61ST ANNUAL

Denver TB Course

(Hybrid Event)

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National Jewish Health®

Pediatric Tuberculosis

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Disclosures

- No financial disclosures or conflicts of interest

Learning Objectives

- Unique challenges of TB diagnosis and treatment in kids
- Pediatric TB diagnostic updates
- Pediatric TB treatment updates
- Future opportunities

Take-Away Points

- For LTBI testing in kids, AAP now recommends TST or IGRA regardless of age (even < 2yo)
- Can use 3HP (kids > 2yo) and 4R regimens for LTBI treat in kids, weight-based dosing
- Samples other than sputum (gastric aspirates or stool) for smear, PCR, and culture testing for kids too young to collect sputum
- Higher risk for progression from TB infection to disease the younger a child is
- Kids with LTBI can jumpstart “reverse” contact tracing to look for adults with active TB

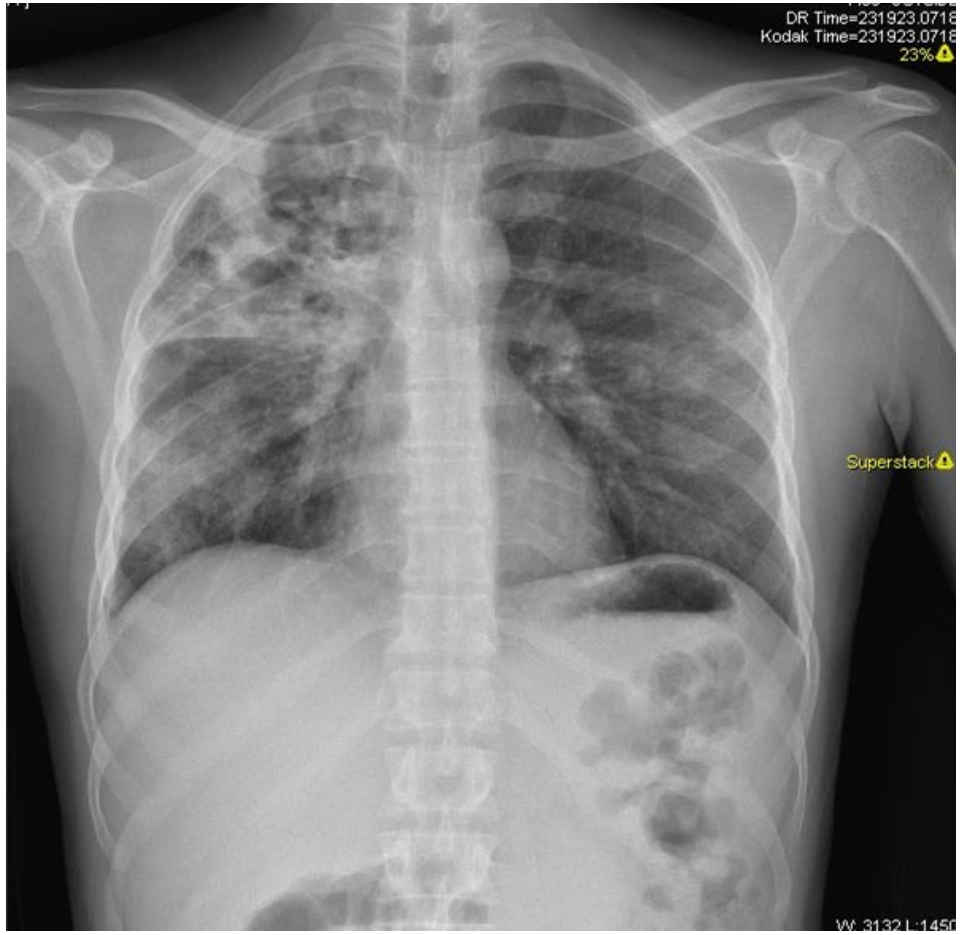
What's different about kids?

- More frequently disseminated or extrapulmonary disease compared to adults
- Often subtle symptoms (e.g. just fever or FTT)
- Sputum samples are paucibacillary (few mycobacteria), thus often smear and culture negative
- Negative testing should not rule out disease if clinical suspicion is high (pulmonary or extra-pulmonary disease)
- Completing treatment courses for both LTBI and active TB often difficult (e.g. toddlers who don't like liquid medications, adolescents who may have other priorities)
- Medications are generally well tolerated (lower rates of hepatitis and other complications)
- Window prophylaxis for kids under 5yo: initiate LTBI regimen for close contacts even with negative initial testing, then retest at 8-10 weeks

Pediatric TB: Helpful Cases and Pearls

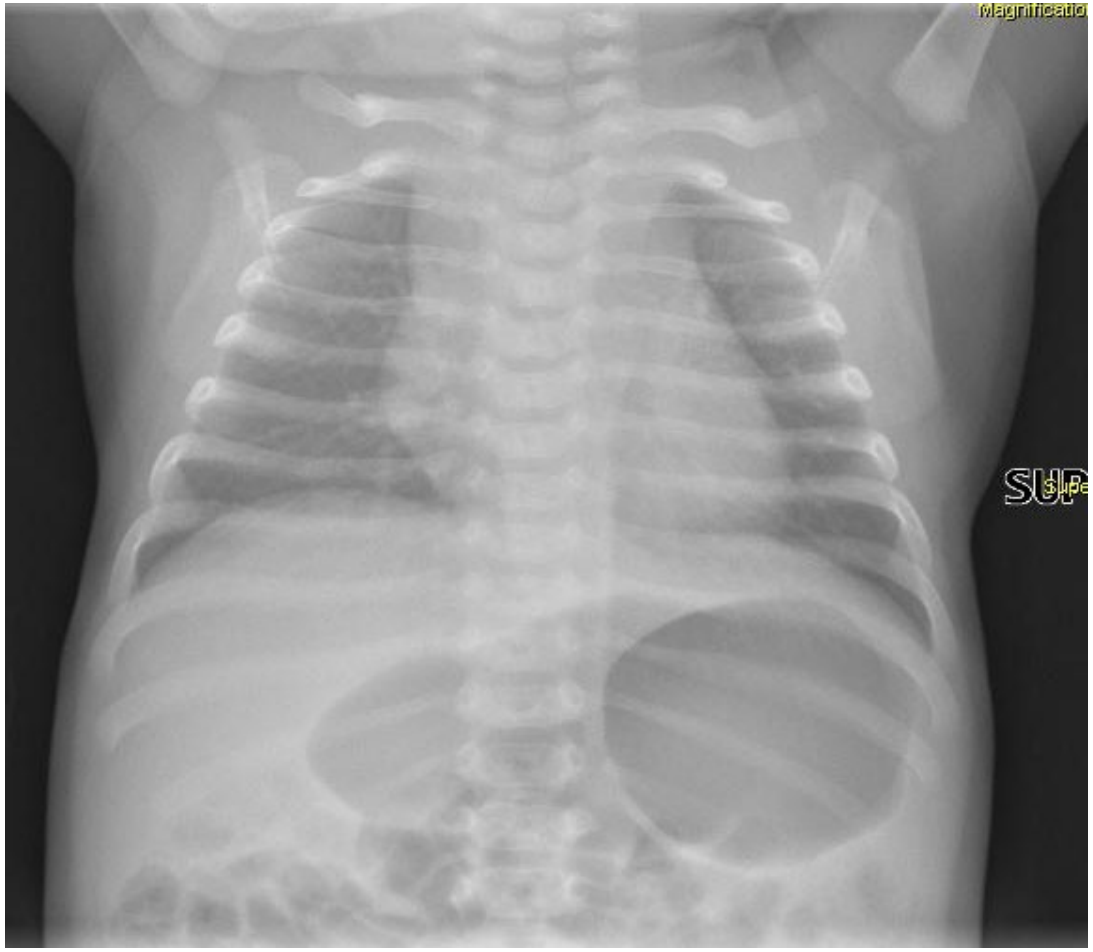
Case 1: Rapid Progression in Peds

- 2 month-old male
- Exposure to father with active TB



Case 1

- 2 month-old male
- Exposure to father with active TB
- Asymptomatic child at initial visit
- Initial CXR:



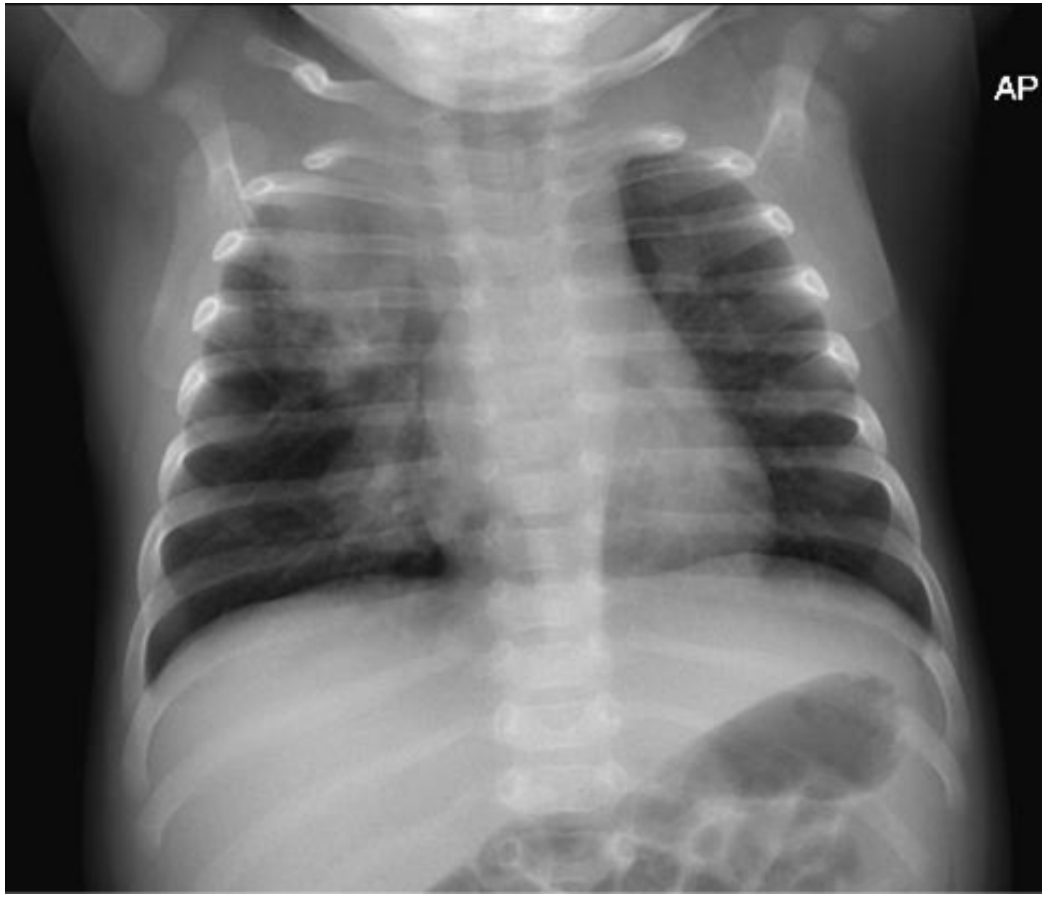
Slide credit: James Gaensbauer

Case 1

- 2 month-old male
- Exposure to father with smear positive cavitary TB
- Asymptomatic child at initial visit
- Initial CXR: Normal
- TST negative
- Treatment for window prophylaxis delayed for about 2 weeks

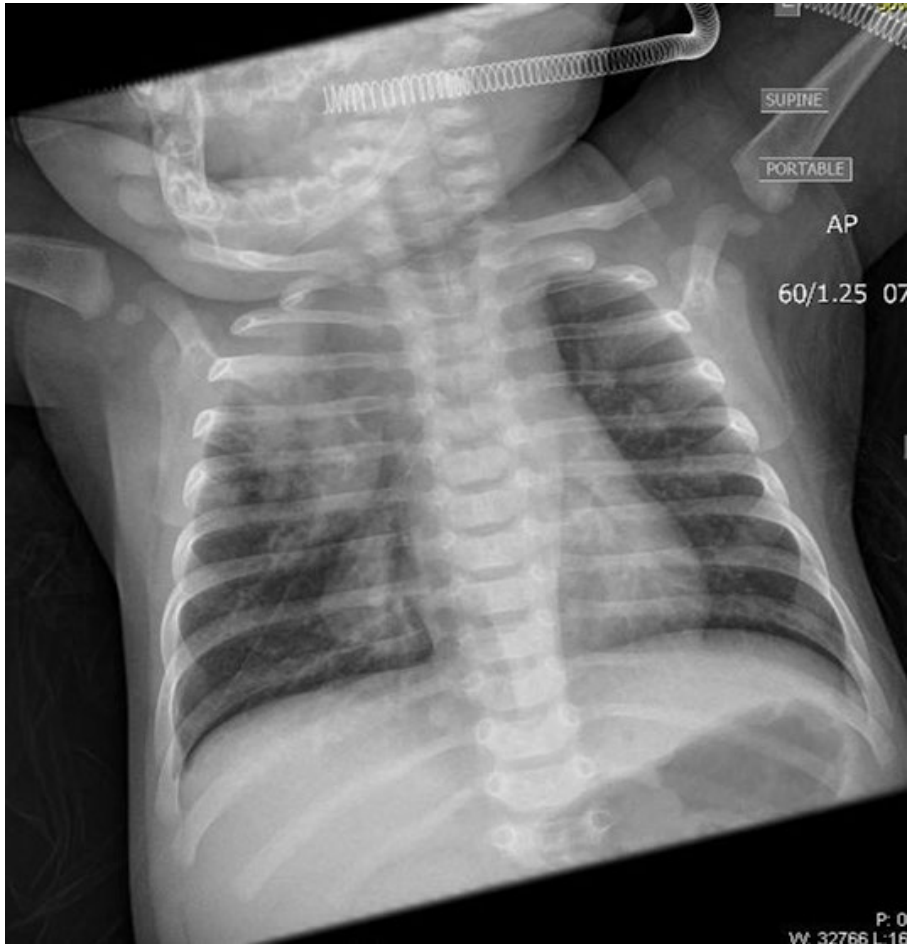
Case 1

- Six weeks after initial presentation, and 4 weeks of rifampin
- Presents to ED with increased work of breathing and lethargy
- Sounded like symptoms had been progressively worsening, but had not presented to care



Case 1

- Admitted to hospital
- Gastric Aspirates: smear +
- 4 drug treatment started (Levofloxacin, INH, Ethambutol, PZA)
- Worsened respiratory distress



Slide credit: James Gaensbauer

Age dependent progression from initial infection to TB disease

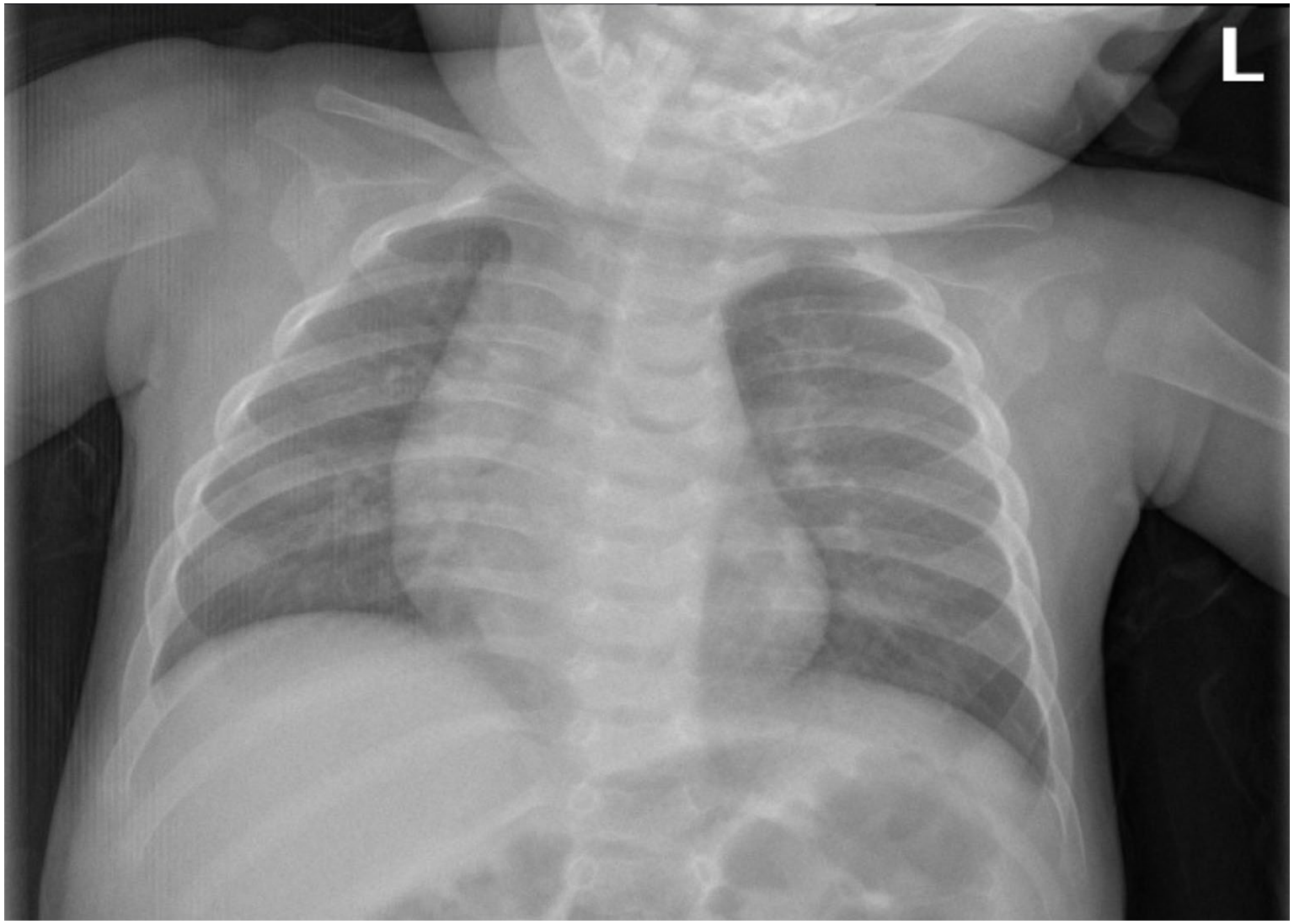
Age	Pulmonary TB	Disseminated TB/ TB meningitis	No Disease
< 1 year	30-40%	10-20%	50%
1-2 years	10-20%	2-5 %	75-80%
2-5 years	5%	0-5%	95%
5-10 years	2%	< 0-5%	98%
> 10 years	10-20%	< 0-5%	80-90%

Adapted from Cruz et al, 2007

Case 2: Peds CXR challenges

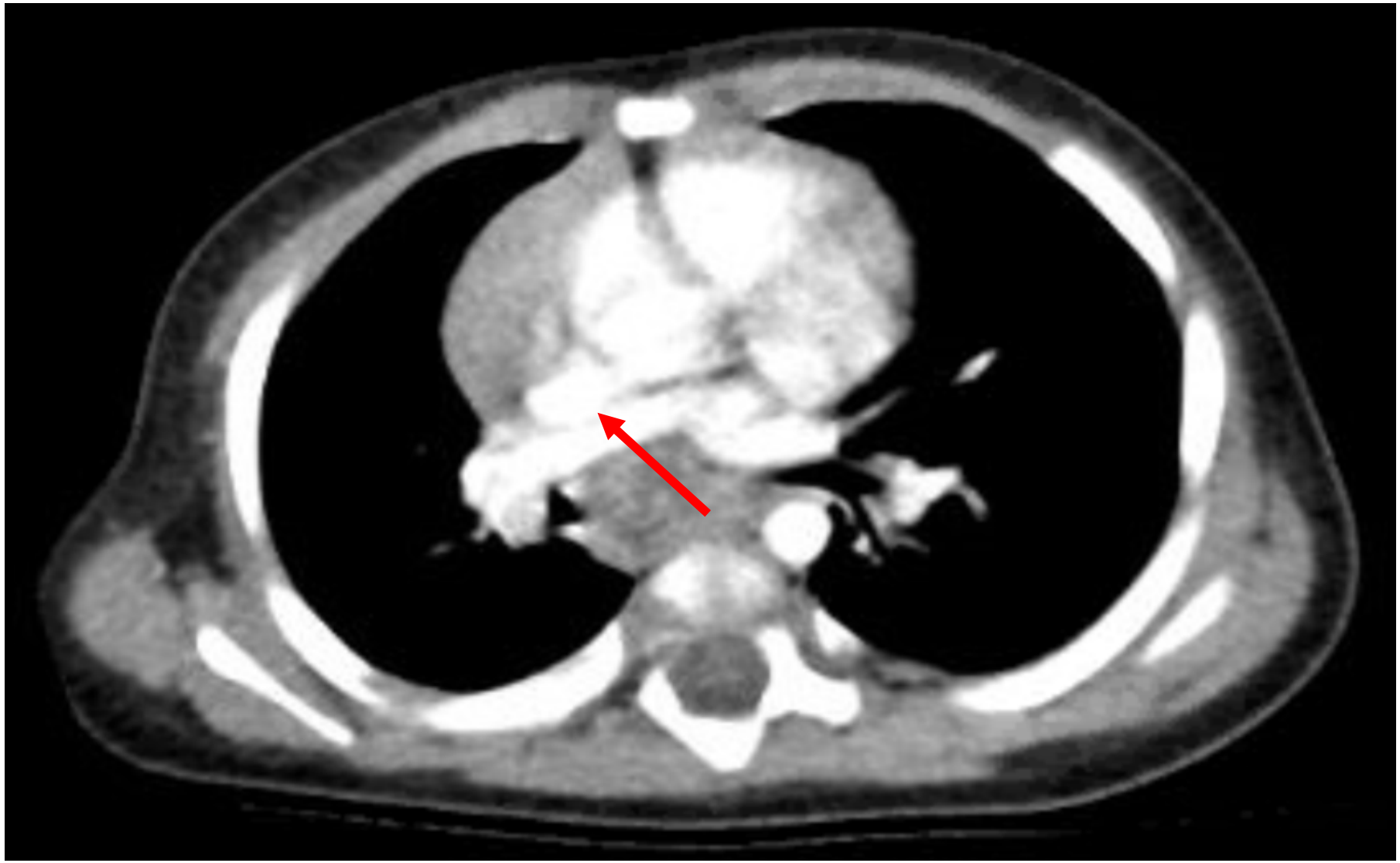
- 7 month-old male
- 18 year-old mother with smear positive pulmonary TB
- Asymptomatic child
- TST 12 mm – positive given close contact with case and age < 4 years

Case 2



Slide credit: James Gaensbauer

Case 2

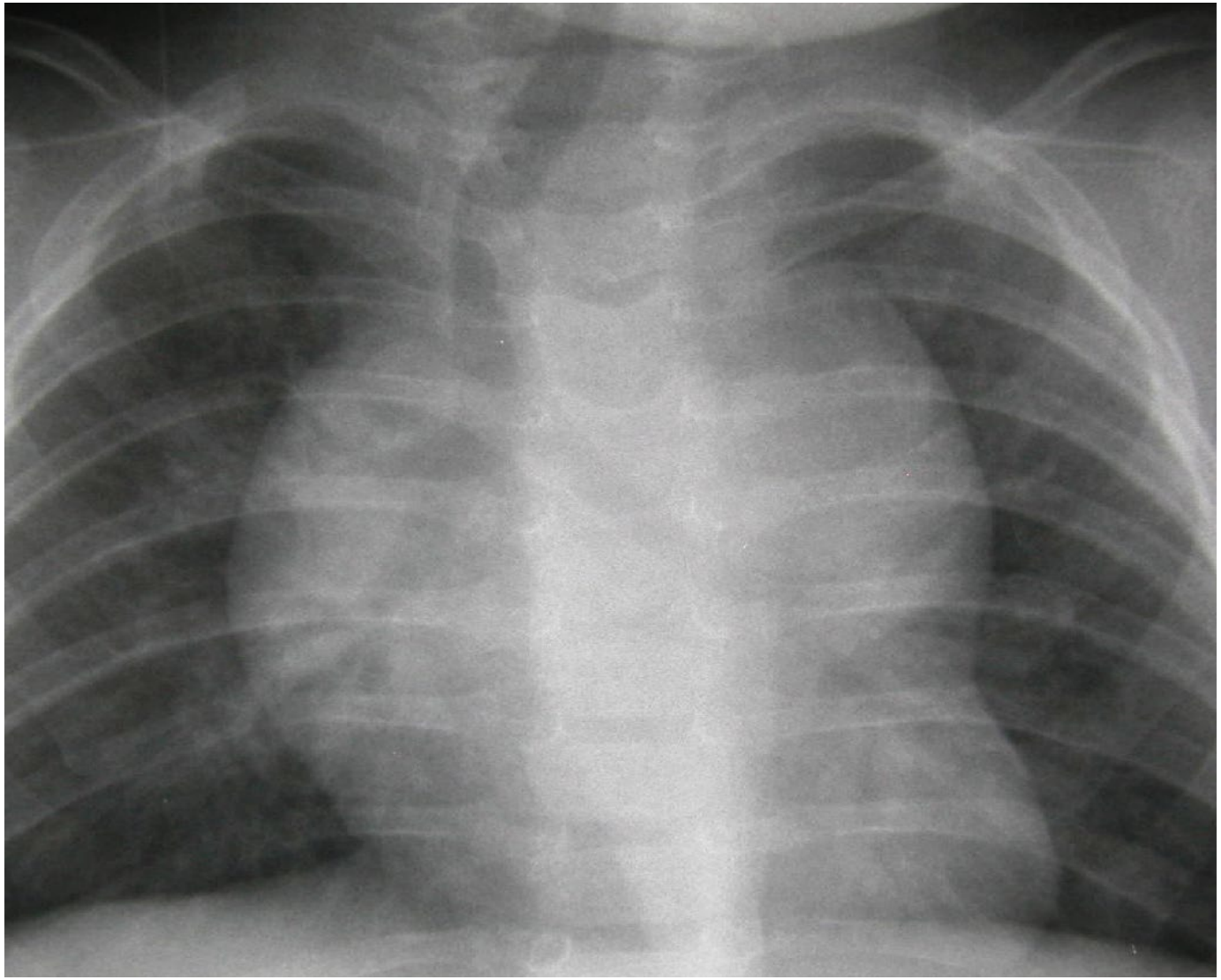


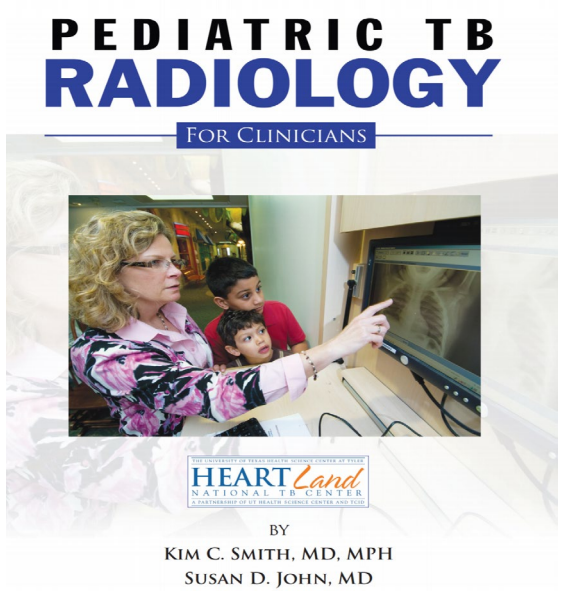
Slide credit: James Gaensbauer

Case 2

- 7 month-old male
- 18 year-old mother with smear positive pulmonary TB
- Asymptomatic child
- TST 12 mm – positive given close contact with case and age < 4 years

- CT shows hilar and subcarinal nodes

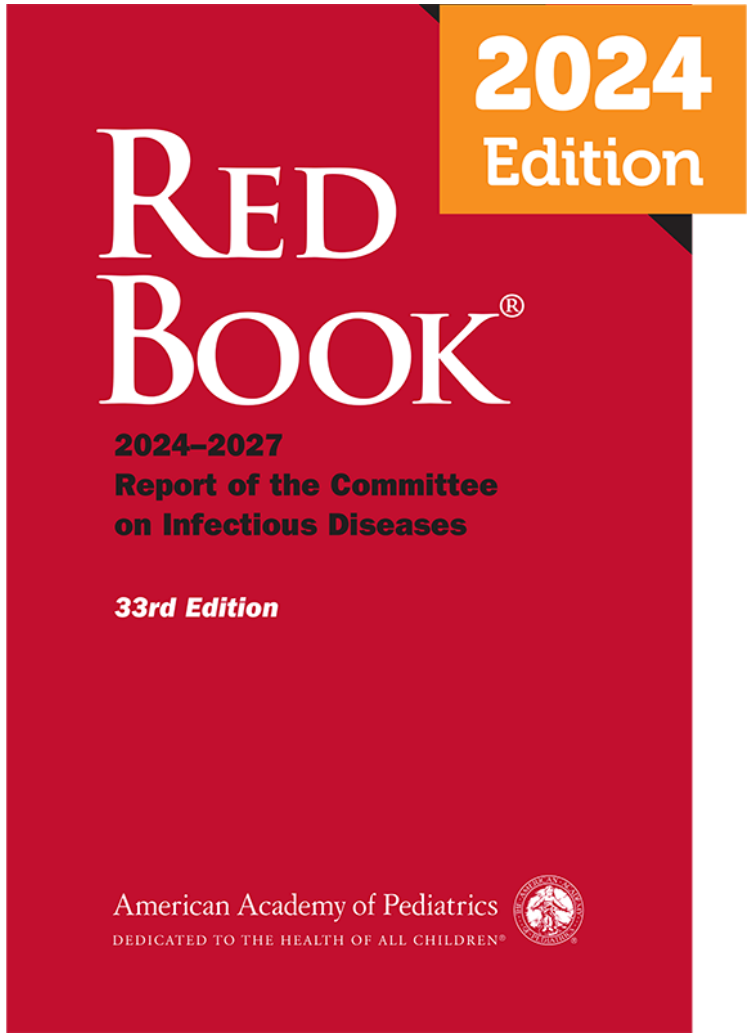


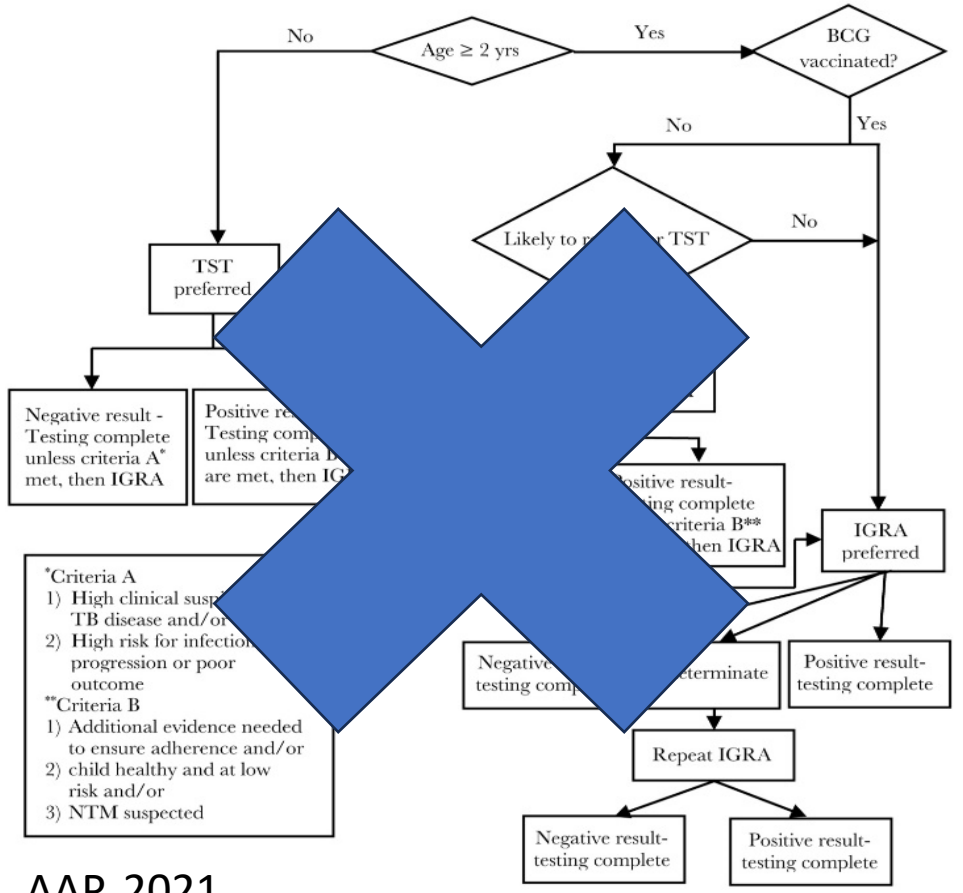


- Smith K and John S. Pediatric TB Radiology for Clinicians. Heartland National TB Center. https://www.heartlandntbc.org/wp-content/uploads/2021/12/pediatric_tb_radiology.pdf

Slide credit: James Gaensbauer

Pediatric TB Diagnostic Updates





AAP, 2021

TB Infection (LTBI)

- Kids older than 1 year
  - IGRAs or TSTs
  - We use almost solely IGRAs in this age group now at Denver Metro TB clinic

Interferon-Gamma Release Assays and Pediatric Public Health Tuberculosis Screening: The San Francisco Program Experience 2005 to 2008 FREE

Jennifer A. Grinsdale, Shamim Islam, Olivia Chang Tran, Christine S. Ho, L. Masae Kawamura, Julie M. Higashi Author Notes

JOURNAL OF THE Pediatric Infectious Diseases Society

Out of 179 foreign-born, BCG-vaccinated patients….

- QFT negative/TST positive discordance occurred in 79% (142/179)
- Rate of discordance < 5 years was 93% compared to 73% in older children
- Kids a higher risk for infection had higher IGRA positivity (see table)
- No true "sensitivity" value for IGRA here because no gold standard test
- Reported NPV 100% for IGRA testing, since no active TB cases occurred among QFT negative patients of with median follow up of 5.7 years

Patient Category	Positive Quantiferon
All patients <15 years	**72/1092 (7%)**
Recent TB contacts	**15/136 (11%)**
Foreign-born noncontacts	**53/807 (7%)**
US-born noncontacts	**4/149 (3%)**
Age 2-<5 years	**9/236 (4%)**

Grinsdale et al, 2014

TB Infection (LTBI)

- Kids under 1 year old
  - TST or IGRA – one is not preferred over the other according to AAP
  - Lots of studies consider concordance (agreement between two tests)
  - Discordance maybe useful as well, at least TST + / IGRA –

IGRA under 2: Denver TB Clinic experience

Demographic/Clinical Characteristics of QFT-tests ordered, children <2 years, n=59 tests (57 children)	
Characteristic	**Value**
Age in months (median (range))	**19 (7-23)**
Testing scenario	
Refugee screening	**24 (41%)**
Health maintenance/high risk demographic	**12 (20%)**
Positive TST (high-risk demographic; no contact)	**7 (12%)**
Contact	**13 (22%)**
Miscellaneous	**3 (5%)**

Test Results				
Negative	Positive	Indeterminate	Unable	Refused
54 (92%)	2 (3%)	0 (0%)	1 (2%)	2 (3%)

Slide credit: James Gaensbauer

Gaensbauer et al, 2020

IGRA under 2: Denver TB Clinic experience

IGRA testing among children <2 years performed well and achieved programmatic goals:

- Positivity rates consistent with older patients in our system and clinical risk
- Low rates of indeterminate results and phlebotomy failure
- Robust mitogen reactions
- Significant reduction in LTBI treatment courses compared to reliance on positive TST
- No incident case of TB in screened population with median follow-up time of 2.96 years

Slide credit: James Gaensbauer

Gaensbauer et al, 2020

IGRA Benefits and Uncertainties

- IGRA Benefits:
  - Increased specificity (particularly in BCG vaccinated population)
  - Single visit
  - Easier documentation
  - Declining skill in placement and interpretation of TST

- IGRA Uncertainties:
  - Lack of gold standard for comparison
  - Indeterminate results
  - False negatives? But consider the discordant (TST + / IGRA -) data
  - Performance in kids < 12 months less certain
  - Discomfort with pediatric phlebotomy – relatively large volume of blood for kids < 1yo

Programmatic Goals in Pediatric TB Control

1. Identify and treat active TB cases
2. Prevent progression from TB infection (LTBI) to TB disease (active TB)
3. Minimize unnecessary medication exposure in children without true LTBI

Table 6. Estimated Cases of TB Disease During Follow-up Period If LTBI Cases Had Been Missed

Age	Untreated TST⁺/QFT⁻ or Indeterminate (Contacts to Contagious TB Cases)	Lifetime Risk of Disease Following Missed/ Untreated LTBI*	Total Expected Cases of TB Disease If LTBI Missed/Left Untreated*	If 90%** of Those Developing Disease Do So Within Available Follow-up Time*	If 75% of Those Developing Disease Do So Within Available Follow-up Time	If 50%** of Those Developing Disease Do So Within Available Follow-up Time
0 to <1	0 (1)	~50%	1	1	1	1
1 to <2	3 (0)	~20%–30%	1	1	1	1
2 to <5	47 (0)	~5%	2	2	2	1
5–10	0 (4)	~2%				
10 to <15	96 (2)	~10%–20%	4–9	4–8	3–7	2–5
All ages	146		8–13	8–12	7–11	5–8

Grinsdale, 2014

TB Disease (Active TB)

- Role of IGRA and TST
  - Prior systematic reviews and meta-analyses showing poor sensitivity (60-70%) for IGRAs
    - Issues with heterogeneity in case definition (culture proven vs clinically defined)
  - Newer data showing 93% sensitivity in culture positive cases for IGRAs (Kay et al, 2018)
    - Slight increase in overall sensitivity if IGRA added to TST, but no improvement if TST added to existing IGRA
- Microbiologic diagnosis
  - Updates with PCR

Kay et al, 2018

Microbiologic Diagnosis

- Challenges: paucibacillary disease/poor aerosolization, sputum samples low yield and challenging in young children
- Alternate options but also low smear/culture sensitivity:
  - Bronchoscopy
  - Induced sputum
  - Gastric aspirates—challenging (protocol attached)
  - Stool testing
  - Biopsy
- Low culture yield also problematic in non-pulmonary samples (CSF)

Xpert MTB/RIF in Pediatrics

WHO 2013 Expert Group/Systematic Review (older data):

- Sensitivity of 55-90% for expectorated sputum, 40-100% for induced sputum, and 40-100% for gastric aspirate samples
- For culture proven disease, the Xpert MTB-RIF had a pooled sensitivity of 66% from both sputum and gastric samples in children, compared with a pooled sensitivity of 22-29% for smear microscopy
- Sensitivity of Xpert MTB/RIF for identifying smear-positive children was 95-96% (depending on sample source) and 55-62% for smear-negative children
- May outperform culture in gastric aspirates, BAL, CSF (though still low overall)

WHO, 2021

Xpert Ultra PCR testing (Cochrane 2022)

- Sputum: sensitivity 75%, specificity 97% compared to culture
- Gastric Aspirate: sensitivity 70%, specificity 94% compared to culture
- Stool: sensitivity 56%, specificity 98% compared to culture
- Nasopharyngeal: sensitivity 43%, specificity 97% compared to culture

Kay et al, 2022

Xpert Ultra PCR (Cochrane 2022) - Sputum

- For a theoretical population of 1000 children where 100 have pulmonary TB (10% prevalence) in sputum via culture
  - 101 would be Xpert Ultra-positive
    - of these, 26 (26%) would not have pulmonary tuberculosis (false positive)
  - 899 would be Xpert Ultra-negative
    - of these, 25 (3%) would have tuberculosis (false negative)

Kay et al, 2022

Xpert Ultra PCR (Cochrane 2022) – Gastric Asp

- For a theoretical population of 1000 children where 100 have pulmonary TB (10% prevalence) in gastric aspirate via culture
  - 123 would be Xpert Ultra-positive
    - of these, 53 (43%) would not have pulmonary tuberculosis (false positive)
  - 877 would be Xpert Ultra-negative
    - of these, 30 (3%) would have tuberculosis (false negative)

Kay et al, 2022

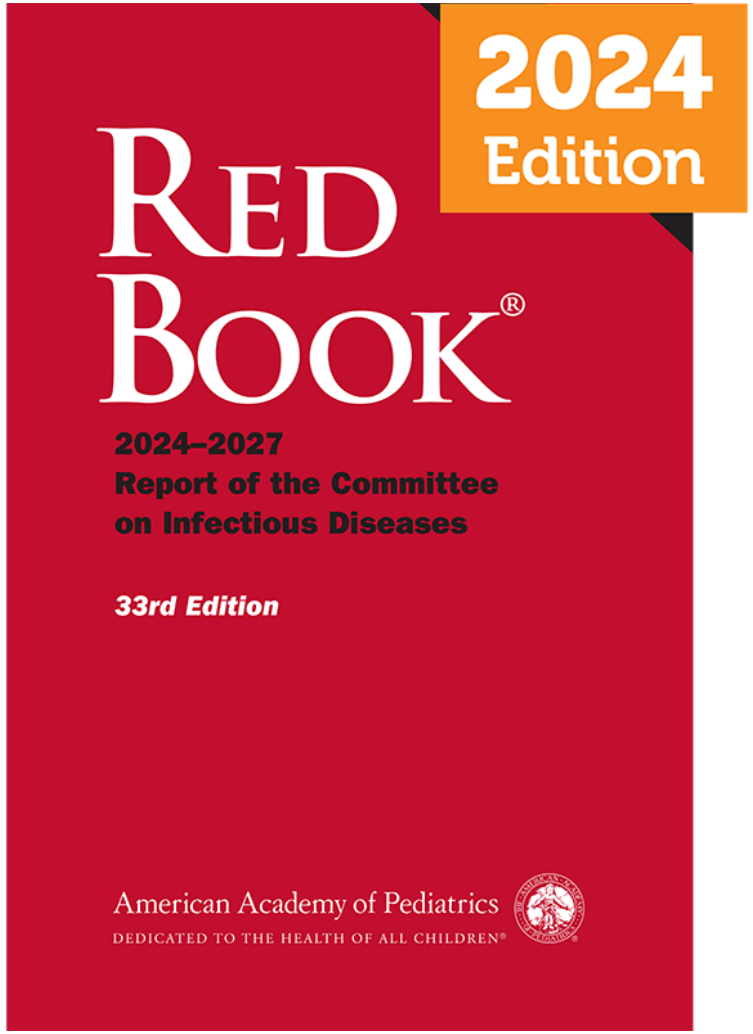
Xpert Ultra PCR (Cochrane 2022) – Stool

- For a theoretical population of 1000 children where 100 have pulmonary TB (10% prevalence) in stool via culture
  - 74 would be Xpert Ultra-positive
    - of these, 18 (24%) would not have pulmonary tuberculosis (false positive)
  - 926 would be Xpert Ultra-negative
    - of these, 44 (5%) would have tuberculosis (false negative)

Kay et al, 2022

Pediatric TB Treatment Updates

AAP: LTBI Regimens for children



- 3 months INH/rifapentine
- 4 months rifampin
- 6/9 months INH
- 6 months of levofloxacin**

AAP, 2024

Treatment for Preventing Tuberculosis in Children and Adolescents: A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

JAMA Pediatr. 2015;169(3):247-255. doi:10.1001/jamapediatrics.2014.3158

- 1058 high risk children age 2-17 years enrolled in the PREVENT TB trial
- 3HP vs 9H, via DOT
- Treatment completion: 88.1% INH/RPT vs. 80.9% INH; p=0.003
- Adverse events leading to treatment discontinuation were more common in INH/RPT patients, but rare overall (1.7%)

No. of TB Cases and Event Rates by Treatment Arm (MITT Population)

Treatment Arm	No.	TB Cases[a]	TB per 100 Patient-Years	Cumulative TB Rate, %
Isoniazid only	434	3	0.27	0.74
Combination drug therapy	471	0	0.00	0.00

Slide credit: James Gaensbauer

Villarino et al, 2015

Window Prophylaxis

- Kids < 5 years old
- Close contacts with active pulmonary cases
- Initial visit
  - Initial testing with TST or IGRA, baseline CXR
  - Start LTBI regimen
- Follow-up visit at 8-10 weeks
  - Re-test with TST or IGRA, only need CXR if new symptoms
  - Stop treatment if testing is negative
  - Continue for full LTBI treatment course if testing is positive
  - Transition to active TB regimen and work up if symptoms develop or CXR changes

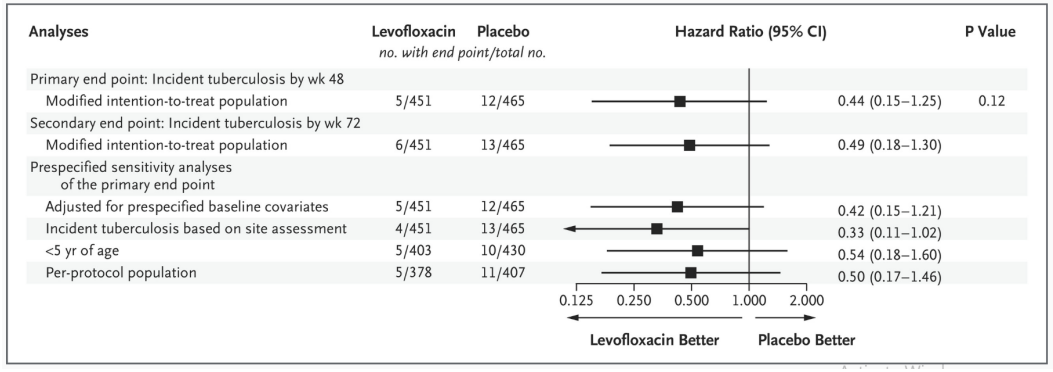
SHINE Trial (NEJM 2022)

- Non-interiority trial
- 4 vs 6-month standard regimen for non-severe, smear negative, drug susceptible TB in kids < 16 years old
- 66% respiratory disease, 30% mixed respiratory and lymphatic disease, 3% lymphadenitis only, 1% other
- 14% with microbiologically confirmed TB (not unusual)
- 4-month regimen was non-inferior

Turkova et al, 2022

TB-CHAMP Trial (NEJM 2024)

- Cluster-randomized, placebo control trial
- Efficacy of levofloxacin preventive therapy for pediatric household contacts to confirmed MDR-TB cases
  - Levofloxacin vs placebo (not another LTBI regimen)
- Study population:
  - Kids < 5yo
  - Kids > 5-17yo with positive IGRA and/or HIV infection
- Outcome of interest: cases of tuberculosis, followed for 1 year
- TB disease developed in 1.1% in levofloxacin group, 2.6% in placebo group (95% CI to 0.15-1.25)
- Clinically significant, not statistically significant?



Hesseling et al, 2024

Research Priorities

- LTBI: evaluation for IGRAs in children under 2yo, particularly under 12mo
- Possible future recommendations around pooled sampling
  - E.g. 2 nasopharyngeal samples and 1 stool sample for PCR to increase sensitivity and less invasive testing
- Global push to decentralize testing – such as more Xpert PCR testing in more places, though still not a wonderful test
- Need for pediatric specific biomarkers
- Need for better non-respiratory sample-based testing
- More data on MDR regimen safety and efficacy in kids
- Role of chest CT in diagnostic algorithms

What's different about kids?

- More frequently disseminated or extrapulmonary than adults
- Often subtle symptoms (e.g. just fever or FTT)
- Sputum samples are paucibacillary (few mycobacteria), thus often smear and culture negative
- Negative testing should not rule out disease if clinical suspicion is high (pulmonary or extra-pulmonary disease)
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Thank you

Questions?

Citations

1. Smith K and John S. Pediatric TB Radiology for Clinicians. Heartland National TB Center. https://www.heartlandntbc.org/wp-content/uploads/2021/12/pediatric_tb_radiology.pdf
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Gastric Aspiration Protocol: Denver Health

- Upon admission nurse to place NG tube
  - Infant: 8 French
  - Child: 10 French
- Confirm placement of NG tube using standard ward methods; if uncertain order 1-view XR
- NPO after 8 PM (if infant unable to tolerate NPO, discuss with ID)
- Inform mycobacteria lab of admission and planned sample timing and collect appropriate tube
- Nurse or Pediatric Resident to obtain gastric aspirate at 0600 or immediately if patient awakens earlier.
  - The patient should remain resting, lying down and NPO until after the procedure (should not get out of bed at all)
- Aspirate stomach contents (typically 5-10 ml) and place immediately in prepared buffered tube
- If no fluid returns, 20 ml of sterile (but not homeostatic) saline should be infused, and then aspiration attempted again immediately.
- If still no significant yield, advance and withdraw the tube slightly while aspirating
- If yield is less than 5–10 ml, roll the child on the left side, advance the tube, aspirating continuously to find the pool of mucous in the stomach
- If still no yield, any collected mucous should be placed in the sample tube
- Sample sent directly to mycobacterial lab for AFB stain and culture
- Call mycobacterial lab to assure sample receipt and immediate buffering
- Patient may eat/move ad lib until next NPO.
- NG tube should remain in place until all three aspirates are obtained

Slide credit: James Gaensbauer