Pediatric Tuberculosis

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Disclosures

- No financial conflicts related to content in this presentation
- Off-label use:
  - HZRE regimens are FDA approved for use in children
  - BUT antibiotics used as alternatives for drug-resistant TB (e.g., fluoroquinolones) may be off label – not approved for TB, or not approved in children. I will only focus on uses consistent with national and international guidelines.
- I received payments from the Moderna COVID vaccine trial (as a participant)
- Research activity: I run a core lab at Seattle Children's Research Institute that performs basic microbiology research for companies developing antibiotics for use in Cystic Fibrosis. I will not discuss any of these drugs or any other products from these companies here. Payments are made to Seattle Children's and not to me.

Risk of Complacence Towards Childhood TB

- Uncommon: 363 cases in children < 15yo in U.S. (CDC 2020)
- Typically, contagious risk is lower than adult cases
  - Paucibacillary disease is common – often smear negative
- Diagnosis is difficult
  - Cultures often difficult to obtain and lower yield
  - More reliance on clinical diagnosis
- BUT….

Age group	N	% total cases (rate)	Incidence per 100K
0–4 years	202	2.4%	1.1
5-14 years	161	1.9%	0.4
15–24 years	840	10.1%	1.9

2022 Data CDC, doi: 10.15585/mmwr.mm7212a1

Additional reasons for concern

- Young children have increased risk for severe/disseminated disease (meningitis, miliary TB)
- Sentinel public health event:
  - Represent recent/ongoing transmission
  - Limited circle of contacts
  - Opportunity to identify infectious cases in community
- Globally - 1.1 mil new pediatric cases in 2021 (<15yo) and approx. 220K pediatric deaths per WHO
- Estimated 20-40% of cases in high burden nations are children <15 yo

Objectives for Lecture

- Explain the key differences in clinical presentation, infectiousness, and diagnosis (including interpretation of chest x-rays) in children vs. adults
- Plan treatment courses for TB disease and TBI in children – including application of new 4-month regimens
- Identify strategies to make medication dosing in children more effective/tolerable
- AND relate other lecture learning objectives to pediatric populations

Risk of Disease Correlates with Age

No clear assoc. between age and risk of initial TB *infection*
BUT risk of TB disease is increased in very young

Highest progression to active disease in infants (<1 yo):

- Disease risk 40-50% following infection
- TB Meningitis or miliary disease = 10-20%
- Mortality risk = 5-10%

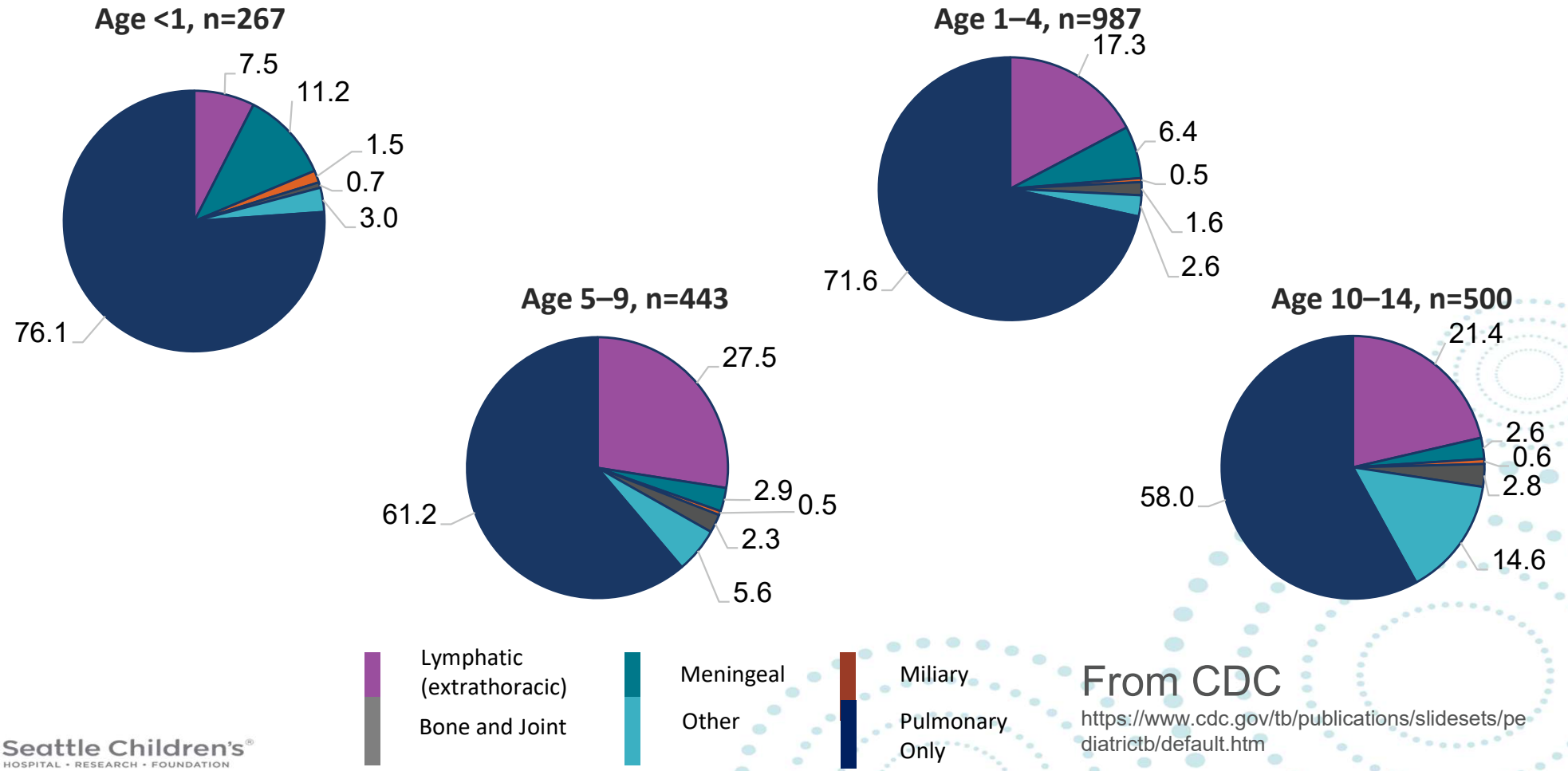
Lowest risk in 5-10 yo

- 2% progress to disease following infection, disseminated disease uncommon

Older children (>10 yo) typically develop adult like disease

Marais, et al 2004

Percentage of TB Cases in Children with Extrapulmonary Involvement by Age Group 2013–2017



From CDC
https://www.cdc.gov/tb/publications/slidesets/pediatrictb/default.htm

Review Four Basic Clinical Scenarios

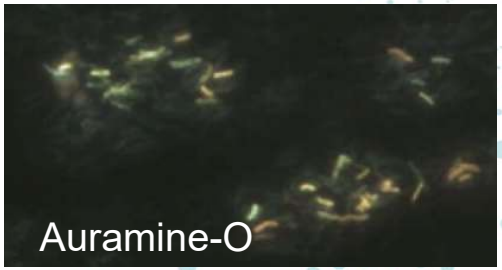
- Infection control & isolation for child with possible TB disease
- Screening healthy children for TB Infection
- Screening, evaluation & treatment of pediatric contacts of contagious TB cases
- Evaluation & treatment of symptomatic children

A 2 yo boy is admitted from clinic with concern for possible TB, due to persistent fevers, positive IGRA and prominent mediastinal lymph nodes on CXR.
What is the most important precaution to prevent new TB infections/exposures?

A. Start patient on treatment as soon as workup completed
B. Isolate patient to a negative pressure room
C. Isolate and screen family caregivers
D. Have patient wear a mask in transit

Transmission

- Airborne aerosol route (<10 micron)
- In general, smear positive status correlates with infectiousness
- **Most childhood TB is smear negative, esp. pre-teens, with lower bacterial burdens (<15% smear+)**
- One series at Texas Children's:
  - 7 of 59 children *potentially infectious*
  - 5 smear positive, mostly teens
  - Potential flags of infectiousness: pulmonary cavities, positive smears, laryngeal disease, extensive pulmonary infection
  - **15% of family caregivers have undiagnosed TB**
- **Parents/caregivers should be screened for TB**



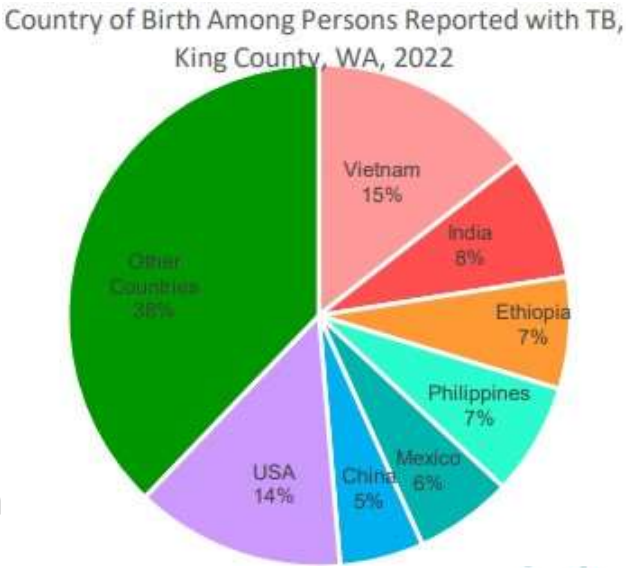
Cruz, et al 2011

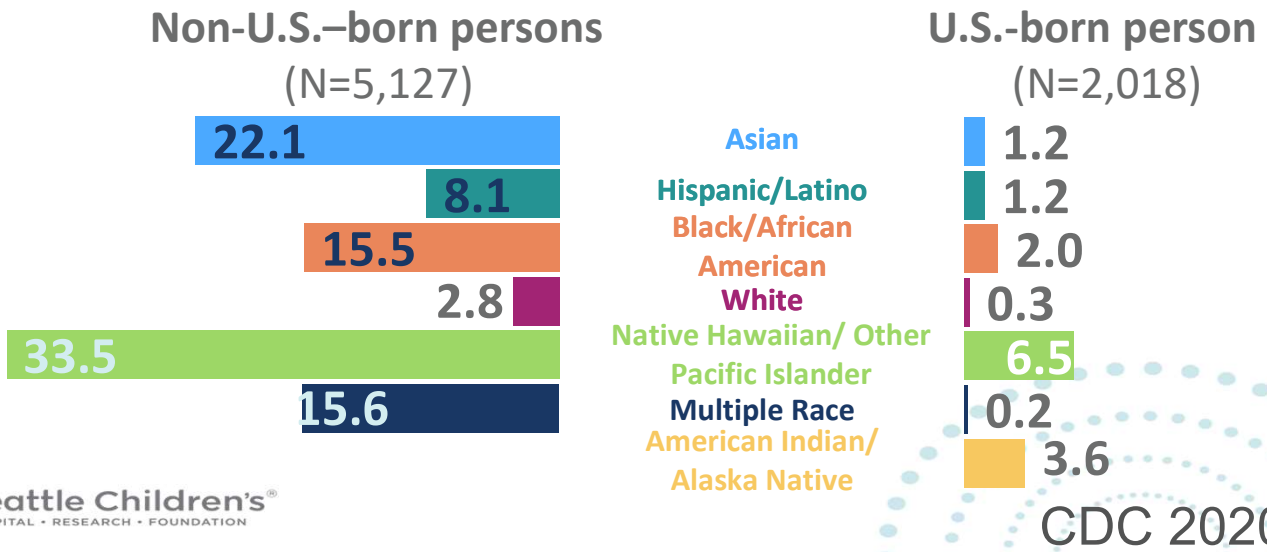
Young children rarely spread TB – adults around them are likely sources of new infections

To understand the epidemiology of childhood TB, you need to understand the epidemiology of adult TB in your community

Epidemiology Childhood TB in United States

- Observational x-sect study at 20 U.S. sites 2005-6
- (Pang, et al. *Pediatrics* 2014 cases in **children < 5yo**)
- 83% of Cases in US Born Children (vs. adults)
- Estimated TB Rates per 100K children:
  - 2.57 All Children
  - 24.03 Foreign-born children
  - 4.81 US born with ≥ 1 foreign born parent
  - 0.75 US born, with US born parents
- Source cases most often in home/family





CDC 2020

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A 6 yo recent adoptee from Ethiopia is seen in clinic for an initial well child exam. She has no symptoms, is HIV neg, and is well grown. Mom reports that she had a normal CXR for immigration, but no other known testing.

Does she need further testing for TB?

A. Yes, for latent TB infection
B. Yes, evaluation for active TB
C. No further screening is necessary

Targeted TB Screening in US

Test following children for TBI with TST or IGRA:

- **Contacts** of confirmed or suspected contagious TB
- With **radiographic or clinical findings** suggesting TB
- **Immigrating** from countries with endemic TB
- With **significant travel** to countries with endemic infection and substantial contact with resident population (e.g. 1 mo or greater)
- With **HIV** (annually)

- Test all children who will receive anti-TNFa agents, high-dose chronic steroids, other significant chemotherapy/immunosuppression, or undergo transplant
- Screen others at risk for TB progression (diabetes mellitus, chronic renal failure, malnutrition, immunodeficiency)

Screen otherwise asymptomatic children in the US w/ risk questionnaire

Based on AAP RedBook

Screen asymptomatic children in the US w/ risk questionnaire

Should be done at first visit and then annual Well Child Checks

- Has a family member or contact had TB disease?
- Has a family member had a positive TST or IGRA?
- Was your child born in a high-risk country? (other than U.S., Canada, Australia, New Zealand, or Western/Northern Europe)
- Has your child traveled to a high-risk country? How much contact did your child have with resident populations?

THESE QUESTIONS REFLECT EPIDIMEOLOGY

Test children responding YES (with a NEW risk)

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Based on AAP RedBook

6 yo girl adoptee from Ethiopia (continued).
You have determined she requires screening for LTBI.
Which test is the best choice to complete TB screening in this girl?

(Hint: On her exam you note a small scar on her right deltoid)

A. IGRA
B. TST
C. IGRA and TST
D. Repeat CXR

bcgatlas.org

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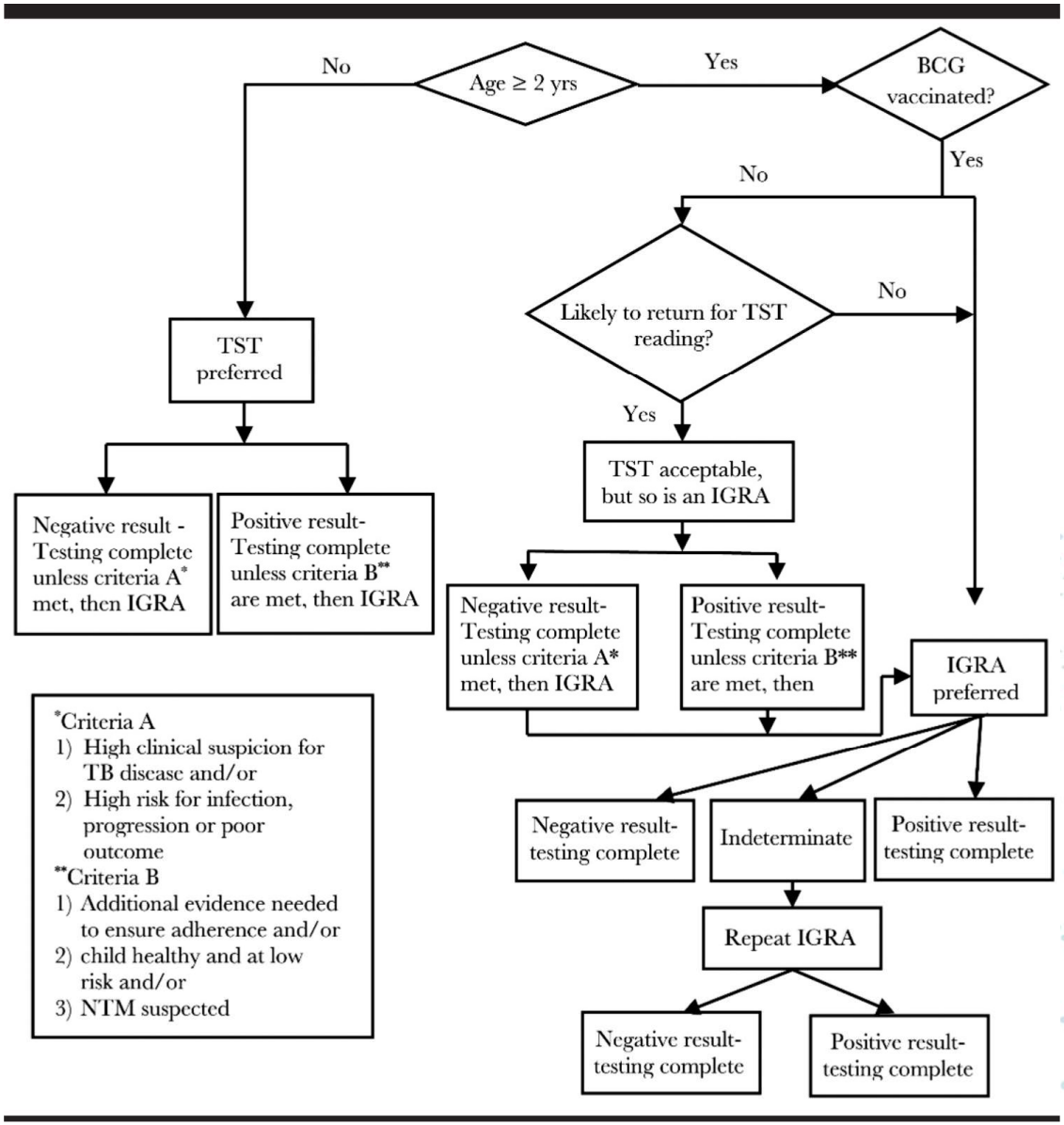
AAP RedBook IGRA vs. TST

Reminder:
TB antigens in IGRA are not present in BCG vaccine or most NTM pathogens



Source: AAP RedBook

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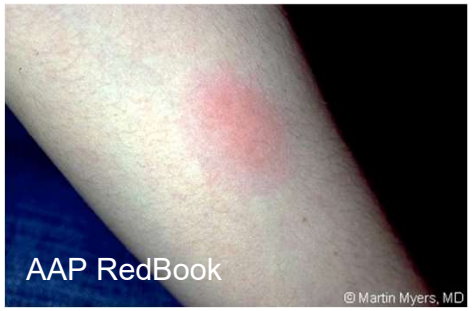
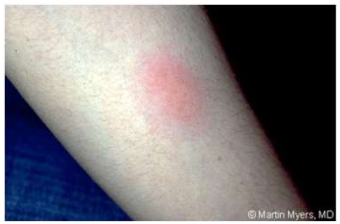
Interpretation of TST?
Similar to adults, **POSITIVE** if:



5 mm or greater

- **Close contact** with known or suspected contagious people with TB disease
- **Suspected** to have **TB disease**:
  - Findings on chest x-ray c/w active or previous TB disease
  - Clinical evidence of tuberculosis disease (PE or lab)
- Children **receiving immunosuppressive** therapy (high dose corticosteroids, anti-TNF agents, post-transplant)
- **HIV infection**

Interpretation of TST? (cont.)



10 mm or greater

- Children at **increased risk of disseminated TB** disease:
  - **Younger than 4 y**
  - Other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
- Children **with likelihood of increased exposure to TB** disease:
  - Born in high-prevalence regions
  - Travel or residence in high-prevalence regions (e.g. 1 mo or longer)
  - Frequently exposed to adults who are: living with HIV, unhoused, injection drug use, incarcerated

15 mm or greater

- Children ≥ 4 years **without any risk factors**

(Generally, do not need testing – sometimes required by schools, volunteer positions, etc.)

6 yo girl adoptee from Ethiopia (continued)
Mom brought her in for a RN visit last week and catch-up vaccines at school's request based on available records. Which of the following vaccines would delay her IGRA today, if the vaccine was given last week?

A. Hepatitis B
B. MMR
C. Meningococcal-conjugate
D. DTaP
E. None of the above

Live virus vaccine in prior 4-6 weeks is contraindication to TST (and IGRA)

- MMR vaccine known to blunt response to PPD (assume similar for IGRAs)
  - Give at same time as TST/IGRA
  - OR WAIT 4-6 weeks post vaccine
- Limited/no data for other live viral vaccines (Varicella, Influenza, Yellow Fever) – general rec is wait 4-6 weeks
- No evidence that inactivated/subunit vaccines affect TST

Should receipt of BCG vaccine affect interpretation of TST?

GENERALLY NO

General Rule: **TEST ONLY IF YOU WOULD TREAT POSITIVES**

- Multiple factors affect how individuals who received BCG react to TST:
  - Age of BCG immunization
  - Time since receiving BCG
  - Number of doses of BCG
  - Strain and quality of BCG given
  - Frequency of TST testing
- The following increase likelihood TST represents disease/infection
  - Symptoms consistent with TB disease
  - Known exposure (more likely to represent TB infection)
  - CXR findings consistent with current or past disease
- **Use IGRA in children 2 or older with prior BCG vaccination**

How should a patient with a positive TST or IGRA be treated?

Determine LTBI vs. TB Disease

- Focused History & Physical for signs and symptoms:
  - Cough > 2 weeks w/o improvement
  - Fever > 1 week/night sweats (maybe shorter)
  - Neurologic symptoms (persistent irritability)
  - Fatigue/malaise
  - Weight loss OR Failure to thrive (Review growth charts!)
  - Symptoms or h/o TB diseases in family/contacts
  - Physical Exam:
    - Lung findings- uncommon (rales, “wheeze” from nodes compressing airway)
    - Neurologic- alertness, behavior, meningeal signs, CNs
    - Check lymph nodes and musculoskeletal symptoms
- Screening Chest X-ray
- If asymptomatic and CXR w/o evidence of active TB: LTBI
- **All children with positive TST/IGRA should be considered for treatment**

Antibiotic regimens for LTBI in Children

- **INH + Rifapentine** weekly x 12 wk (SAT/DOT), age>2y ★
  - Data for >2 yo, HIV negative children/adolescents INH (>12y:15 mg/kg, 2-11y 25mg/kg, weekly)
  - Once weekly dosing
  - Rifapentine: 10-14kg=300mg, 14.1-25kg=450mg, 25.1-32kg=600mg, 32.1-49.9kg=750mg, >50kg=900mg
  - Isoniazid: ≥12 yo 15 mg/kg; 2-11 yo 25 mg/kg (Max 900 mg)
- **Rifampin** (15-20 mg/kg, max 600mg) daily x 4 mo ★
  - Use if concern for INH resistance or INH intolerance
- **INH + Rifampin** daily x 3 mo (alternate to above)
- **INH** (10-20 mg/kg, max 300) daily x 9 mo
  - Use when rifamycins cannot be used
  - Pyridoxine recommended for: exclusively breastfed, malnourished, diets poor in B6, HIV+
  - Hepatotoxicity rare in children
  - Alternate DOT twice weekly (20-40 mg/kg, max 900) x 9 mo

★ Better Compliance

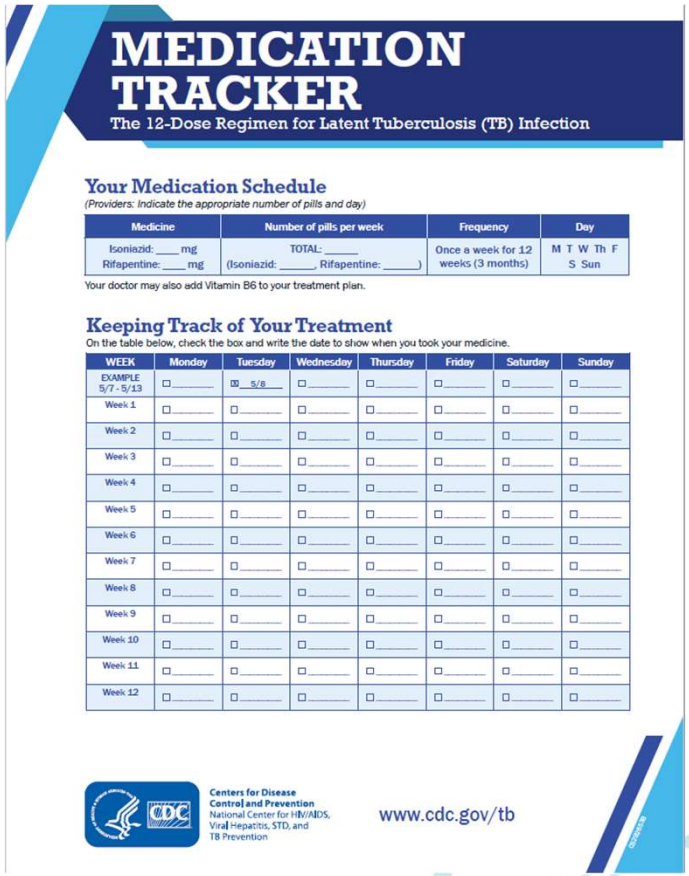
Antibiotic regimens for LTBI in Children

- Better Completion Rates
  - Cruz and Starke, 2018
  - 9H – SAT 52% completed
  - 4R – SAT 84% completed
  - 3HP – DOT 97% completed

PEDIATRICS 2018 doi: 10.1542/peds.2017-2838

Worksheets available to help your LTBI Patients

https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm



MEDICATION TRACKER

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Your Medication Schedule

(Providers: Indicate the appropriate number of pills and day)

Medicine	Number of pills per week	Frequency	Day
Isoniazid: ___ mg Rifapentine: ___ mg	TOTAL: _____ (Isoniazid: _____, Rifapentine: _____)	Once a week for 12 weeks (3 months)	M T W Th F S Sun

Your doctor may also add Vitamin B6 to your treatment plan.

Keeping Track of Your Treatment

On the table below, check the box and write the date to show when you took your medicine.

WEEK	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
EXAMPLE 5/7 - 5/13	☐	☒ 5/8	☐	☐	☐	☐	☐
Week 1	☐	☐	☐	☐	☐	☐	☐
Week 2	☐	☐	☐	☐	☐	☐	☐
Week 3	☐	☐	☐	☐	☐	☐	☐
Week 4	☐	☐	☐	☐	☐	☐	☐
Week 5	☐	☐	☐	☐	☐	☐	☐
Week 6	☐	☐	☐	☐	☐	☐	☐
Week 7	☐	☐	☐	☐	☐	☐	☐
Week 8	☐	☐	☐	☐	☐	☐	☐
Week 9	☐	☐	☐	☐	☐	☐	☐
Week 10	☐	☐	☐	☐	☐	☐	☐
Week 11	☐	☐	☐	☐	☐	☐	☐
Week 12	☐	☐	☐	☐	☐	☐	☐

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

www.cdc.gov/tb

SYMPTOM CHECKLIST

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Patient Name: _____

Normal Side Effects

Most people can take their TB medicines without any problems. The rifapentine medicine may cause your urine (pee), saliva, tears, or sweat to appear an orange-red color. This is normal and the color may fade over time.

STOP taking your medicine and CALL your TB doctor or nurse right away if you have any of the problems below:

- ☐ Dizzy or lightheaded when sitting or standing
- ☐ Less appetite, or no appetite for food
- ☐ Stomach upset, nausea, or vomiting
- ☐ Stomach pain or stomach cramps
- ☐ Pain in your lower chest or heartburn
- ☐ Flu-like symptoms with or without fever
- ☐ Severe tiredness or weakness
- ☐ Fevers or chills
- ☐ Severe diarrhea or light colored stools (poop)
- ☐ Brown, tea-colored, or cola-colored urine
- ☐ Skin or whites of your eyes appear yellow
- ☐ Skin rash or itching
- ☐ Bruises, or red or purple spots on your skin that you cannot explain
- ☐ Nosebleeds, or bleeding from your gums or around your teeth
- ☐ Shortness of breath
- ☐ Pain or tingling in your hands, arms, or legs
- ☐ Feelings of sadness or depression

Please talk to your doctor or nurse if you have any questions or concerns about treatment for latent TB infection.

Doctor/Clinic Contact Information

Name of the staff caring for you: _____

Phone number: _____

Address: _____

Hours: _____

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

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A 35 yo M from Mexico is diagnosed with smear positive pulmonary TB. Household contacts include: 8 yo daughter and 3 yo son. Both children have no sx, normal PE, normal CXR and IGRAs are negative.

What is the appropriate next step for the children?

A. 3 yo should start INH/RPT or RIF
B. 3 yo & 8 yo should start INH
C. 3 yo & 8 yo should start INH/RPT
D. 3 yo & 8 yo repeat IGRA or TST in 8-10 wk
E. Start 3 yo on HRZE for 6 mo

“Window Therapy”

- Young Children (<5yo) = INCREASED RISK
- Or other children at increased risk (HIV+, immunosuppressed)
- If normal history and physical: Start LTBI treatment after 1st TST/IGRA (even if negative)
- If 1st TST/IGRA negative:
  - Repeat testing 8-10 weeks after last contact with contagious case – If negative can stop LTBI treatment
  - Immunocompromised – consider completion of LTBI treatment

Screening & LTBI Key points:

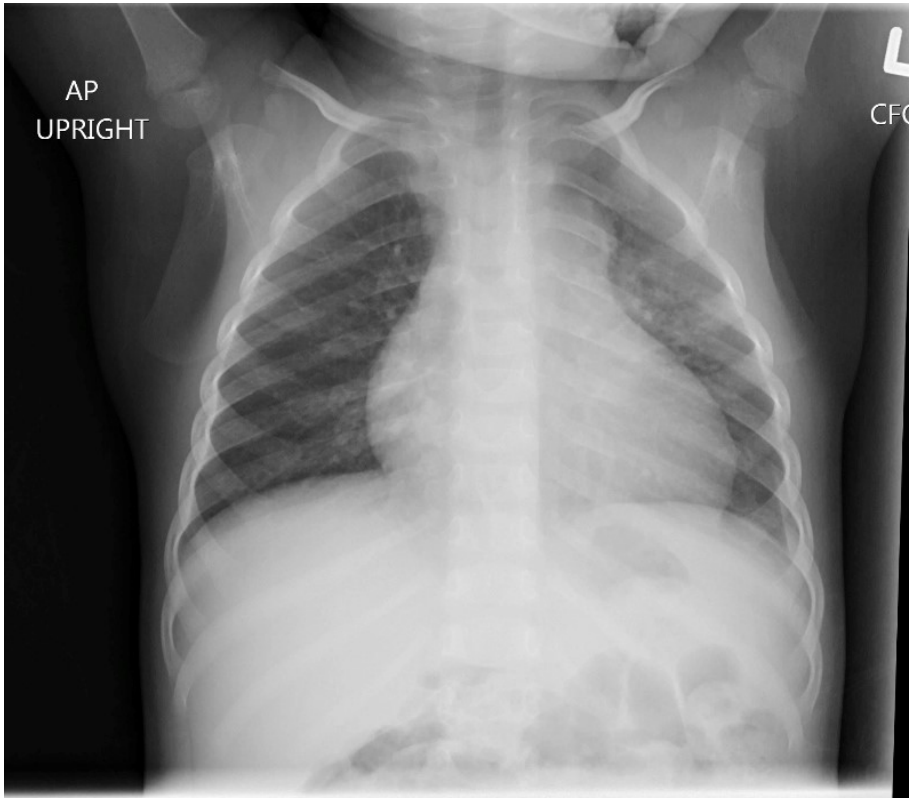
- Screening- may use TST or IGRA
  - IGRA acceptable in 2 yo or older
  - TST preferred in younger than 2 yo
- Young children are at increased risk:
  - Use lower 10 mm cut off for TST for all children <4 yo
  - If exposed- perform complete evaluation
  - "Window" therapy recommended for under 5 yo until 2nd IGRA/TST

- Regimens for LTBI treatment are similar to adults with weight-based dosing BUT INH-RPT only for >2 yo

Case: 18 mo girl rash, fever, cough

- 2.5 wk daily fevers, Tmax 102.9F
- At onset, clinical dx of Strep pharyngitis - 5d azithro, no improvement
- 2 wk ago developed nodules on bilateral shins
- 1.5 wk ago developed cough - Rx: albuterol w/o improvement
- Sent to ED for evaluation, with elevated inflammatory markers
- FH/SH: Paternal GF visiting from Nigeria x 6 wks, had *stomach* illness. Patient is US born to Nigerian parents.

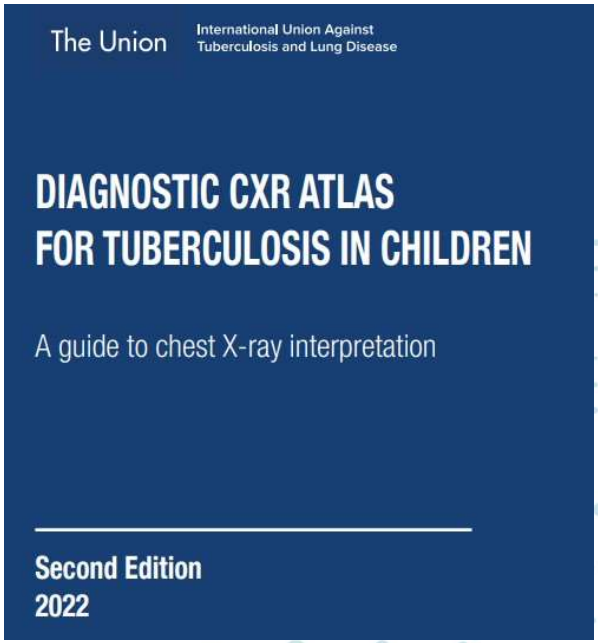
CXR



Chest X-ray findings in children

- Features suggesting TB:
  - Primary complex
  - Mediastinal lymphadenopathy
  - Bronchial compression
  - Chronic consolidation
  - Calcification
  - Miliary pattern
  - Cavity or Lesion in upper lobe(s) is less common in children

https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children



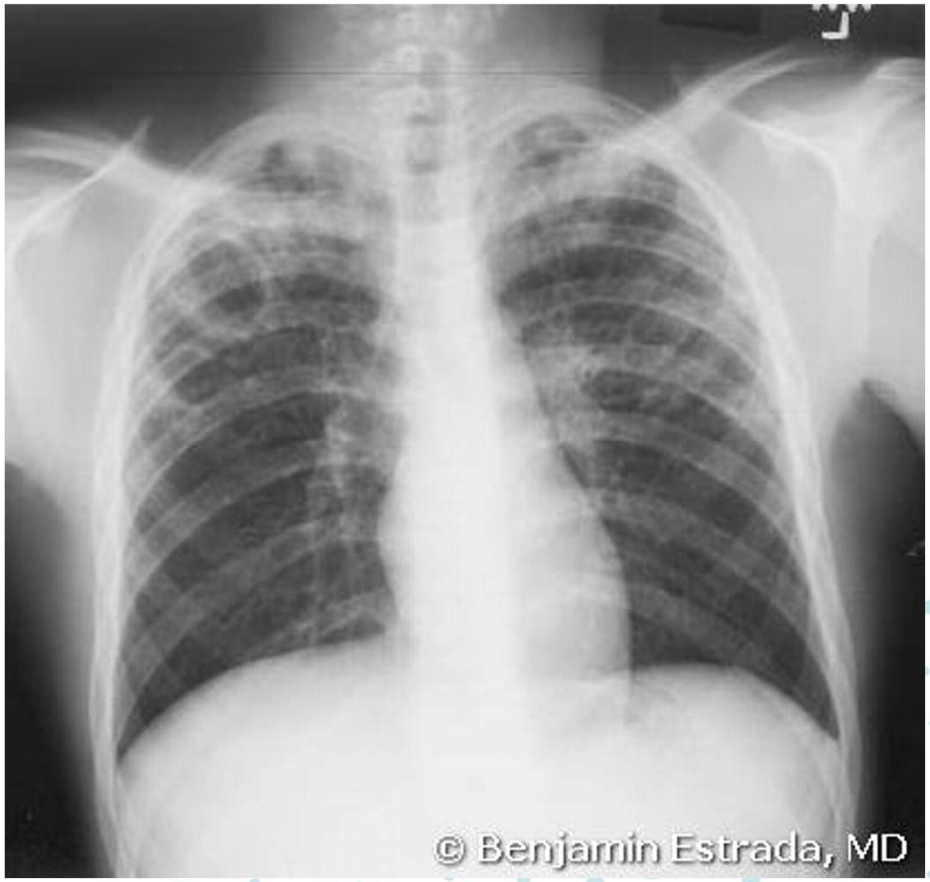
Childhood TB - Various X ray Presentations:

Adult type pulmonary disease

UNUSUAL for children (but more common in teens)

- Cavitary lesions are uncommon
- Parenchymal lesions are variable but often limited
- Node involvement is often prominent

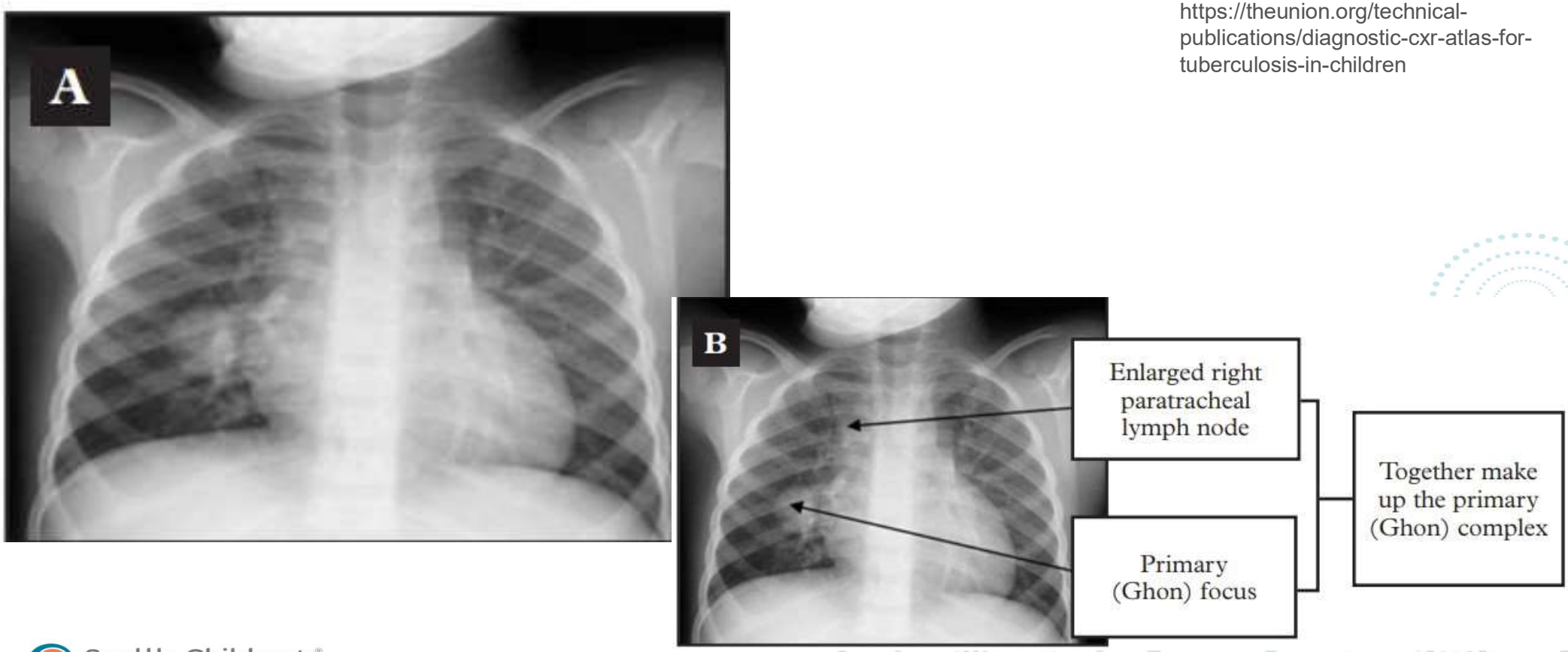
- Teenagers CXR more closely resemble adults



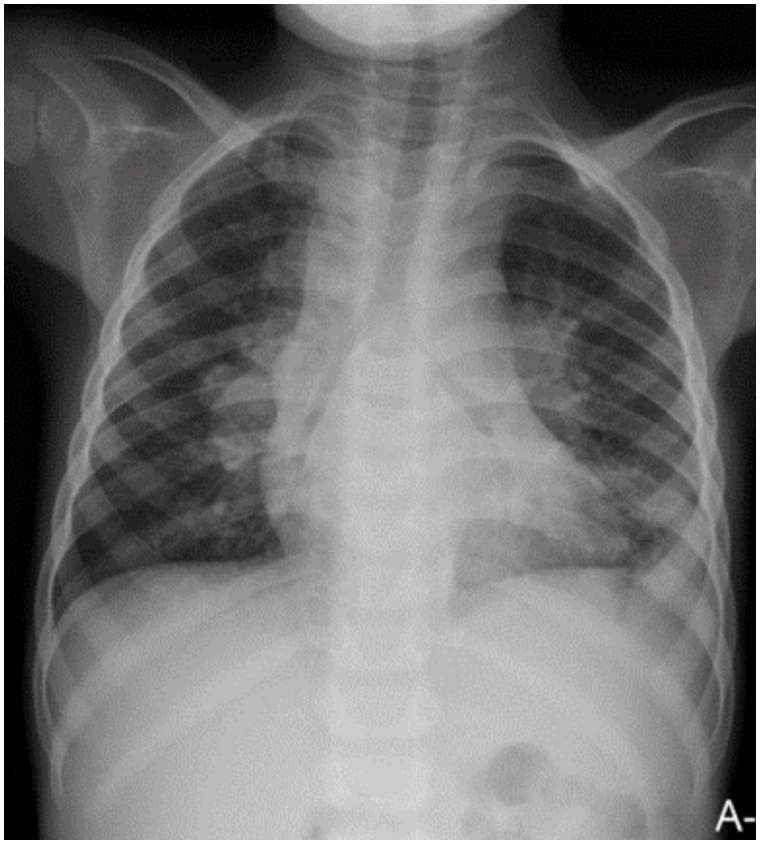
AAP RedBook 2012

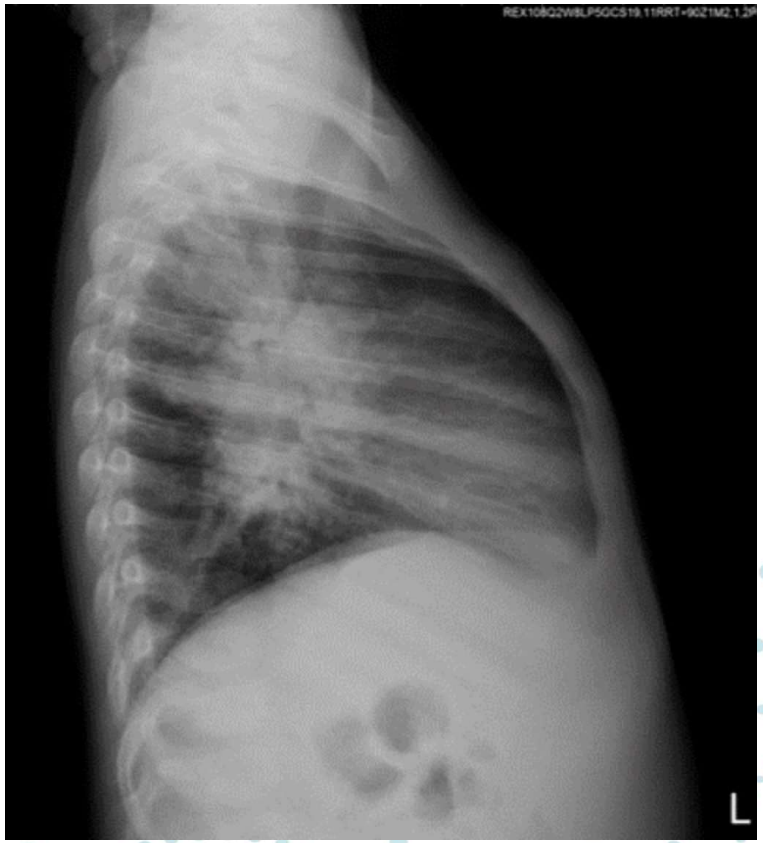
Primary Complex

https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children



Mediastinal lymphadenopathy





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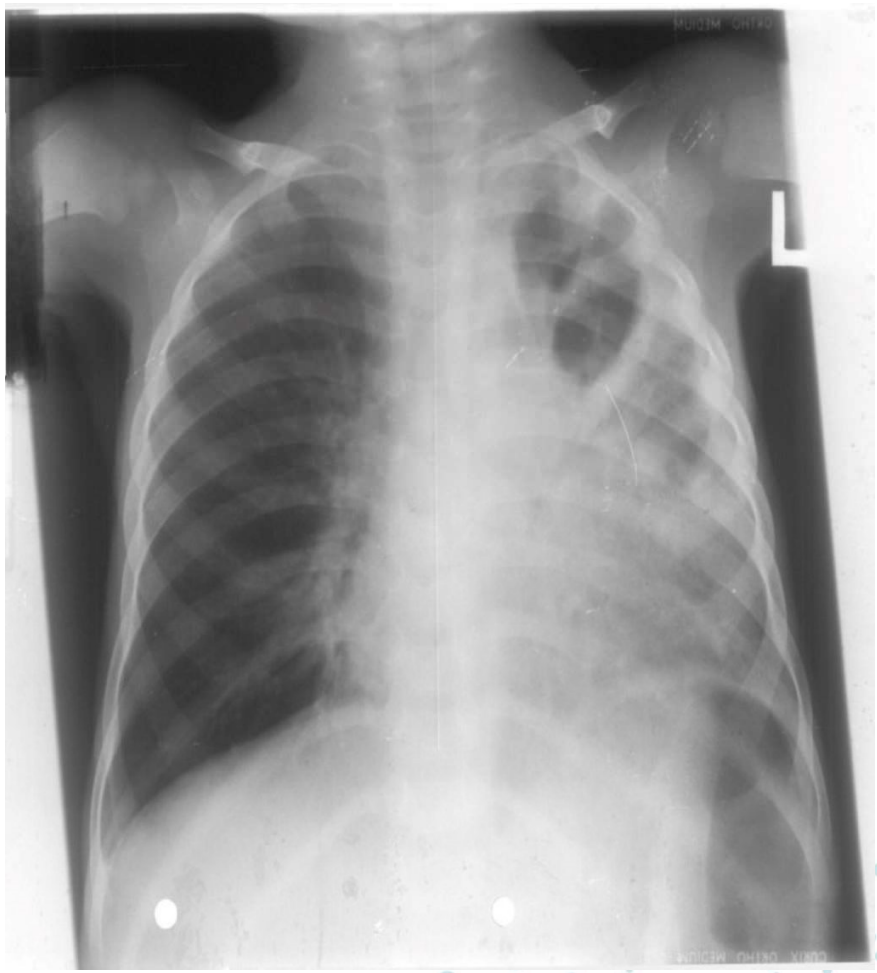
Severe cavitary disease in 19mo



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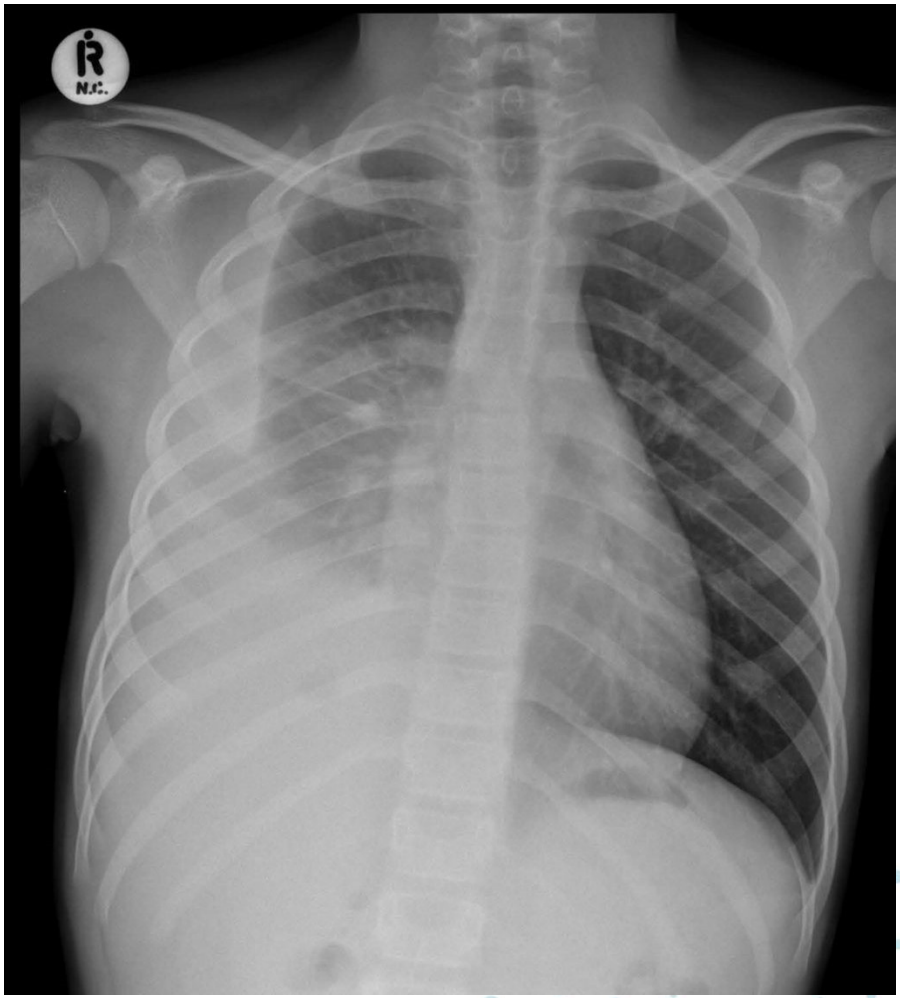
Pleural effusion



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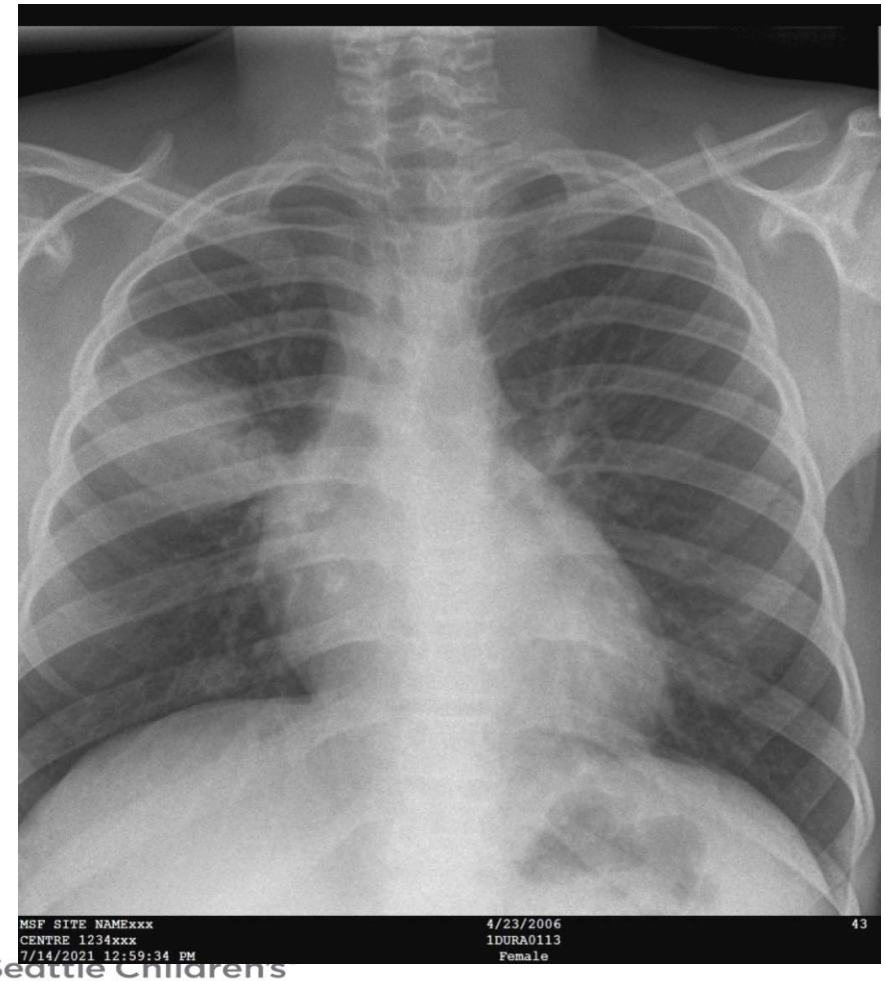
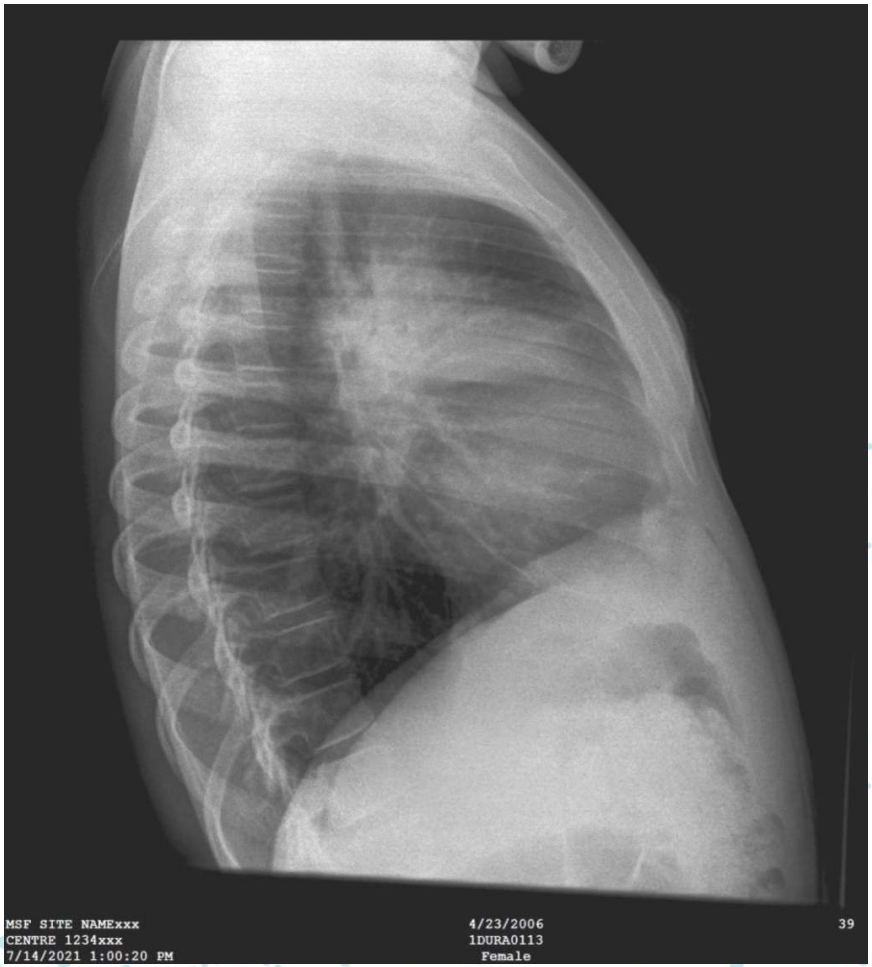
Consolidation - segmental





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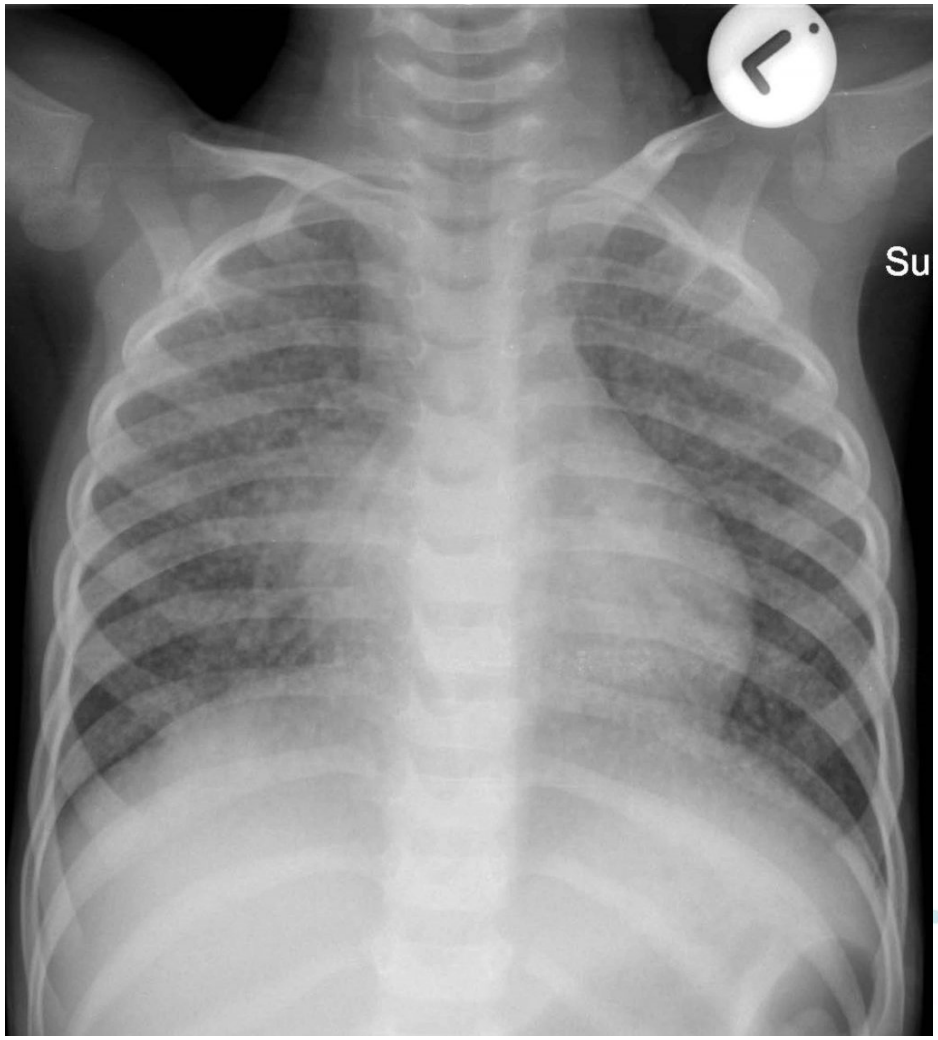
Milliary Pattern



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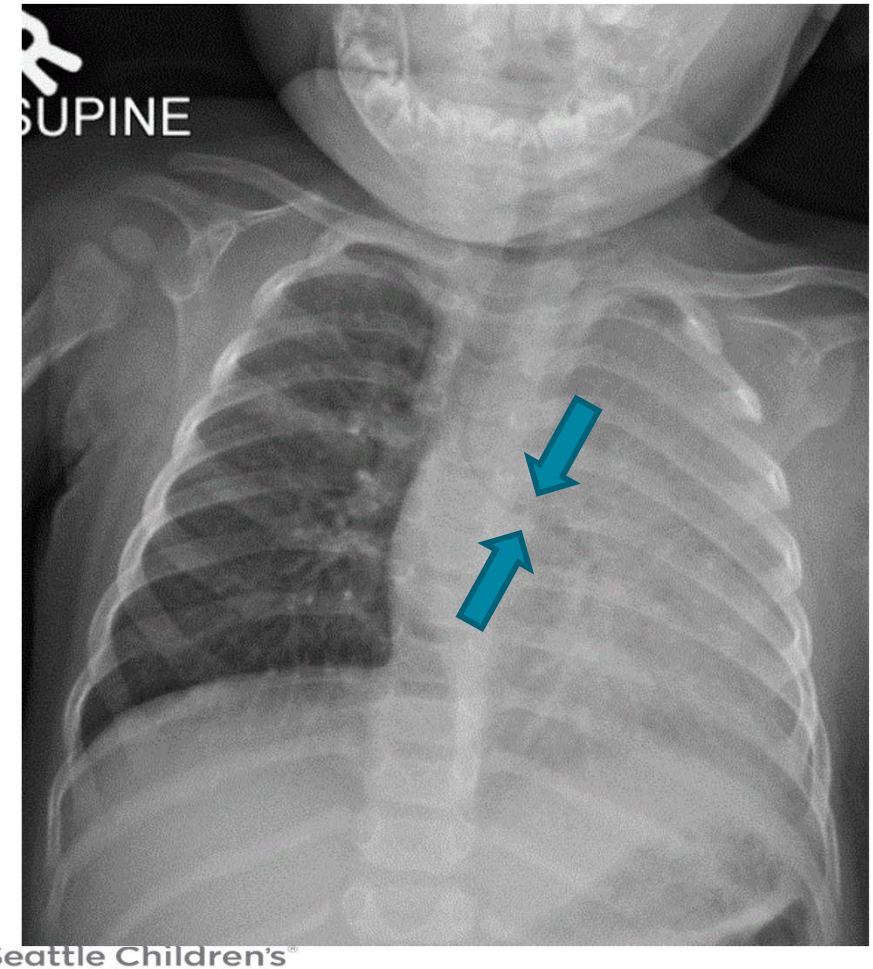
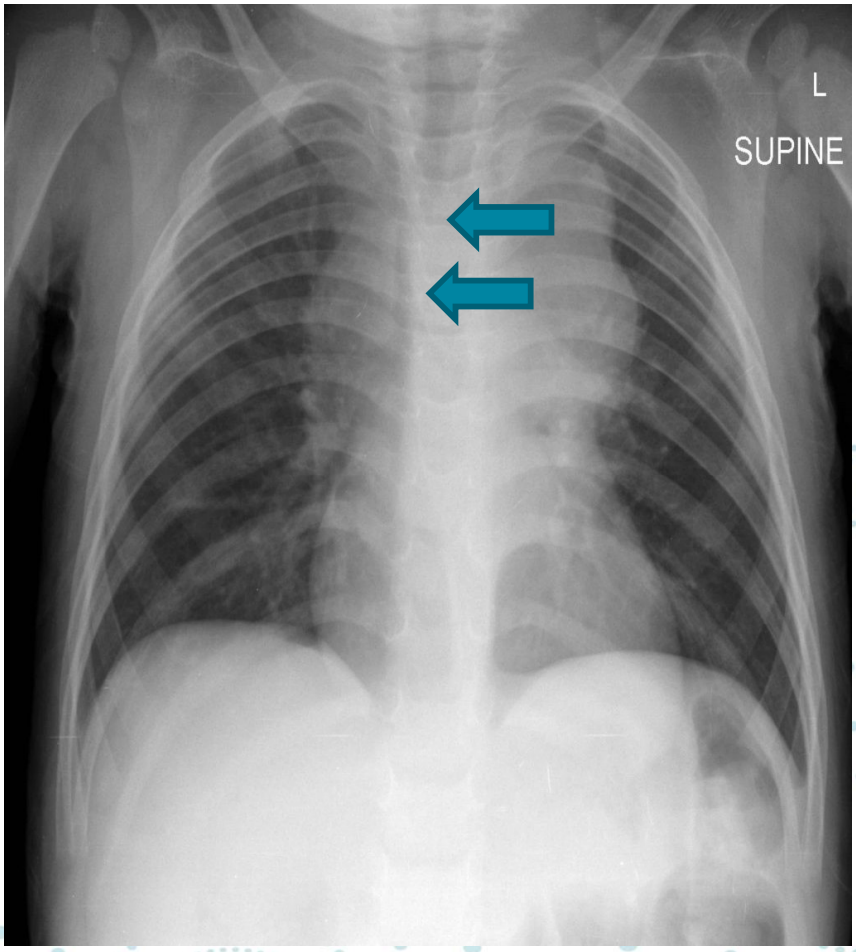
Complicated lymph node and parenchymal disease





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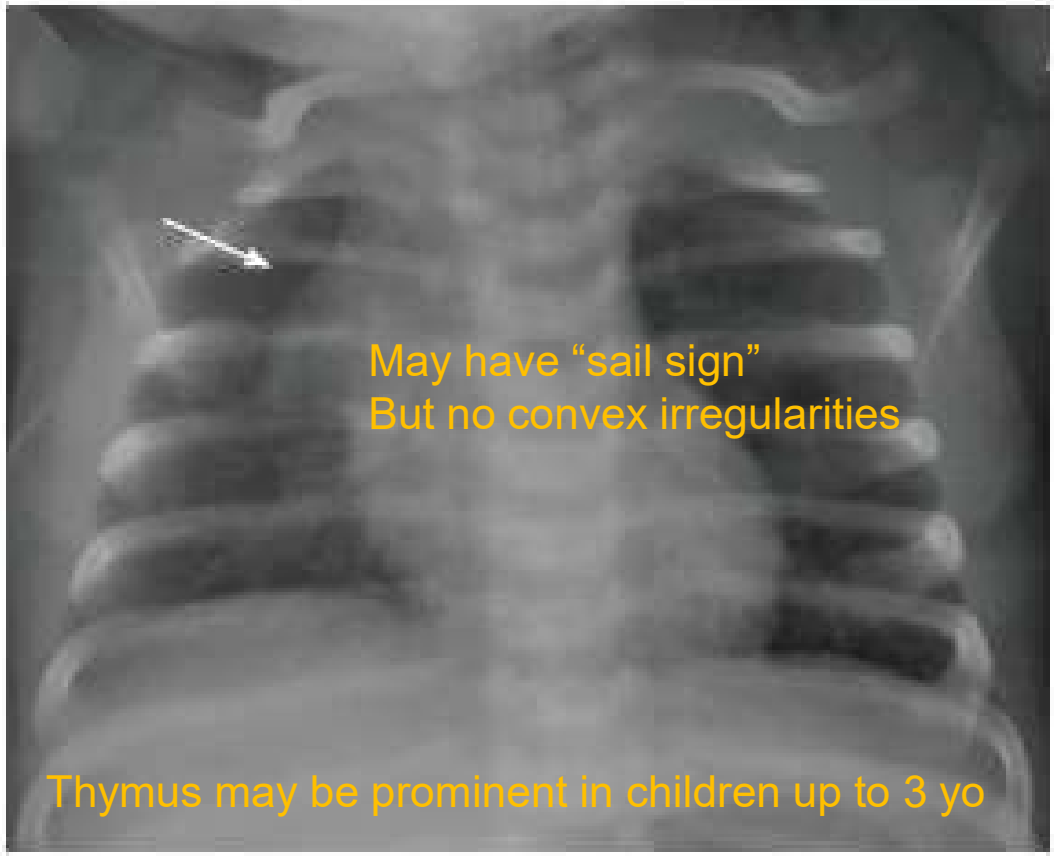
https://atlaschild.theunion.org/

Lymphadenopathy ???



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World J Clin Pediatr. 2017 Feb 8; 6(1): 10–23.

Case: 18 mo girl rash, fever, cough (cont.)
TST in this patient was 16mm frank induration, with blistering of site. How would you evaluate further?

A. Collect throat swabs x3
B. Collect gastric aspirate/lavage x3
C. Collect sputum x3
D. Send an IGRA

Specimens for Culture

- Expectorated sputum
- Induced sputum
  - can be done in young children with RT expertise (requires deep NP suction)
- Gastric aspirate (preferred if sputum not possible)
  - young children, collected in AM after NPO (inpatient admission)
  - Video instructions from Curry Center Website:
    http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-guide-gastric-aspirate-procedure
- Tissue (Lymph node, bone, synovial fluid, pleura)
- CSF (LP for ALL CHILDREN<12mo, or if any neurologic concerns)
- PCR/NAAT/Xpert testing in addition to smear if available

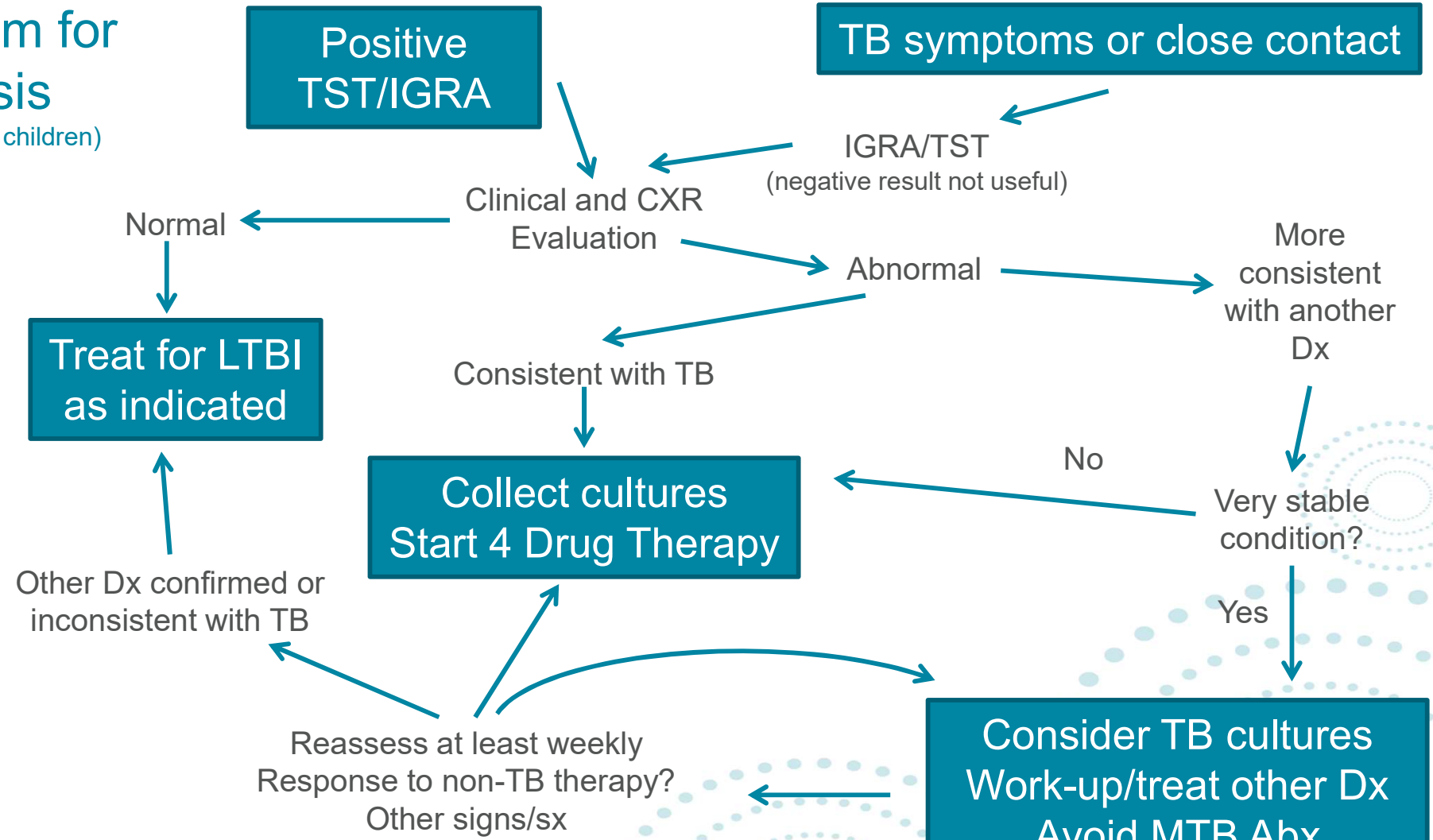
- **RELATIVES/CONTACTS**

All 3 Gastric aspirates have negative smears. Other work-up does not reveal cause of ongoing fevers. What next?

A. Wait for culture results, no antibiotics
B. Wait for culture results, start INH for +ve TST
C. Start treatment for TB disease
D. BAL for AFB cultures

Algorithm for Diagnosis

(preadolescent children)



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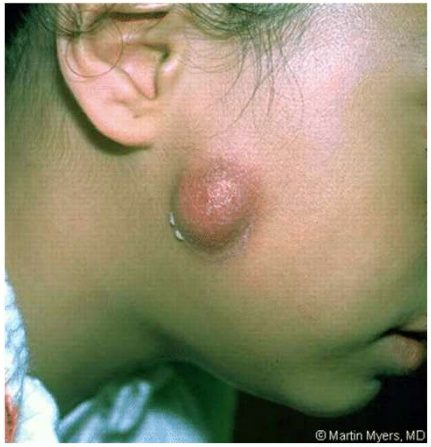
Assess for Extrapulmonary Tuberculosis

- TB Meningitis — meningitis not responding to antibiotics, subacute onset, communicating hydrocephalus, stroke/vasculitis, and/or elevated intracranial pressure
- TB Adenitis — painless, fixed, enlarged lymph nodes, especially in the cervical region, with or without fistula formation (may also be NTM)



- Pleural TB
- Pericardial TB
- Abdominal TB
- TB of bone/joints
- Vertebral TB
- Skin
- Renal
- Eye
- GU

Decision to treat

- Most childhood TB is SMEAR Negative in young children
- Culture yield is likely only 40-60%
- **Negative micro eval *does not* rule out TB in children**
- **If you have high clinical suspicion ➔TREAT!**
- Diagnosis made on combination of:
  - clinical suspicion
  - possible contacts/risk of exposure
  - TST/IGRA (only + is helpful, negative will not rule out)
  - ruling out other likely diagnoses
  - response to treatment (if not improving reconsider alternate Dx)
- You will treat some children for TB who have another diagnosis
- Obtain baseline labs/HIV testing

Dosing: First Line Drugs

Drug	Dose and Range (mg/kg/day)	Maximum Daily Dose (mg)	Formulation (Not all inclusive)
Isoniazid	10 (10-15)	300	Tabs: 100 mg, 300 mg Syrup: 10 mg/mL *
Rifampin	15 (15-20) 2021 RedBook 20-30 mg/kg for infants/toddlers or meningitis	600	Caps: 150 mg, 300 mg May be compounded
Pyrazinamide	35 (30-40)	2000	Tabs: 500 mg
Ethambutol	20 (15-25)	1000	Tabs: 100 mg, 400 mg

Weight band tables are helpful

5x/week = daily (helps with DOT, consider community resources such as school RN)

Intermittent dosing possible in continuation phase but less evidence than in adults to support practice – see CDC/WHO guidelines (3x/wk preferred see AAP RedBook)

Regimens for Extrapulmonary TB: same. But for meningitis some experts recommend: increased RIF dose and substitute amikacin or ethionamide in place of EMB

*contains sorbitol- risk of GI upset/diarrhea (consider crushing tablets)

What drug regimen would you use in this patient (20 kg weight)?

Drug	Dose and Range (mg/kg/day)
Isoniazid	10 (10-15)
Rifampin	15 (15-20)
Pyrazinamide	35 (30-40)
Ethambutol	20 (15-25)

A. INH 200mg, RIF 300mg, PZA 625mg - Daily

B. INH 200mg, RIF 300mg, PZA 625mg, EMB 400mg - Daily

C. INH 200mg, RIF 300mg, PZA 625mg, EMB 400mg – 3X/week

D. INH 100mg, RIF 150mg, PZA 625mg, MOX 200mg

Important follow-up

- Provide DOT whenever possible
- Assess compliance and challenges
  - multiple daily medications can be hard, especially in a toddler
- Are signs/symptoms improving?
- Monitor for side effects & include family education (red secretions, jaundice, rash, anorexia, etc.)
- DO MEDS NEED ADJUSTMENT FOR WEIGHT?

Duration of therapy

- Standard duration is 6 months
  - Follow-up cultures difficult: alternately use CXR (2 mo – likely not normal, should not be worse) and clinical symptoms
  - Meningitis/Skeletal) -12 mo - 2HRZ(E or alt)/10HR
  - *M bovis* - 9 mo – 2HR(ZE)/7HR
- Extend to 9 months if initial CXR demonstrates cavity or cultures remain positive after 9 months

Duration of therapy – Shorter Regimen

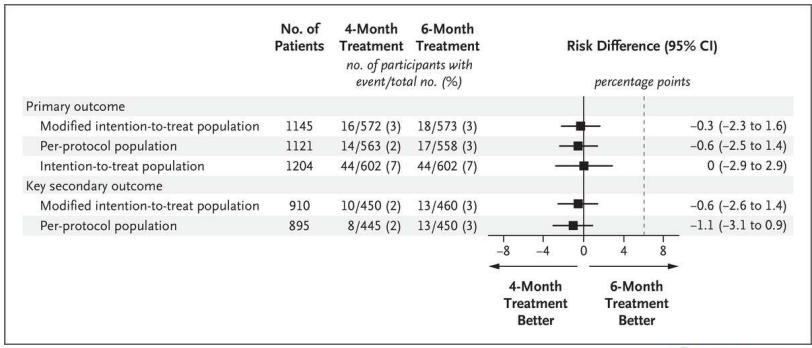
- Standard duration is 6 months
- SHINE Trial: shorter course for non-severe, drug susceptible TB – requires:
  - Age 3mo to <16yo
  - Peripheral or nonobstructing thoracic lymph node Dz
  - Uncomplicated plural effusion
  - **respiratory smear neg**, non-cavitary, **<single lobe**
  - No miliary pattern
- 4 Months: 2HRZ(E)/2HR
- Alternate 4 mo regimen for ≥12 yo and ≥40 kg
  - 8 weeks Isoniazid/Rifapentine/Moxifloxacin/Pyrazinamide
  - 9 weeks Isoniazid/Rifapentine/Moxifloxacin

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535



	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)

A Turkova et al. N Engl J Med 2022;386:911-922.

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First Line Drugs: Adverse Effects

Drug	Adverse Effects	Monitoring
Isoniazid	Hepatotoxicity Rash Peripheral neuropathy Psychosis	Jaundice Liver enzymes PRN Clinical observation, symptoms Consider need for B6, symptoms **Supplement B6 if breastfeed**
Rifampin	Orange body fluids Hyperbilirubinemia Hepatotoxicity	Advise parents! Liver enzymes PRN
Pyrazinamide	Hepatotoxicity Arthralgia Rash	Jaundice Liver enzymes PRN Clinical observation Clinical observation
Ethambutol	Optic neuritis	Color visual exam if able (clinical optic neuritis is rare in children)

Draw baseline labs, but subsequent labs are only checked if symptoms, other hepatotoxic drugs, or other baseline conditions (such as liver disease)

Suggestions for medication administration

- It may take a little while to get the child in a routine – **avoid establishing a power struggle**
- If they can take pills, usually that is easiest
  - Practice with small candy and have a reward system
  - Try tipping head forward for capsules and back for tablets
  - If can do capsules but not tablets, consider crushing tabs and filling empty capsules

- Crushed pills/capsules can be *mixed* in food
  - Practice first without medicine, then with crushed candies
  - Chocolate syrup, jelly/jam, apple sauce, peanut butter/Nutella

- Crush and suspend in liquid (water) and give with syringe or medication pacifier
- Syrups (INH) and suspension (RIF) may be available, but may cause GI upset (INH due to sorbital) or need to be compounded (RIF)
- If stuck use an NG Tube

http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-online-presentation/resources

Regimens for MDR-TB, RR-TB Similar to Adults

CONSULT AN EXPERT!
Principles the same as adults
But not all regimens tested in children or adequate PK data

Longer regimen (based on CDC/ATS guidance) GOAL: AT LEAST 5 Active Drugs Consider drug resistance of Region and Contact (Patient if available)		
Step 1: Use one fluoroquinolone		
Levofloxacin or Moxifloxacin		
Step 2 – Add both		
Bedaquiline (age 5 & up)	Linezolid	
Step 3 – Add both		
Clofazimine (not crushable)	Cycloserine/terizidone	

Regimens for MDR-TB Similar to Adults (Can consider shorter course treatments)

KEEP ADDING to get to minimum of 4-6 active drugs		
Step 4 – Add injectable drug if needed		
Amikacin	Streptomycin (resistance a concern)	~~Capreomycin~~ ~~Kanamycin~~
Step 5 – If needed additional oral agents (or avoiding injectable)		
Delamanid (age 3y & up)	Pyrazinamide	Ethambutol
Step 6 – If limited options		
Imipenem or meropenem plus amox/clav	Ethionamide or prthionamide	P-Aminosalicyclic acid

Other regimens:
Bedaquiline-pretomanid-linezolid – under study in children
Shorter bedaquiline regimens (9-12 mo) – may be considered in nonsevere disease

Take Home Points – Active TB Disease

- Childhood TB is ***often culture negative***
- Complete work-up whenever there is high suspicion:
  - Collect best culture specimens possible (admit to inpatient if needed)
  - Identify a source case
  - Positive IGRA/TST are useful in diagnosis
  - **Negative IGRA, TST or cultures DO NOT RULE OUT TB DISEASE**
- Children <5 yo - Risk for disseminated disease is HIGH vs. adults
- Children tolerate meds well, principles of therapy similar to adults

For 18 mo GIRL with 2.5 wks fever:

- Eventually 1 of 3 gastric aspirates grew:
  - *M. tuberculosis* complex
  - Susceptible to all 1st line drugs

- Fever resolved, clinically much improved
- Source not definitively identified

Key Resources

AAP Red Book:
http://aapredbook.aappublications.org

WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents
https://www.who.int/publications/i/item/9789240046764

Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

https://www.cdc.gov/tb/publications/guidelines/default.htm

http://www.currytbcenter.ucsf.edu/topics-interest/pediatric-tb

Call: Seattle Children's ID Service 206-987-7777
Or your local children's hospital ID Service

Other Diagnostic Testing

- Xpert on non-sputum and sputum samples
  - More sensitive than smear
  - Most labs will need to validate gastric specimens (not FDA approved and therefore most labs will not perform)
  - But less sensitive vs. culture
- Developing technologies
  - Transcriptional profiling
- Still not as sensitive as culture and culture is still only 40-60% sensitive vs. composite clinical diagnosis