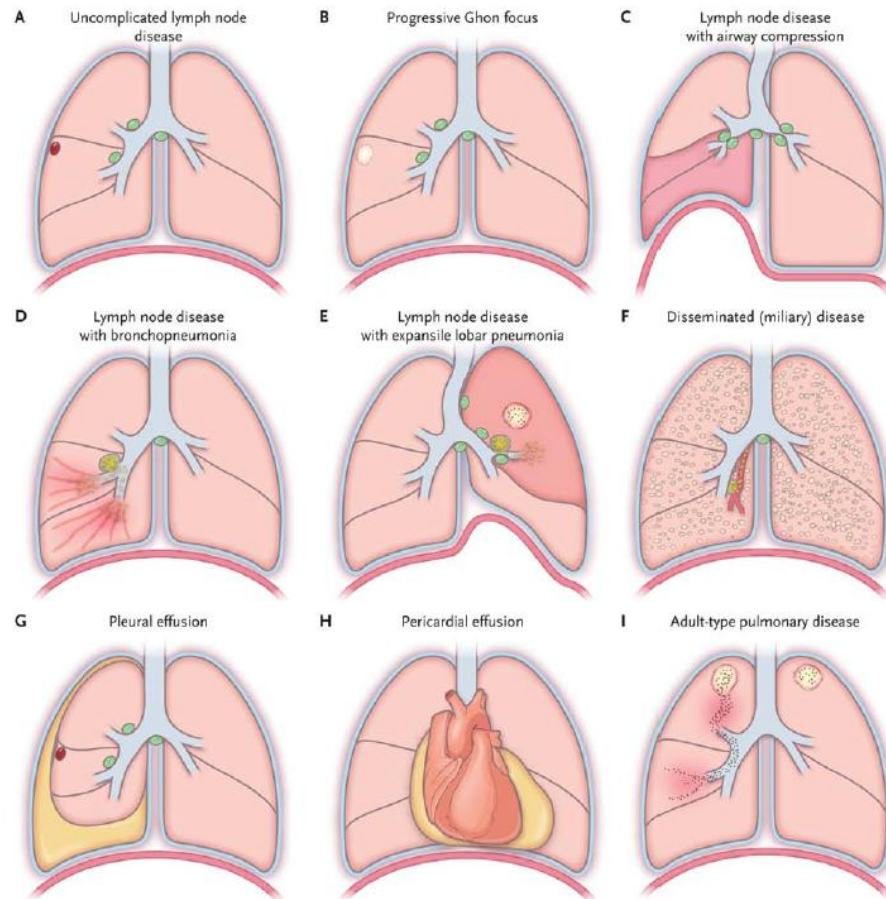
Step 2: Chest X-Ray

Evaluation of Pediatric TB with Chest X-ray

- **PA and Lateral films for childhood TB**
- Quality Assessment
 - Over/Under penetrated
 - Be able to see the intervertebral spaces through the heart shadow
 - Rotation
 - Check for symmetry: clavicle heads equidistant from midline
 - Inspiration:
 - Should see 8-9 posterior ribs
- Systematic Assessment
- **Cannot always trust a radiologist's read**

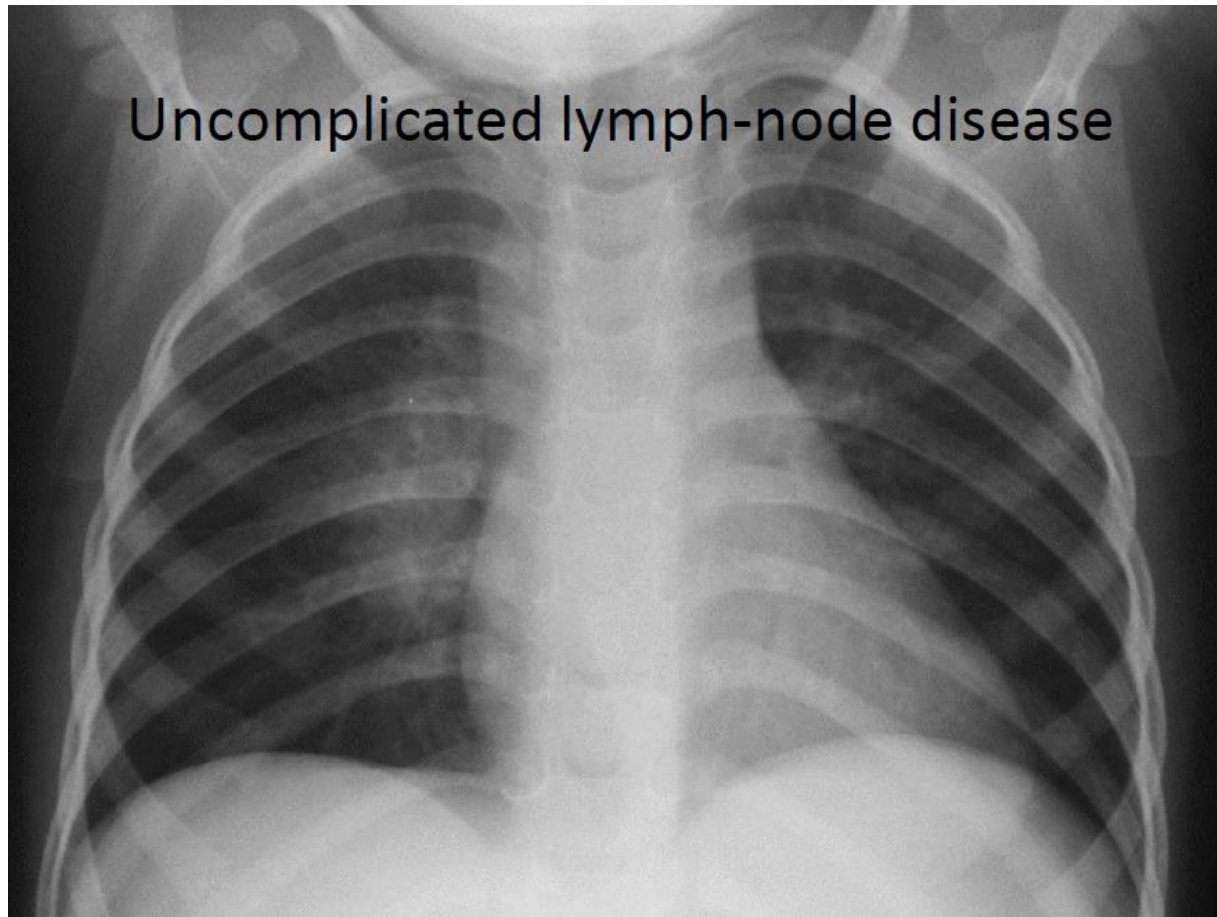
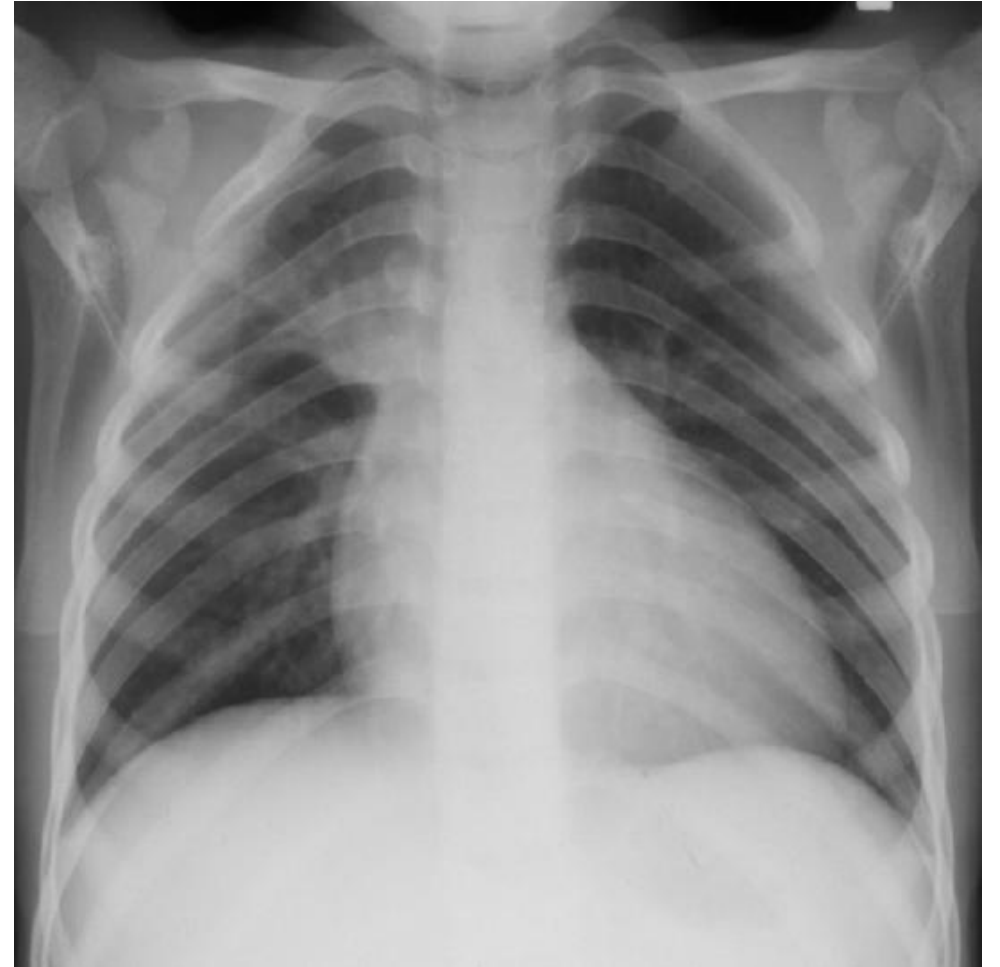


Pediatric Intrathoracic TB disease

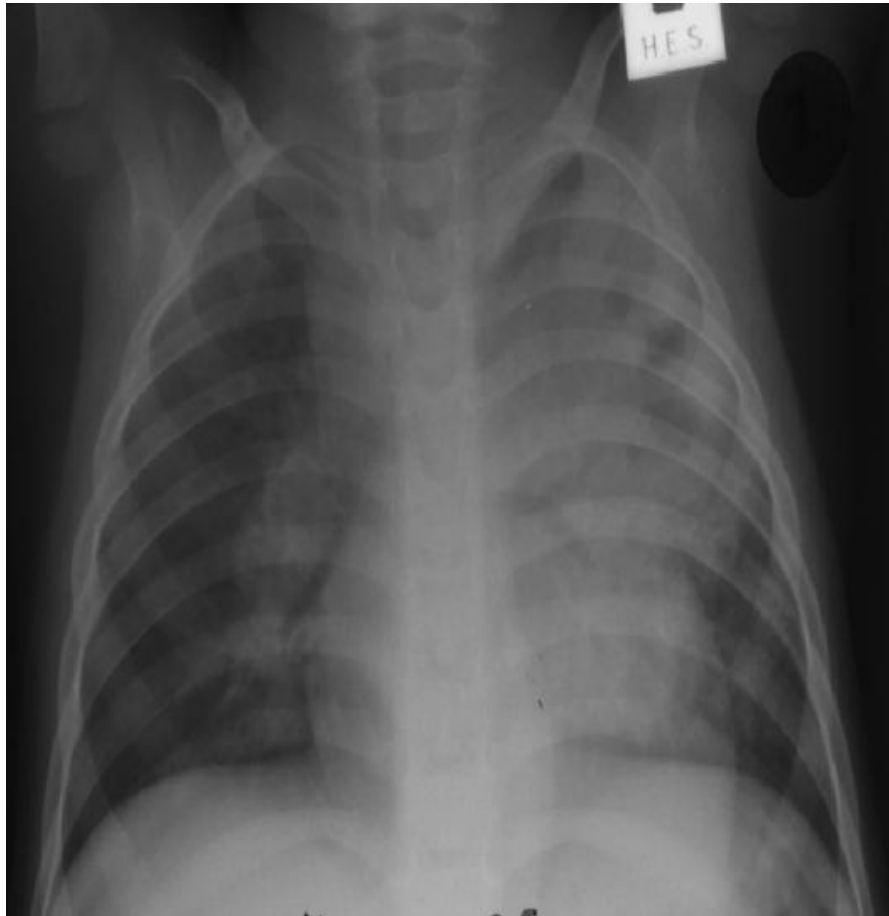


- Many more presentations in children than adults
- Many involving LN
 - Ghon focus and uncomplicated disease
 - Airway compression
 - Bronchopneumonia
 - Lobar pneumonia
- Fewer cavities – occur within lobar disease

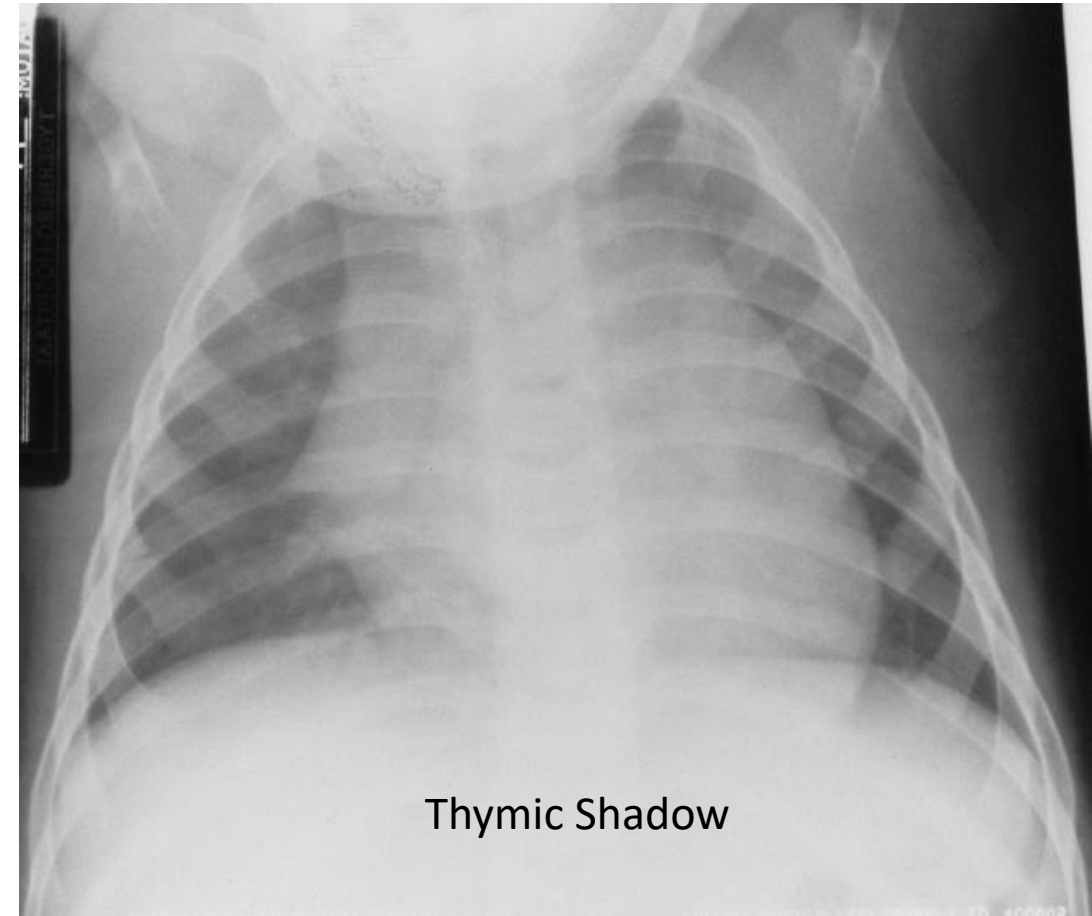
Hilar and Mediastinal Adenopathy



Hilar and Mediastinal Adenopathy

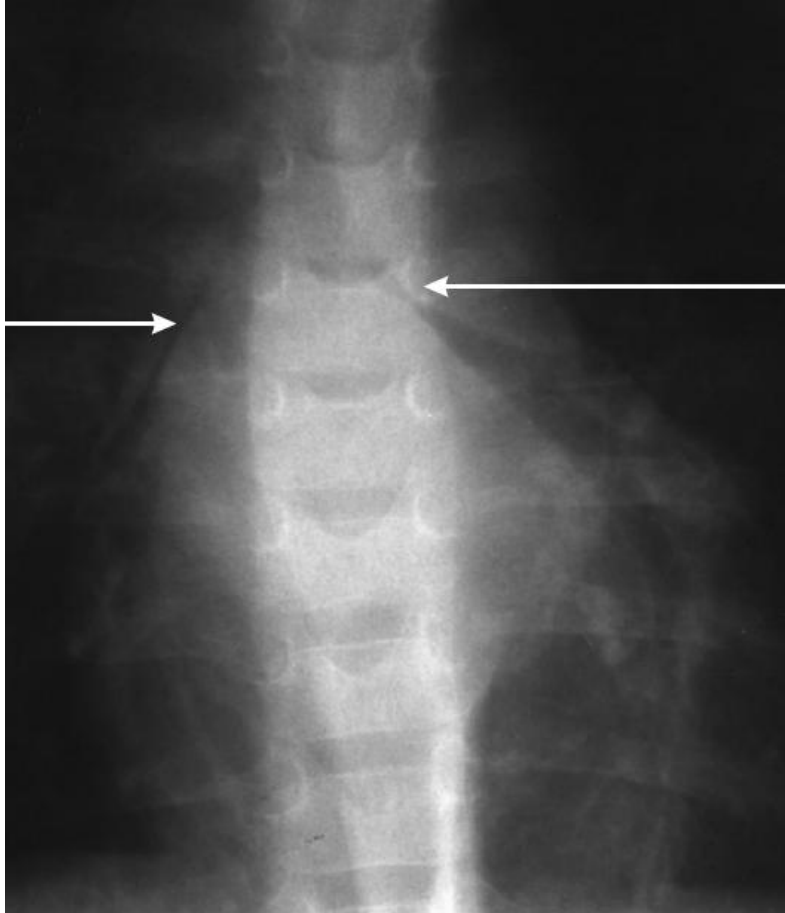


Right hilar & paratracheal nodes
LUL consolidation with cavity



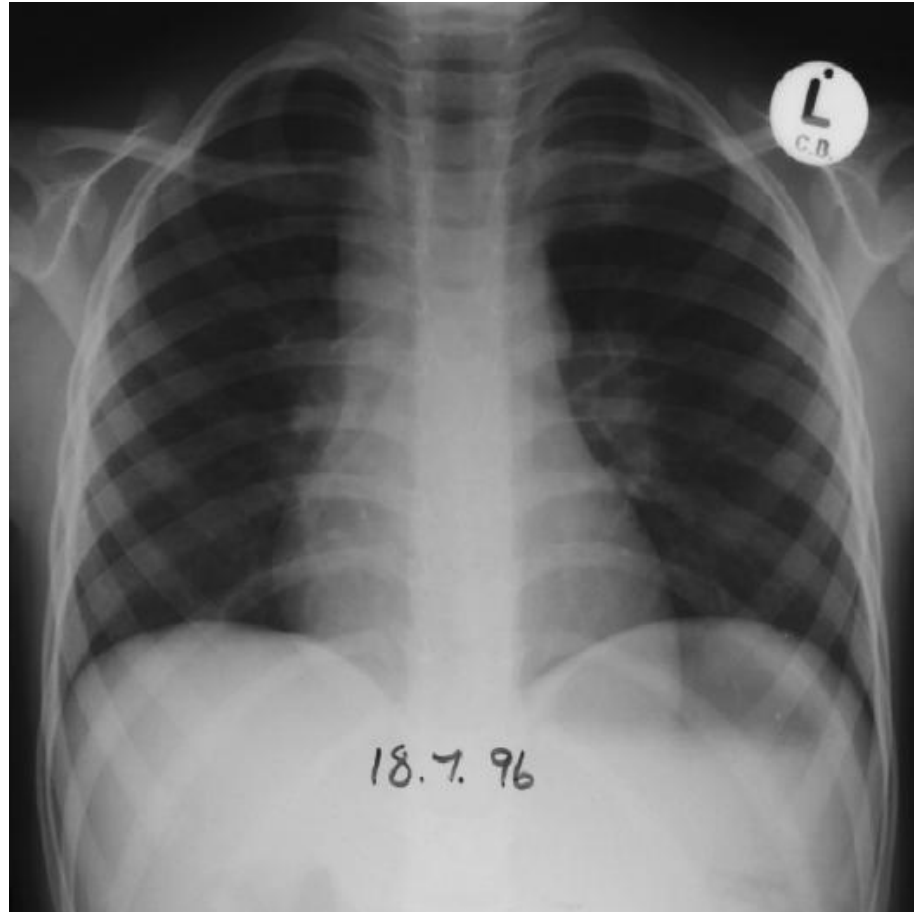
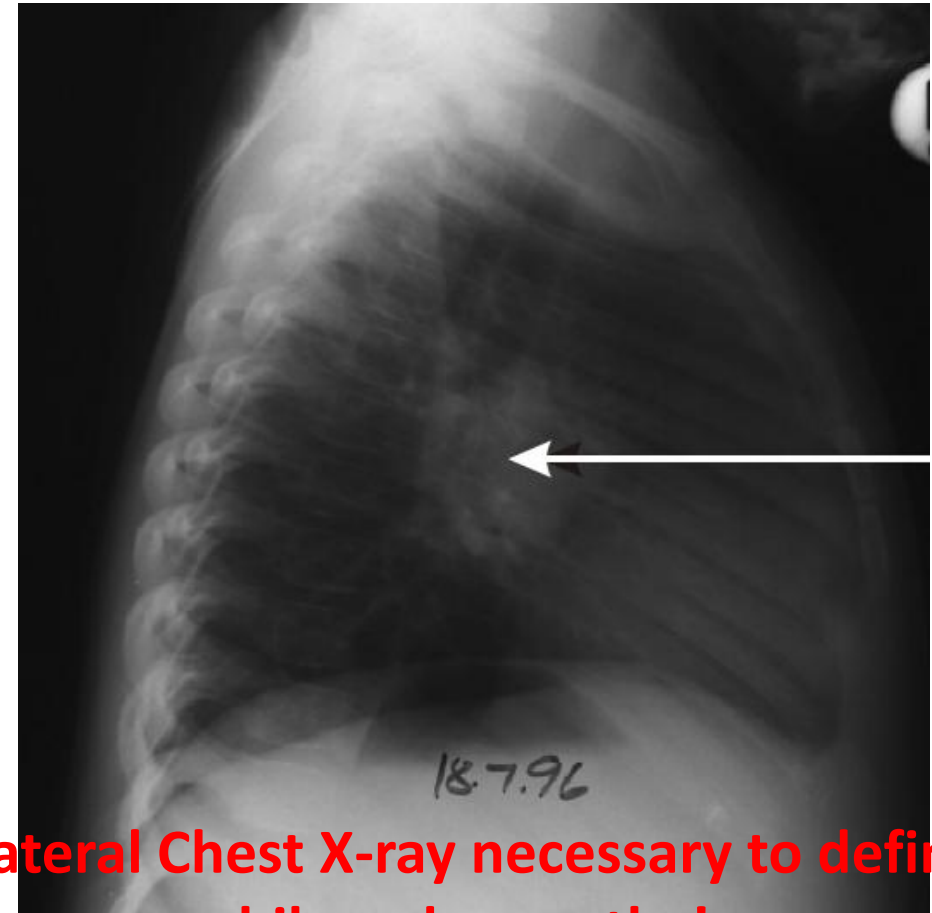
Thymic Shadow

Clues to Hilar and Mediastinal Adenopathy



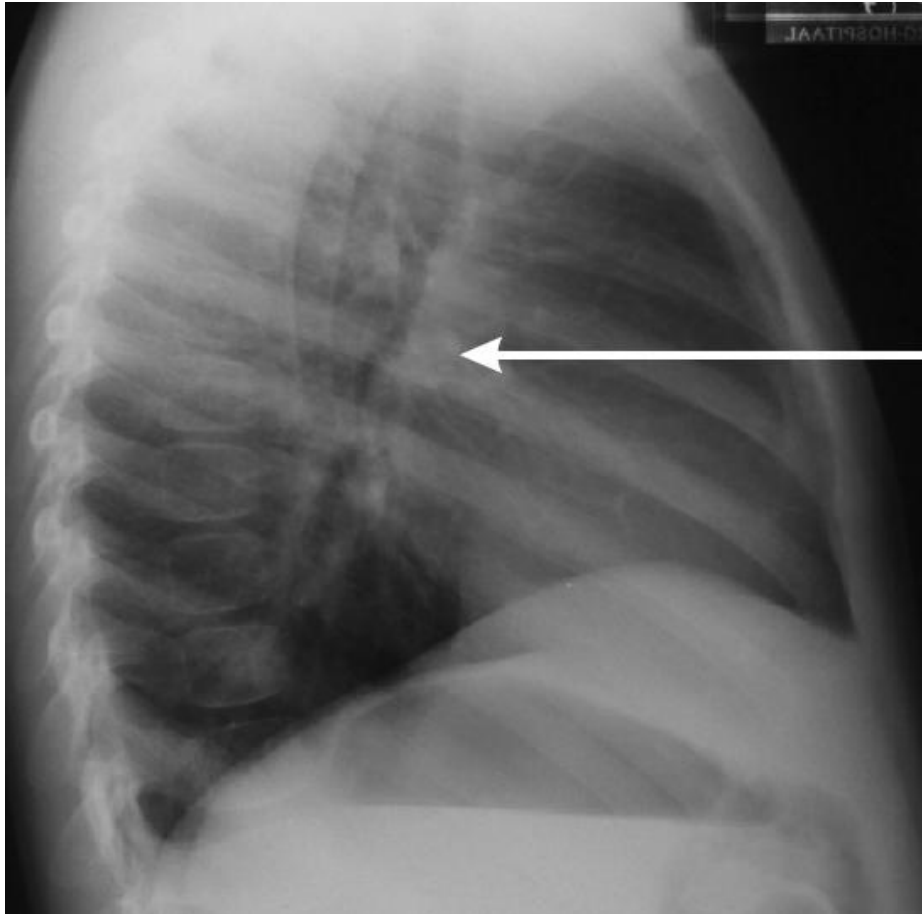
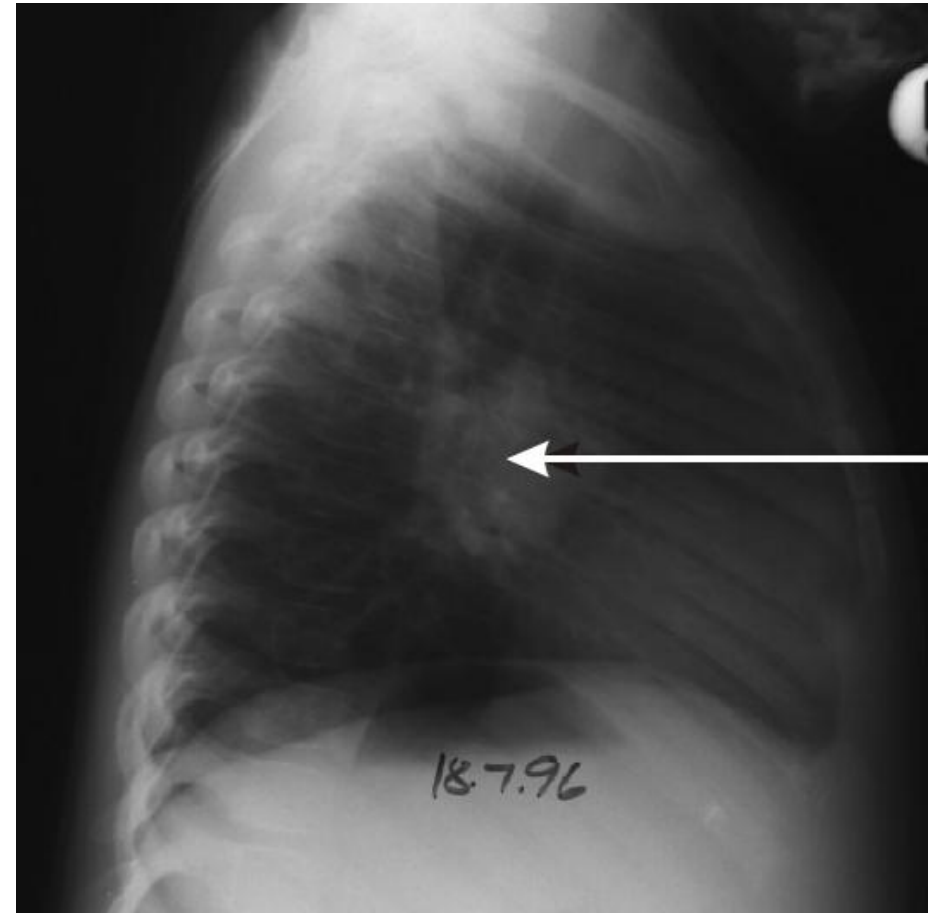
**Indirect visualization of adenopathy
through the compression of large
airways**

More Clues to Hilar and Mediastinal Adenopathy



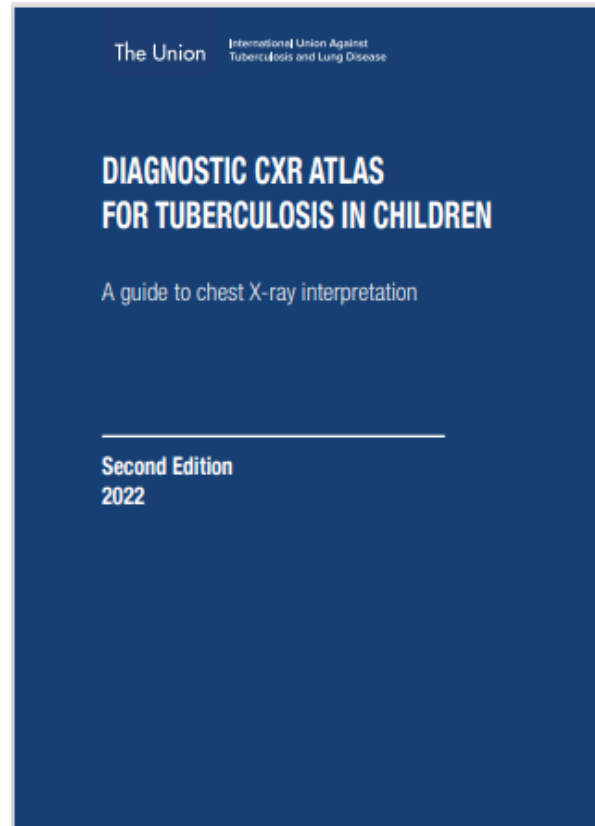
**Lateral Chest X-ray necessary to define
hilar adenopathy!**

Interpreting Lateral Films for Hilar Adenopathy



Tools to Assist with CXR Reading in Children

- [Diagnostic CXR Atlas for Tuberculosis in Children | The Union](#)

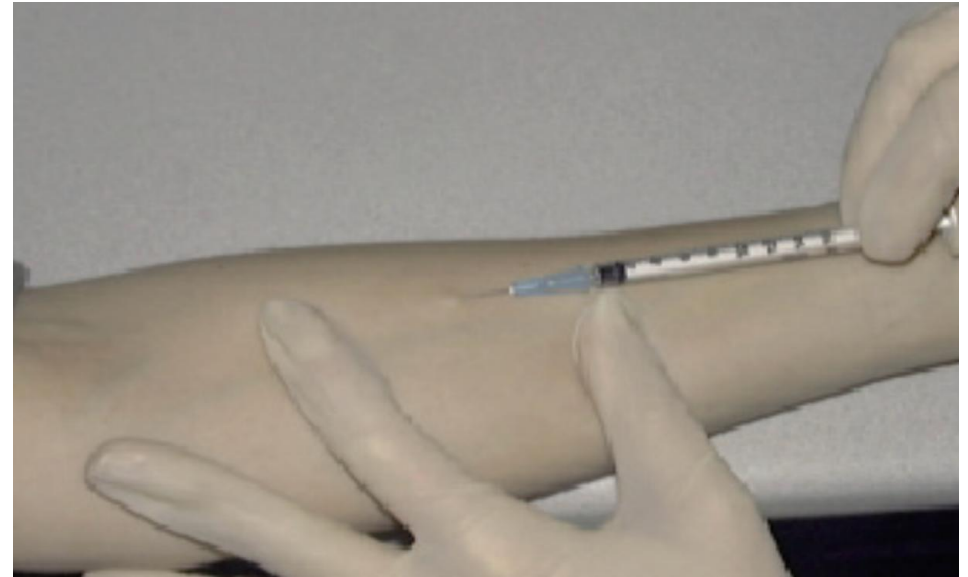


TB is a **CLINICAL** Diagnosis in Children

Step 3: TB Infection

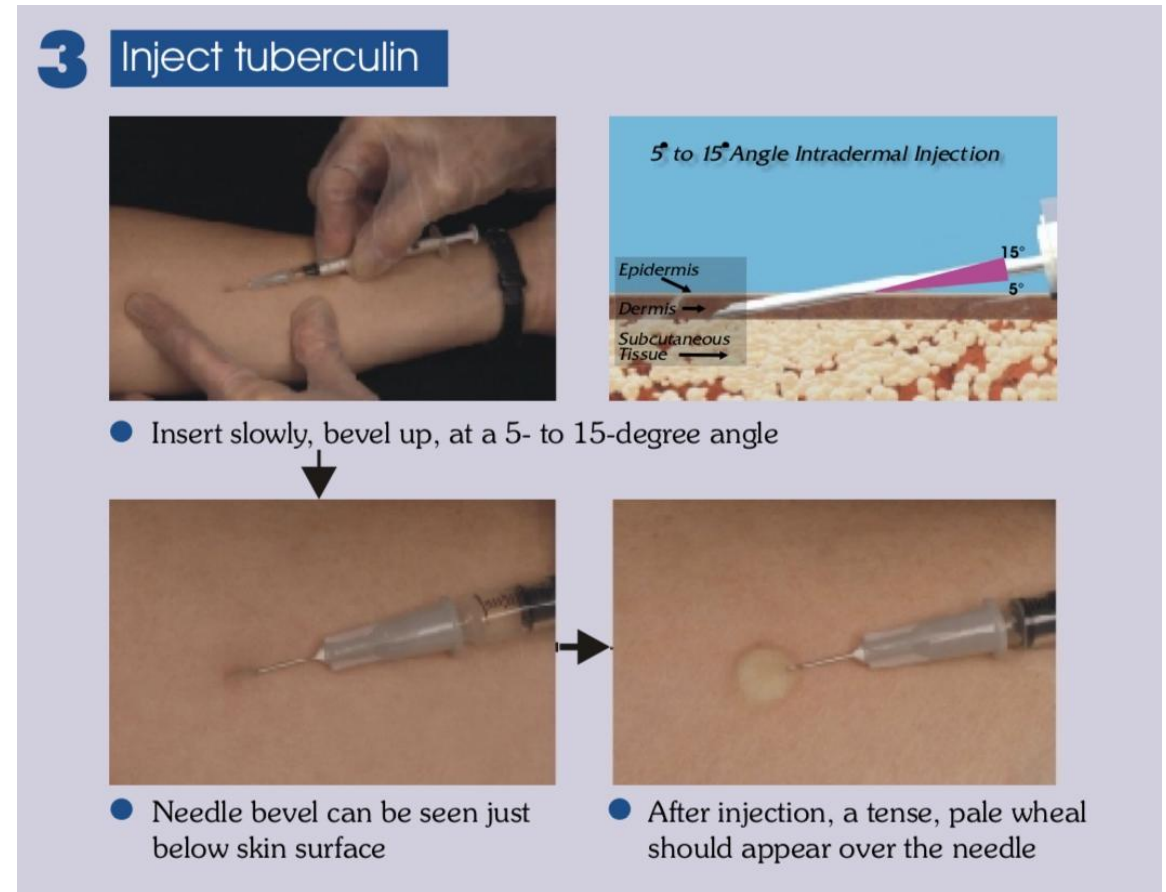
TST: Screening for TB Infection

- Detects infection with *M. tuberculosis*
 - Measures immune response and not the mycobacteria itself
- Especially helpful when you have a child TB suspect without a h/o a TB contact
 - Can be used to screen children with known contacts (NOT absolutely necessary)
- Record as mm, not as pos/neg.
 - Child's immune status required for appropriate interpretation.



TST Placement

1. Locate and clean injection site
 - 2-4 inches below elbow joint (palm up) without sores/scars
2. Prepare syringe
 - 0.1mL (5TU); 27-gauge needle $\frac{1}{4}$ - $\frac{1}{2}$ inch long
3. Inject tuberculin (ppd) 
4. Check skin test
 - Wheal should be 6-10mm (diameter).
 - Can repeat 2 inches away
5. Record Information: date, time, site, lot number



TST Assessment



TST Assessment:

- 48-72 hours after placement
- Induration NOT erythema!
- Measure in millimeters of induration perpendicular to the long axis of the arm
- Record in mm
 - NOT positive/negative!

Is this a positive TST?

TST: Screening for TB Infection

<5 mm	≥5mm	≥10 mm
Negative in all populations	Positive in immunocompromised individuals	Positive in all populations
HIV+, severe malnutrition (marasmus or Kwashiorkor)		

False Positive: BCG vaccination, NTM, incorrect reading

False Negative: HIV+ children (or other primary immunodeficiency), severe TB disease, viral infection (measles, varicella), steroids, incubation period (2-10 weeks) , incorrect placement or reading

“TST does NOT rule out M. tuberculosis infection or the possibility of TB in a child”

There is no TST cutoff that distinguishes TB infection from TB disease.

IGRA: Interferon Gamma Release Assay

IGRA Limitations:

1. Technical difficulty (QFN)
2. Does not distinguish between latent and active disease
3. Does not predict progression to active disease
4. Imperfect sensitivity
5. Improved specificity: BCG not a concern
6. **Fewer but growing data** in children
7. Window period 8-12 weeks



Interferon Gamma Release Assays: Use in Children

- Similar to the TST, IGRAs do not distinguish between TB infection and TB disease
 - Negative IGRA does not rule out either in child with suspicious findings
- No cross reactivity with *M. bovis* (BCG vaccine) or *M. avium* complex (MAC)
- IGRA testing is now acceptable for children of **ANY** age
 - Though large blood volume for small children and HD's may not have pediatric phlebotomy

IGRA Diagnostic Accuracy for Definite/Probable TB

Index test	Sensitivity		Specificity	
	Participants (studies)	Sensitivity (95%CI)	Participants (studies)	Specificity (95%CI)
TST 5 mm	265 (13)	91 (84-98)	217 (4)	70 (17-100)
TST 10 mm	321 (15)	84 (75-93)	276 (5)	88 (62-100)
TST 15 mm	389 (11)	67 (50-83)	131 (3)	92 (71-100)
QFT-G	74 (5)	92 (82-100)	82 (1)	35 (0-80)
QFT-IT	393 (13)	77 (65-88)	568 (6)	92 (86-100)
QFT-G/QFT-IT combined	431 (17)	83 (75-92)	323 (7)	91 (78-100)
T-SPOT	336 (9)	84 (63-100)	143 (4)	94 (87-100)

TB is a **CLINICAL** Diagnosis in Children

Step 4: Sputum (or swallowed sputum)

Challenges with Sputum-based TB Diagnosis in Pediatrics

1. Poor sensitivity given the paucibacilliary nature of pediatric TB
 - 30% of pediatric TB is culture positive under optimal conditions
2. Relatively more difficult to obtain samples in children
 - Training
 - Specialized equipment
 - Electricity
 - Competency in handling rare adverse events
 - Hospital admission

Microbiological confirmation is helpful, but NOT necessary to make a diagnosis of TB in young children



Current Diagnostics are Poorly Sensitive for Pediatric TB and all require *Sputum*



	Smear Microscopy	Culture	Xpert MTB/RIF Ultra
Timing of Results	Minutes/days	2-6 weeks	Hours/days
Limit of Detection	10,000 cfu/mL	10-100 cfu/mL	16 cfu/mL
Sensitivity in Children	~10%	~40%	~30%

Mixed Results with Yield of Induced Sputum

	Patients	Culture positive	Smear positive	Culture or smear positive	Cumulative yield
Total	250	58 (23%)	29 (12%)	62 (25%)	100%
Induced sputum					
Total	250	51 (20%)	25 (10%)	54 (22%)	87%
First specimen	250	37 (15%)	19 (8%)	41 (16%)	66%
Second specimen	244	27 (11%)	13 (5%)	30 (12%)	79%
Third specimen	227	29 (13%)	11 (5%)	31 (14%)	87%
Gastric lavage					
Total	250	38 (15%)	17 (7%)	40 (16%)	64%
First specimen	250	19 (8%)	8 (3%)	20 (8%)	32%
Second specimen	244	22 (9%)	12 (5%)	26 (11%)	56%
Third specimen	234	18 (8%)	10 (4%)	22 (9%)	64%

Data are number or %.

Table: Cumulative yield of *M tuberculosis* from repeated induced sputum or gastric lavage specimens

One induced sputum has been shown to have similar sensitivity to 3 gastric lavages in hospitalized children

Community Based Care

Method	Gastric lavage +ve	Gastric lavage -ve	Total
Induced sputum +ve	41 (2.2)	67 (3.6)	108 (5.8)
Induced sputum -ve	86 (4.6)	1675 (89.6)	1761 (94.2)
Total	127 (6.8)	1742 (93.2)	1869 (100)

Values in parentheses are percentages.
 κ statistic = 0.31.

Induced sputum has not been as sensitive among clinic patients

Meta-analysis: Xpert MTB/RIF (Ultra) for Pulmonary TB in Children

Index test	Effect (95% CI)	Number of participants (studies)	Test result	Number of results per 1000 patients tested(95% CI)			Certainty of the evidence (GRADE)
				Prevalence 1%	Prevalence 10%	Prevalence 20%	
Xpert MTB/RIF	Pooled sensitivity 0.65 (95% CI 0.55 to 0.73) *	493 (23)	True-positives	6 (6 to 7)	65 (55 to 73)	129 (111 to 146)	⊕⊕⊕○
			False-negatives	4 (3 to 4)	35 (27 to 45)	71 (54 to 89)	MODERATE a,b
	Pooled specificity 0.99 (95% CI 0.98 to 0.99)	6119 (23)	True-negatives	980 (971 to 985)	891 (883 to 896)	792 (785 to 796)	⊕⊕⊕○
			False-positives	10 (5 to 19)	9 (4 to 17)	8 (4 to 15)	MODERATE ^c
Xpert Ultra	Pooled sensitivity 0.73 (95% CI 0.65 to 0.80) *	136 (3)	True-positives	7 (6 to 8)	73 (65 to 80)	146 (129 to 159)	⊕⊕○○
			False-negatives	3 (2 to 4)	27 (20 to 35)	54 (41 to 71)	LOW ^{d,e}
	Pooled specificity 0.97 (95% CI 0.96 to 0.98)	551 (3)	True-negatives	960 (950 to 970)	873 (864 to 882)	776 (768 to 784)	⊕⊕⊕⊕
			False-positives	30 (20 to 40)	27 (18 to 36)	24 (16 to 32)	HIGH

*Sensitivity compared against culture positive pulmonary TB

Pooled Sensitivity of Xpert MTB/RIF by Specimen Type

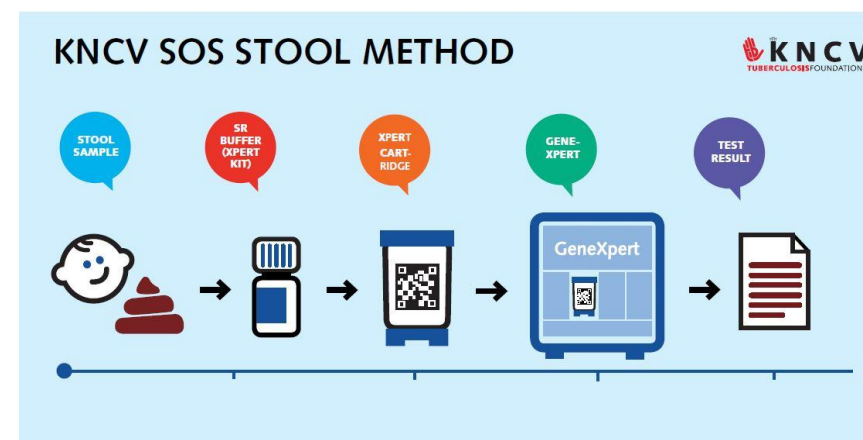
	Gastric Aspirate	Sputum	Stool	Nasopharyngeal aspirate
Pooled Sensitivity (95% CI)	73.0% (52.9% to 86.7%)	64.6% (55.3% to 72.9%)	61.5% (44.1% to 76.4%)	45.7% (27.6% to 65.1%)

- TB lymphadenitis: pooled sensitivity 0.90 (95% CI 0.56 - 0.99)
- TB meningitis pooled sensitivity 0.54 (95%CI 0.28 - 0.78)

Stool Xpert: An Alternative, Non-invasive Specimen for Ruling In Pediatric TB Disease

Stool can be used as an alternative to respiratory specimens

Specimen type (population)	Sensitivity	Specificity	Certainty of evidence
Xpert MTB/RIF			
Sputum	0.65	0.99	Moderate
Gastric aspirate	0.73	0.98	Very low (se) to low (sp)
NPA	0.46	1.00	Moderate (se) to high (sp)
Stool	0.61	0.98	Low (se) to moderate (sp)
Stool (HIV-positive)	0.70	0.98	Low (se) to high (sp)
Xpert Ultra			
Sputum	0.73	0.97	Low (se) to high (sp)
Gastric aspirate	0.64	0.95	Moderate
NPA	0.46	0.98	Very low (se) to low (sp)
Stool	0.53	0.98	Moderate



- KNCV Simple One Step Stool Processing
- A preprocessing step required prior to inserting specimen into Xpert cartridge
- Simple and centrifuge free!

Are pediatric TB diagnoses difficult to make?

It is difficult to *confirm* a diagnosis of TB in many children, but it is usually not difficult to make a clinical diagnosis of TB in a child

Often helpful (sometimes essential) to have an isolate with susceptibilities when Drug Resistant TB is suspected.

Common Mistakes in Pediatric TB Diagnosis

- Asking an adult-focused history (cough, fever, weight loss, night sweats)
- Not obtaining the *lateral* CXR
- Poor radiology read: *missing the adenopathy*
- Assuming you can “*rule out*” TB with gastric aspirate
- Excluding TB with a negative IGRA
- Delaying TPT initiation due to diagnostic uncertainty

Case 1: Persistent Fever

Persistent Fever in a 4-year-old

History

- 4 year old, born at 25 weeks gestation
- Chronic respiratory failure with trach, HME
- CP, GT no nissen
- Presents with 3 days of fever, increased secretions and worsening respiratory distress
- **Admit to hospital for acute on chronic respiratory failure with VAP/VAT**

Contact

- Smear pos/NAAT pos no RIF resistance
- Shared sleeping space

Physical Exam

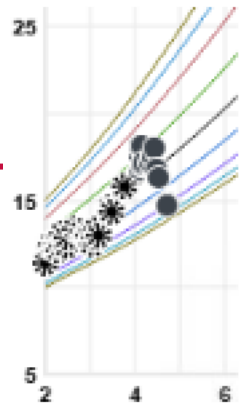
- Growth chart: + weight loss over 6 months

Laboratory

- CXR – LLL opacity without hilar adenopathy c/w atelectasis vs pna
- Respiratory panel: +RSV, +rhino/entero
- Cefepime → ciprofloxacin (pulm rec)
- Gastric aspirate x3

Plan

- Start TPT pending resolution respiratory symptoms

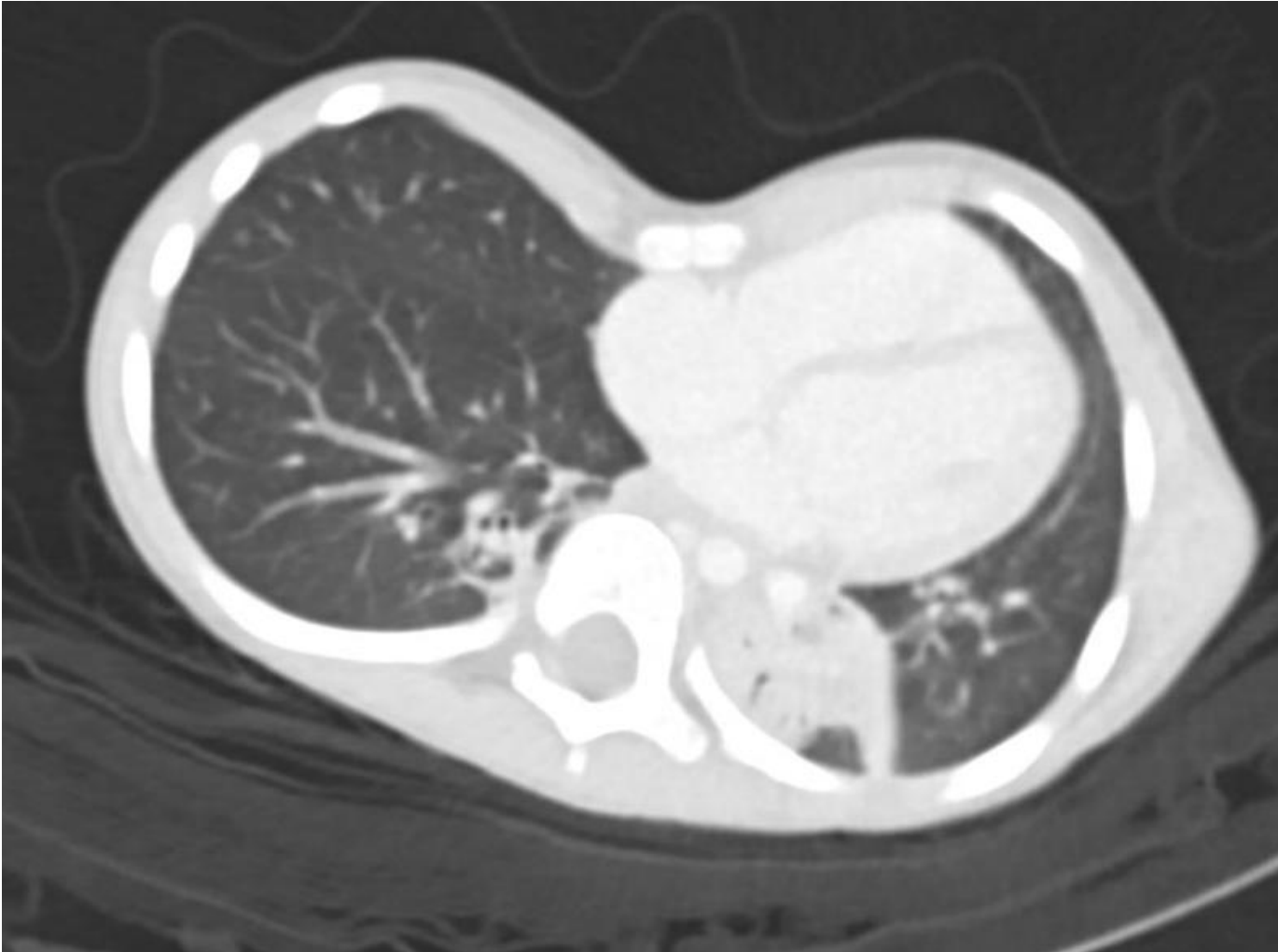


Persistent Fever in a 4-year-old

Course

- Returned few days later with new LRTI symptoms
- Admitted to PICU
- Respiratory panel: +paraflu
- CXR: bilateral perihilar interstitial opacities, no change in LLL opacity
- CBC: $16 > 11.7 < 530$
- CRP 3.5 mg/dL
- Hospital course:
 - Persistent respiratory distress
 - Daily high spiking fevers
- BAL – inflamed airways, moderate white mucus with plugging
- Chest CT

Persistent Fever in a 4-year-old



- Near complete LLL collapse/atelectasis
- Multifocal consolidations LUL, RLL
- Enlarged mediastinal and bilateral hilar LAD – nonspecific
- “presumed TB LAD could be considered in the appropriate clinical setting”

TB or not TB?

Persistent Fever in a 4-year-old

- Team started HRZE and broadened antibiotics for VAP/VAT
- Fever resolved within 24 hours
- BAL cultures grew *M. tuberculosis* ~4 weeks later

Case 2: Unilateral Wheeze

Unilateral Wheeze

History

- Subjective fever
- 2-3 weeks of cough + URI x2-3 days
- Active
- No weight loss/FTT

Contact

- Smear pos/NAAT pos no RIF resistance
- Shared sleeping space

Physical Exam

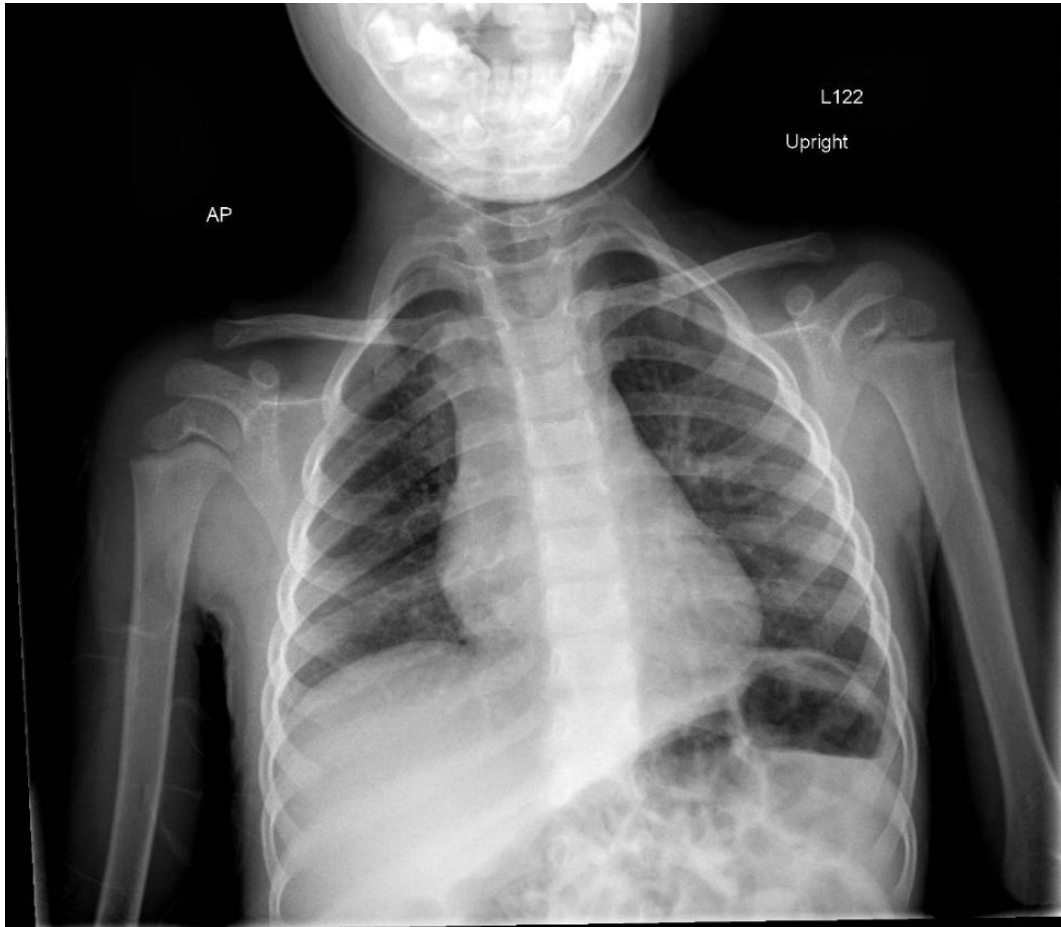
- RUL wheeze
- R cervical LAD

Laboratory

- QFN positive
- CXR normal 2 weeks ago, TPT not yet started
- HIV neg
- Rhino/enterovirus positive

Admit to hospital for gastric aspirate

Unilateral Wheeze



Limited evaluation due to decreased lung volumes and patient rotation to the right. Persistent right upper lobe pulmonary opacity. Prominent right paratracheal soft tissues could be due to adenopathy versus artifact from low lung volumes. Clinical, laboratory and imaging follow-up to assess for active tuberculosis infection.

Unilateral wheeze

Admitted

- 3 early morning gastric aspirates
- Chest CT (poor quality CXR)
 - Ghon Complex/ Primary TB:
 - Small central calcified nodule
 - R paratracheal and hilar adenopathy
- HRZE



Unilateral wheeze

Admitted

- 3 early morning gastric aspirates
- Chest CT (poor quality CXR)
 - Ghon Complex/ Primary TB:
 - Small central calcified nodule
 - R paratracheal and hilar adenopathy
- HRZE



What did the radiologist miss?

Unilateral Wheeze – Represented 8 days later

- Woke up in the middle of the night crying, initially fell back asleep but then awake again and was weak and fussy
- Rhinorrhea, cough and fever had resolved

ED Course:

- Afebrile. HR 180s. SaO2 60s on RA.
- VBG: 7.26/45; respiratory viral panel negative.
- NS bolus (20 mg/kg); BiPAP initiated but did not improve oxygenation
- CXR showed complete white out of R lung
- Emergently intubated

Unilateral Wheeze



Unilateral Wheeze



Bronchoscopy

- Copious secretions
- Small piece of pedunculated tissue in R mainstem bronchus causing near complete occlusion (granulomatous tissue?)

Unilateral Wheeze



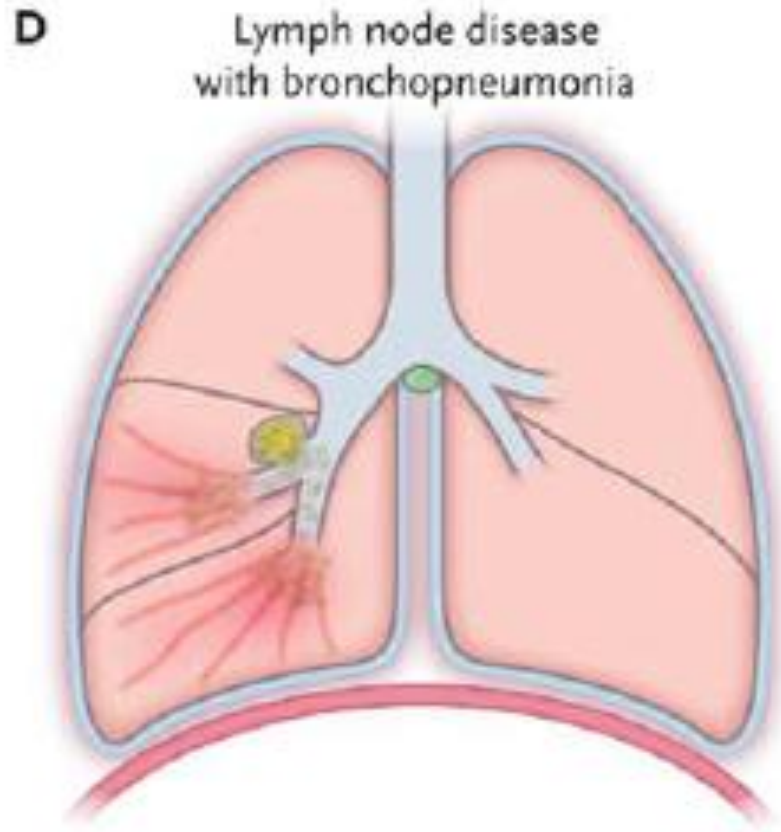
Slightly decreased prominence R upper mediastinal and R hilar necrotic LAD with persistent mass effect on surrounding structures

Decreased narrowing R mainstem bronchus, persistent mild narrowing of RUL bronchus

Similar RUL consolidation adjusted to mediastinal LAD

New RUL septal thickening and groundglass attenuation possible compression of venous vasculature by mediastinal LAD

Unilateral Wheeze



- **Endobronchial TB: common complication of primary complex**
- Intubated ~week, steroids, airway too small for intervention
- Endobronchial washing: Xpert and culture positive

Best Practices for TB Screening in Children

Window Prophylaxis for Young Children

- Children < 5 years of age
- Close contact of INFECTIOUS TB index patient
 - Last exposure < 8 weeks prior
- No clinical symptoms consistent with TB disease
- TST or IGRA negative
- CXR negative

Window Prophylaxis for Young Children

- vDOT may be considered
- Second TST/IGRA should occur 8-10 weeks later AND when infant is > 6 months old
- High risk children (by exposure or child's risk of progression):
 - Weigh risk/benefit with family
 - Family often decides to continue 4R for few more weeks

Best Practices for Pediatric Consults

Pediatric Consults

Lessons learned

- Send age, weight (preferably in kg) with every consult
- Send pediatric history and be specific about what was asked (follow slides here)
- Happy to read a CXR that is accompanied by clinical history
- Happy to review your clinical decision making and/or see a complicated patient!



Prevention and Health Promotion Administration

<https://phpa.health.Maryland.gov>