

TB 101: Pediatric TB Diagnosis and Treatment

Nicole Salazar-Austin, MD, ScM

Johns Hopkins University School of Medicine

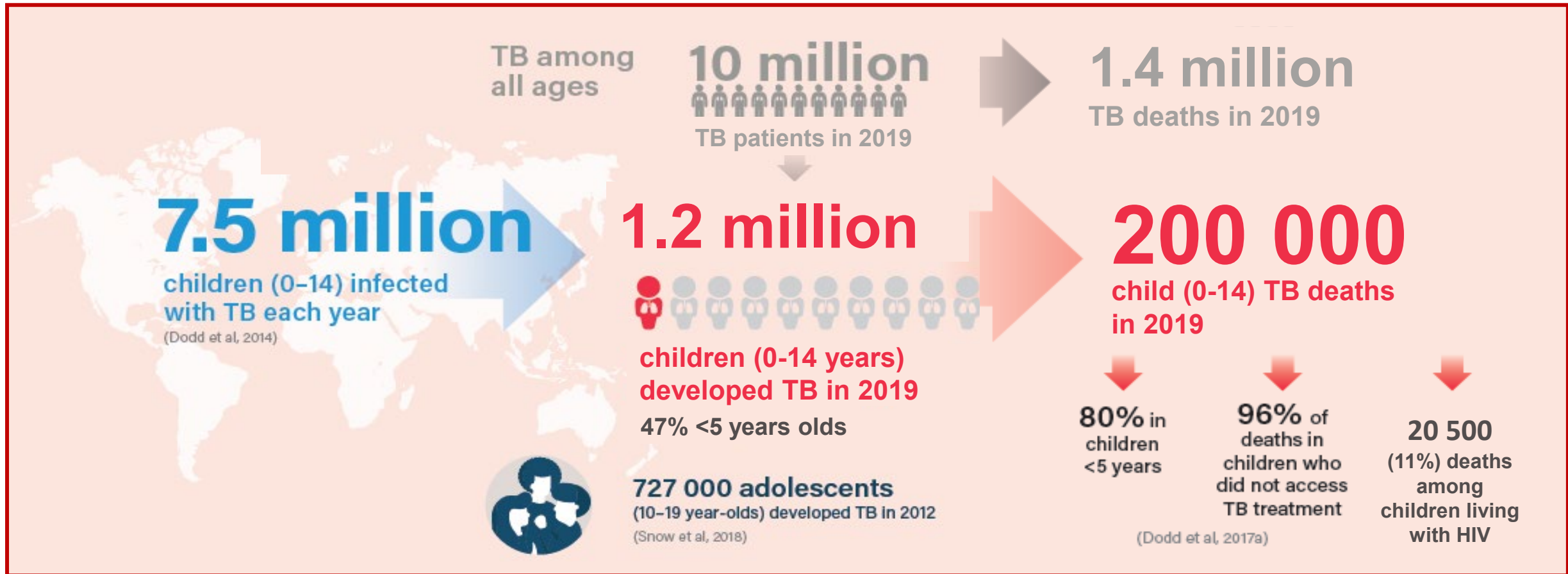
18 August 2023

Outline

- Pediatric TB Epidemiology – US and Global
- Pediatric TB Diagnosis
- Pediatric TB Treatment

Pediatric TB Epidemiology

Pediatric TB Global Burden Estimates



Background: Pediatric Tuberculosis in the U.S. 2007-17

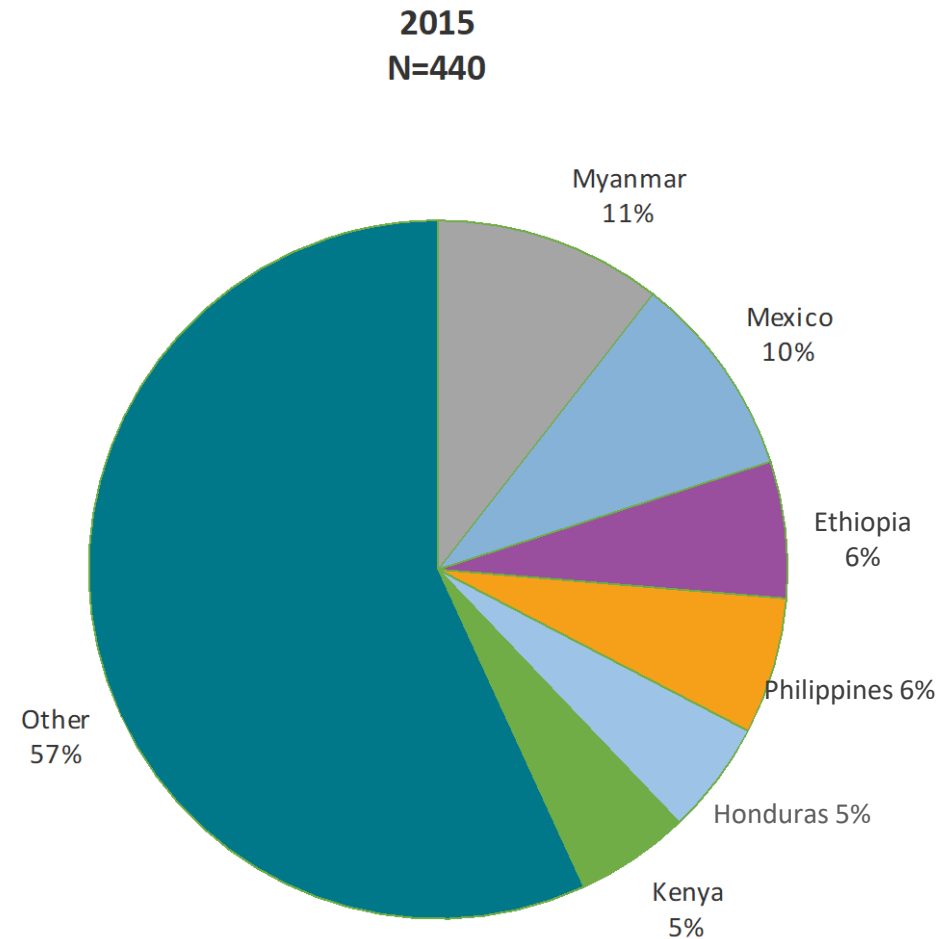
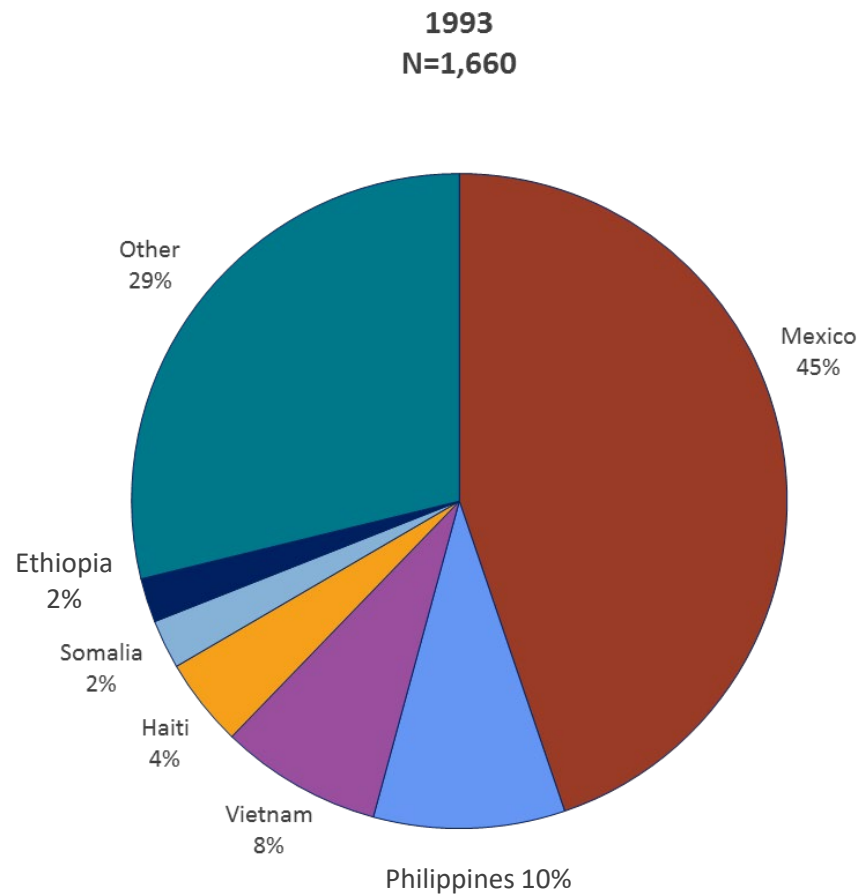
- ~4% of TB cases in the US annually are children < 15 years
- ~10% of TB cases in the US are in adolescents and young adults
- <1% of pediatric TB cases are HIV+

Age	US-Born	Non-US Born	Total
< 15 years	2977 (85%)	919 (56%)	3896 (75%)
<1 years	448 (13%)	26 (2%)	474 (9%)
1-4 years	1503 (43%)	253 (15%)	1756 (34%)
5-14 years	1026 (29%)	640 (39%)	1666 (32%)
15-17 years	543 (15%)	736 (45%)	1279 (25%)

Epidemiology: United States

- TB case rates for all ages are higher in urban, low-income areas, and in nonwhite racial and ethnic minorities
- Specific groups with high LTBI and TB disease rates:
 - Immigrants and refugees from high-prevalence regions (Asia, Africa, Latin America, countries of the former Soviet Union)
 - International adoptees
 - Travelers to countries with high-prevalence
 - Homeless people
 - Residents of correctional facilities

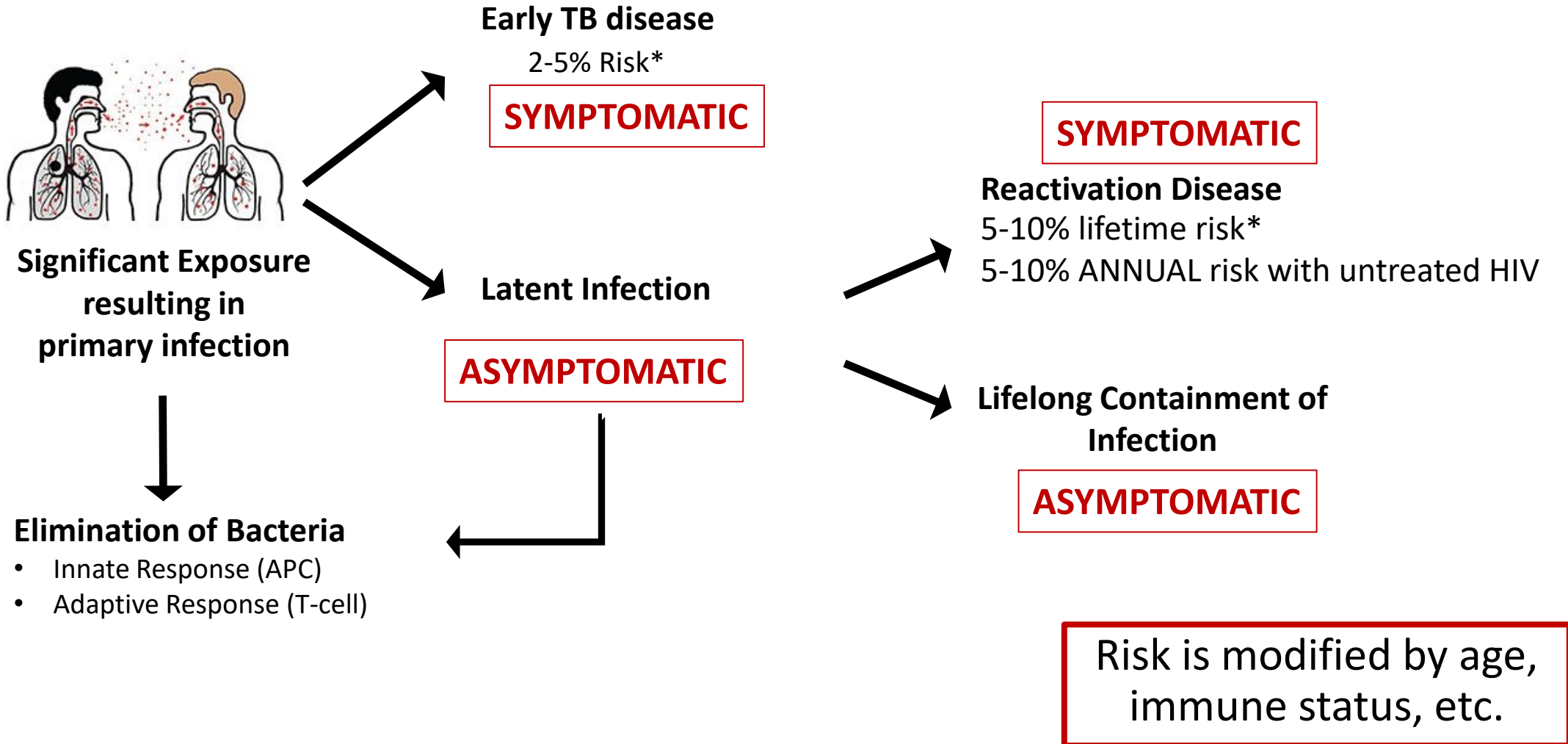
Percentage of Pediatric TB Cases Born Outside US by Birth Country, 1993 and 2015



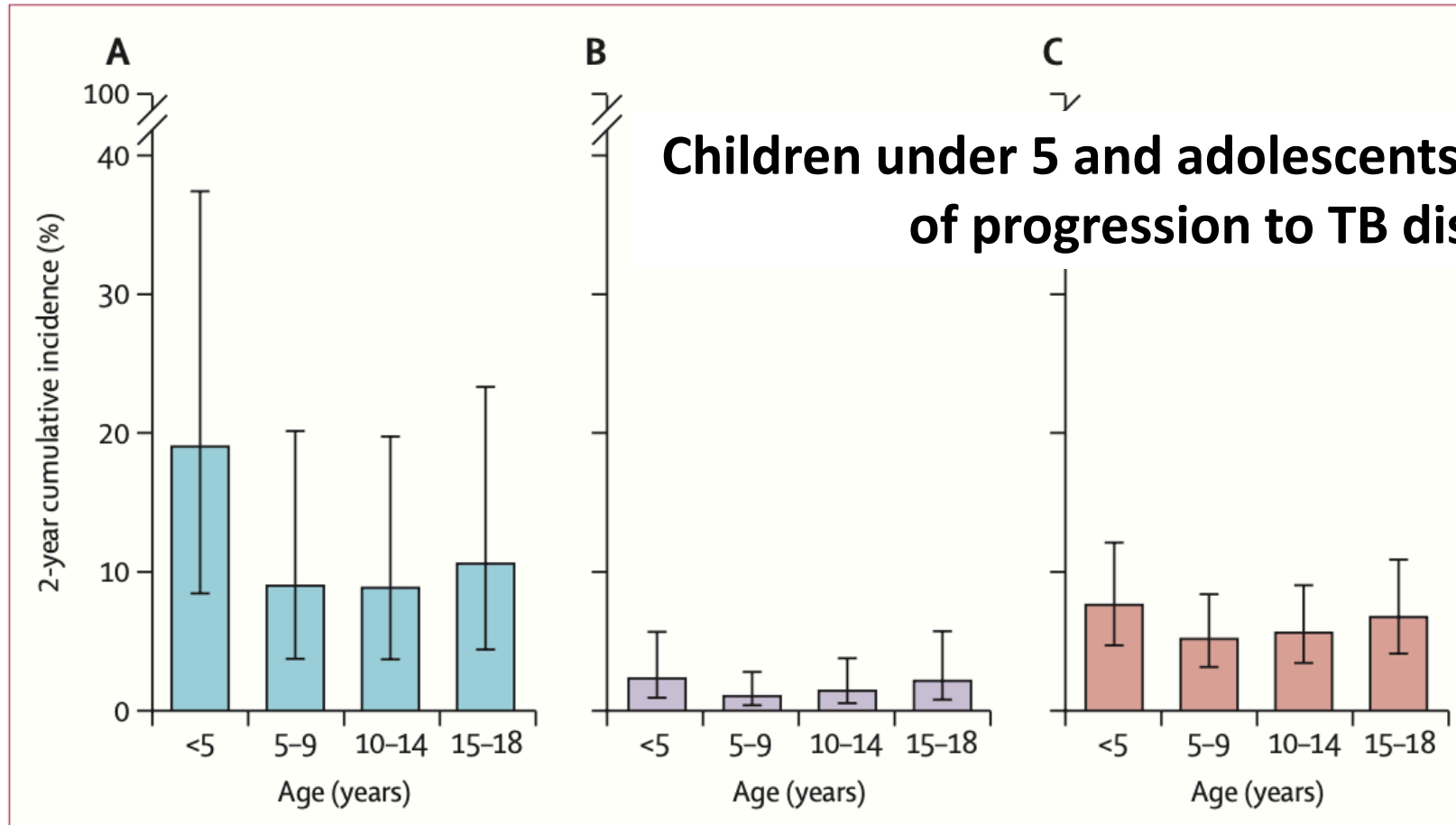
Transmission of *M. tuberculosis* to Children

- Children are often infected by an adult or adolescent in the immediate household
- Casual extra-familial contact is less often the source of infection
 - e.g., rural farms and migrant farm workers
- Children rarely infect other children or adults:
 - Tubercle bacilli are relatively sparse in secretions
 - Children with pulmonary TB rarely cough
 - Cough, when present, lacks the tussive force needed to aerosolize bacilli

Risk of Progression to TB Disease



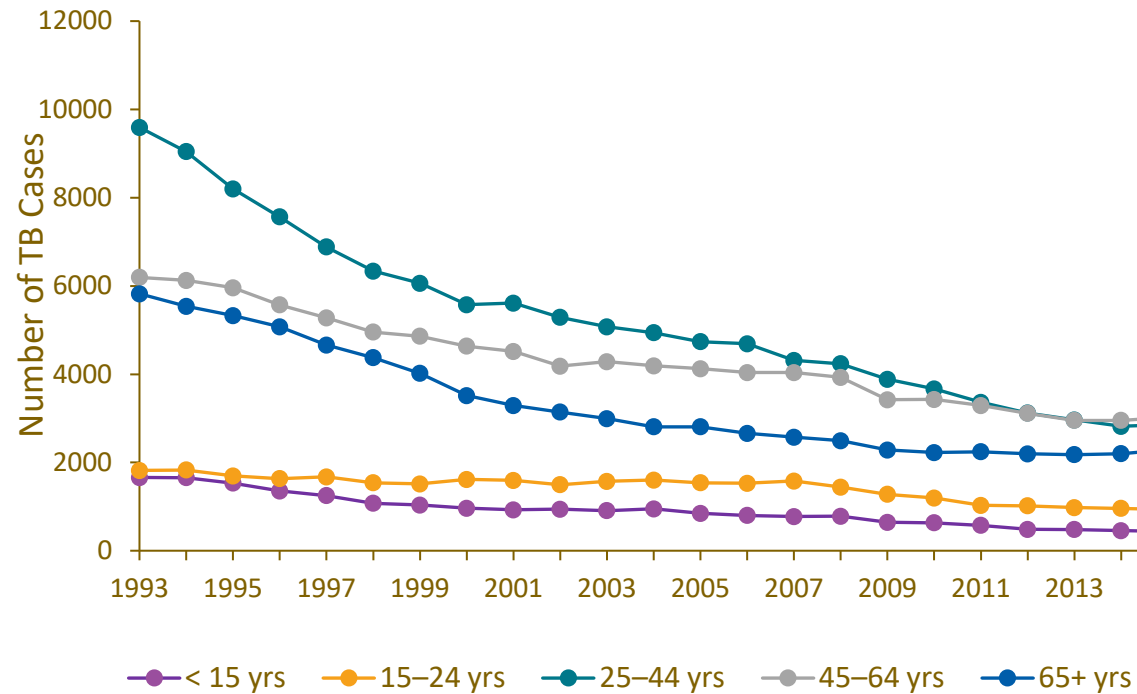
Risk of Tuberculosis Disease by Age



Increased Risk of Progression of LTBI to TB Disease

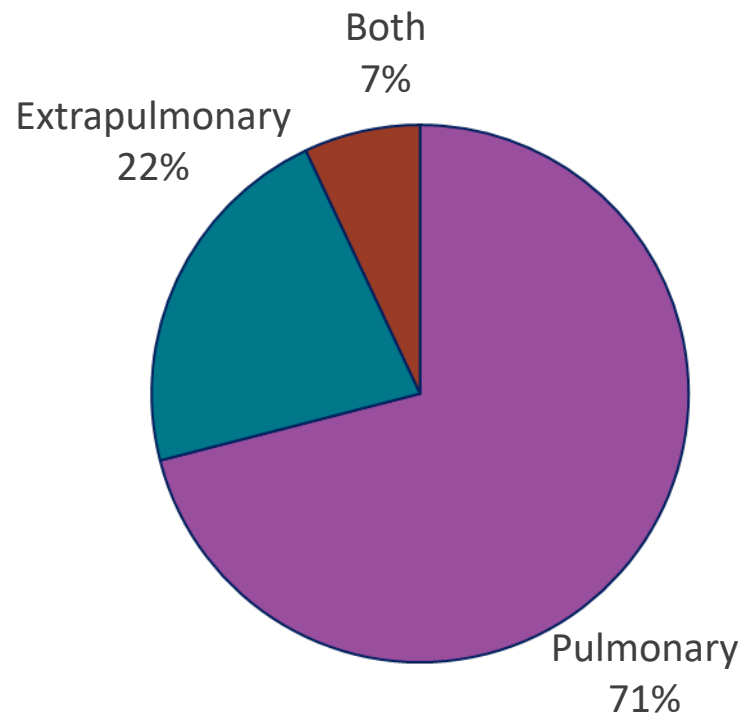
- Age groups:
 - Infants and young children
 - Post pubertal adolescents
- Recent infection:
 - Highest risk in first 6 months after infection
 - Remains high for 2 years
- Recent immigration
- Immunodeficiency:
 - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
 - Immunosuppressive drugs:
 - Prolonged or high-dose corticosteroid therapy
 - Chemotherapy
 - Tumor necrosis factor (TNF-alpha) antagonists used to treat rheumatoid arthritis and Crohn disease

TB in the United States 1993 - 2016



Pediatric TB is uncommon in the US; diagnosis requires a high index of suspicion

Pediatric TB Cases by Site of Disease, 1993–2015



Any extrapulmonary involvement* (totaling 29.5%)	
Extrapulmonary site	(%)
Lymphatic	(18.8)
Meningeal	(3.6)
Miliary	(1.3)
Bone & Joint	(1.5)
Other	(4.3)

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both. Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

How Children with Tuberculosis are Identified

1. Presentation with a symptomatic illness
2. Discovery of a child with pulmonary tuberculosis during contact investigation of an adult with tuberculosis
 - Few or no symptoms
 - Evaluation: (+) TST/IGRA and abnormal CXR
 - In some areas of U.S. up to 50% of children with TB are discovered in this manner
 - Before significant symptoms have developed

Pediatric TB Diagnosis

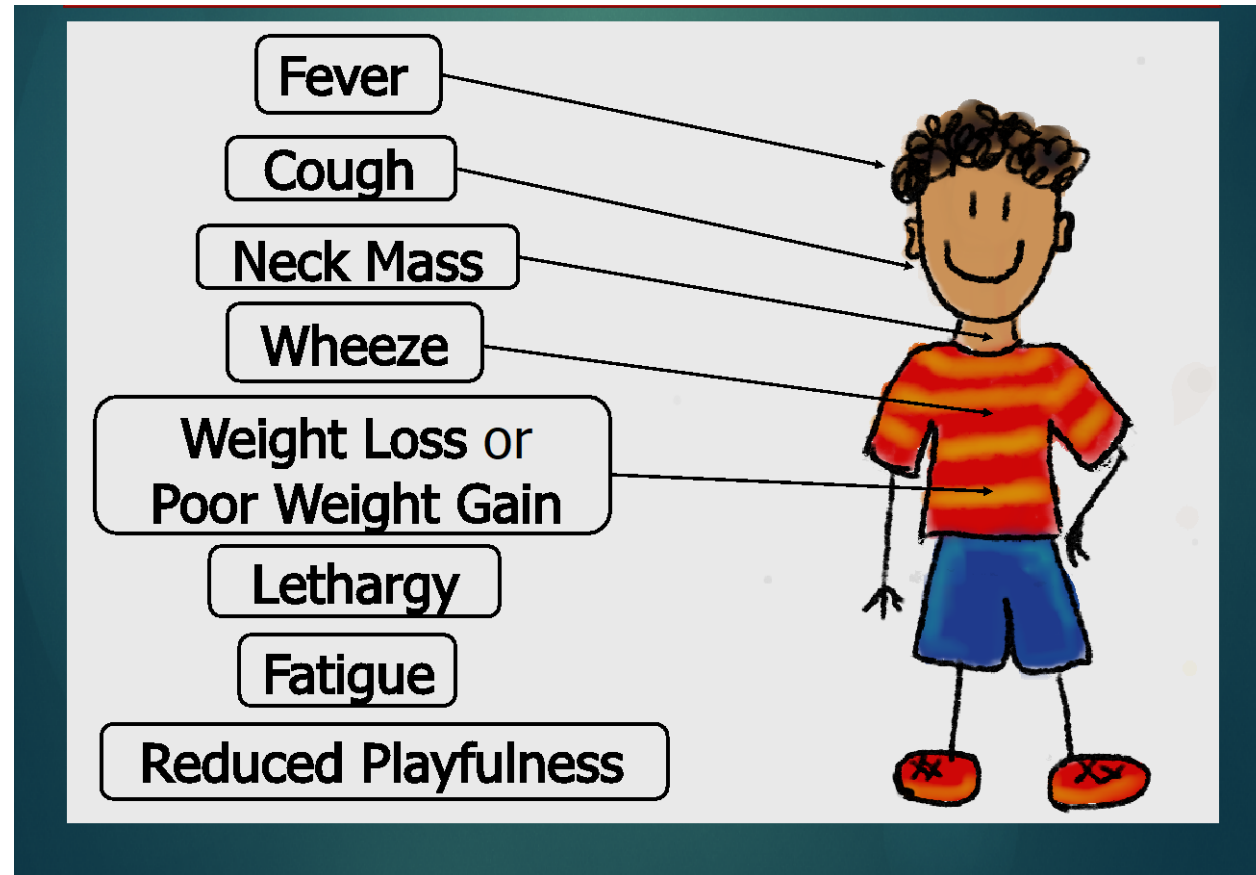
Difficulties in the Diagnosis of TB in Children

- Children are often asymptomatic or symptoms are nonspecific:
 - Nonspecific Sx: Fever, poor appetite, poor weight gain or weight loss
 - Approximately 22-30% of disease is extrapulmonary
 - Meningitis and miliary disease tend to develop soon after infection
 - 70-80% occur in children 0-4 years of age
- Physical examination may be normal
- Epidemiologic link (the adult source case)
 - Crucial to identify the adult source case for the child
 - Provides strong evidence that the child suspected of having TB disease actually has TB
 - May be the only isolate available for susceptibility testing

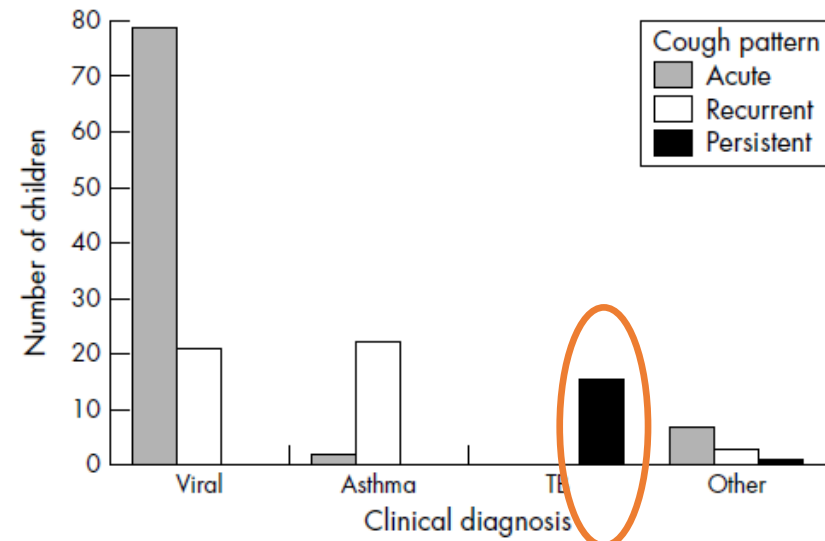
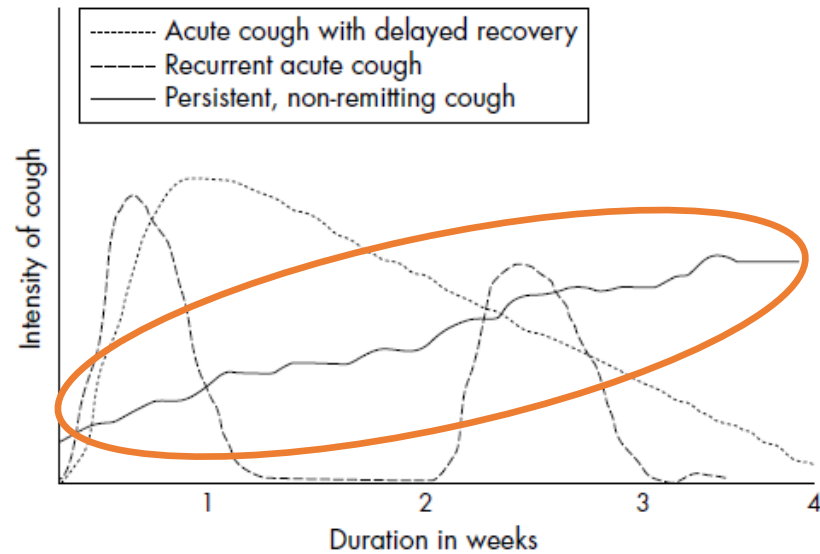
Key Messages about TB Diagnosis in Children

- Clinical diagnosis of TB disease is **NOT** difficult in children,
- Bacteriologic confirmation of TB disease **IS** difficult in children
- Diagnosis of TB disease in children requires a **high index of suspicion**

Evaluating a Child: TB Symptom Screen



Pediatric TB: Persistent, Non-Remitting Cough



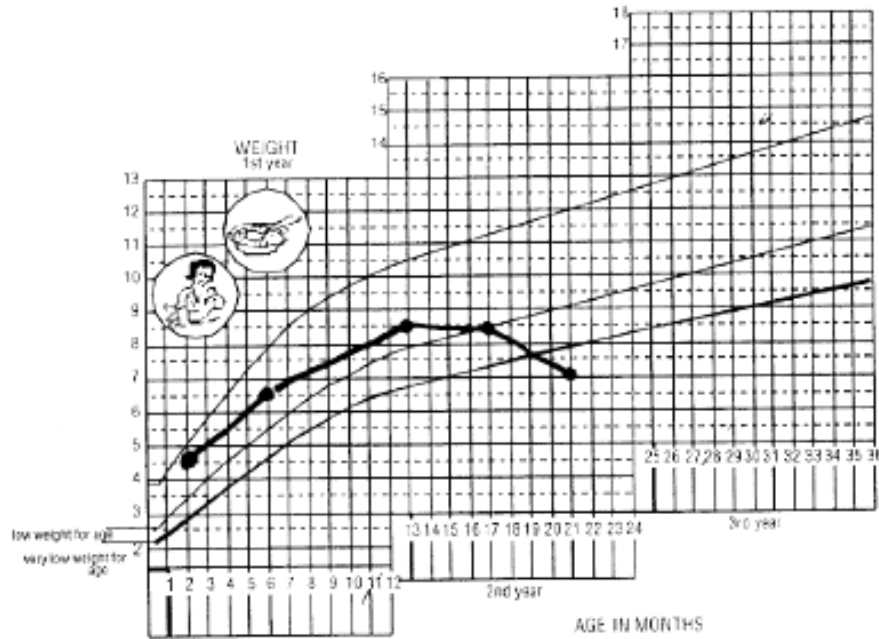
Pediatric TB Symptoms Vary Greatly

Table 2. Frequency of Diagnostic Findings in Active Tuberculosis Cases

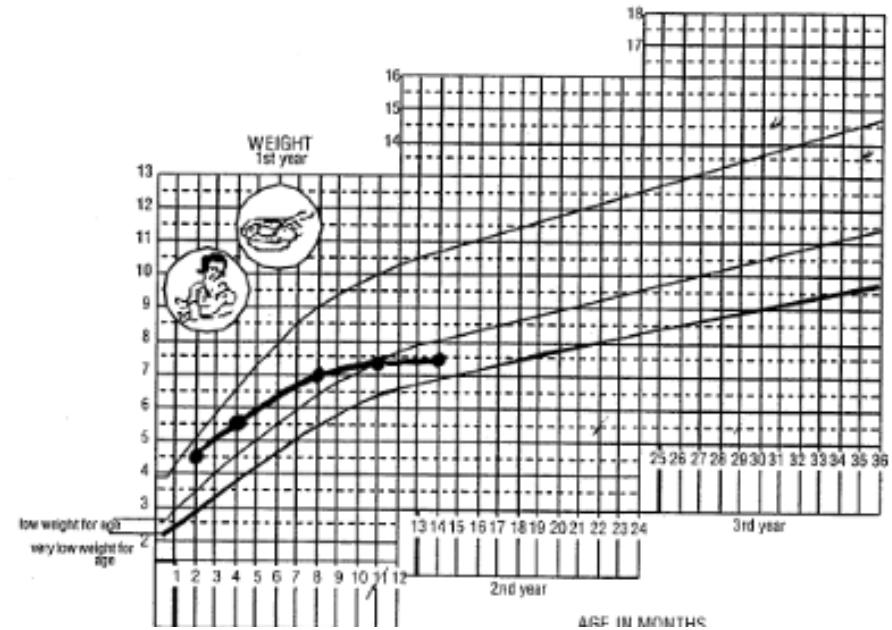
Finding	No. (%)		
	Age ≤5 y	Age >5 y	All Children
Signs and symptoms			
Loss of appetite	14 (23)	0	14 (18)
Cough	42 (70)	9 (50)	51 (65)
Dyspnea	1 (2)	0	1 (1)
Fever	26 (43)	4 (22)	30 (38)
Weight loss	19 (32)	0	19 (24)
Productive sputum	14 (23)	7 (39)	21 (27)
Purulent sputum	1 (2)	0	1 (1)
Sweating	6 (10)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

- No symptom that will definitively diagnose TB disease in children
- A combination of symptoms provides good diagnostic accuracy in HIV negative children
 1. Persistent, non-remitting cough for > 2 weeks
 2. Documented weight loss or FTT
 3. Reported fatigue (perceived decrease in playfulness/activity)
- But these will still only identify 4 of 5 children
- Time is often the best diagnostic predictor!

Evaluating a Child: Growth Assessment

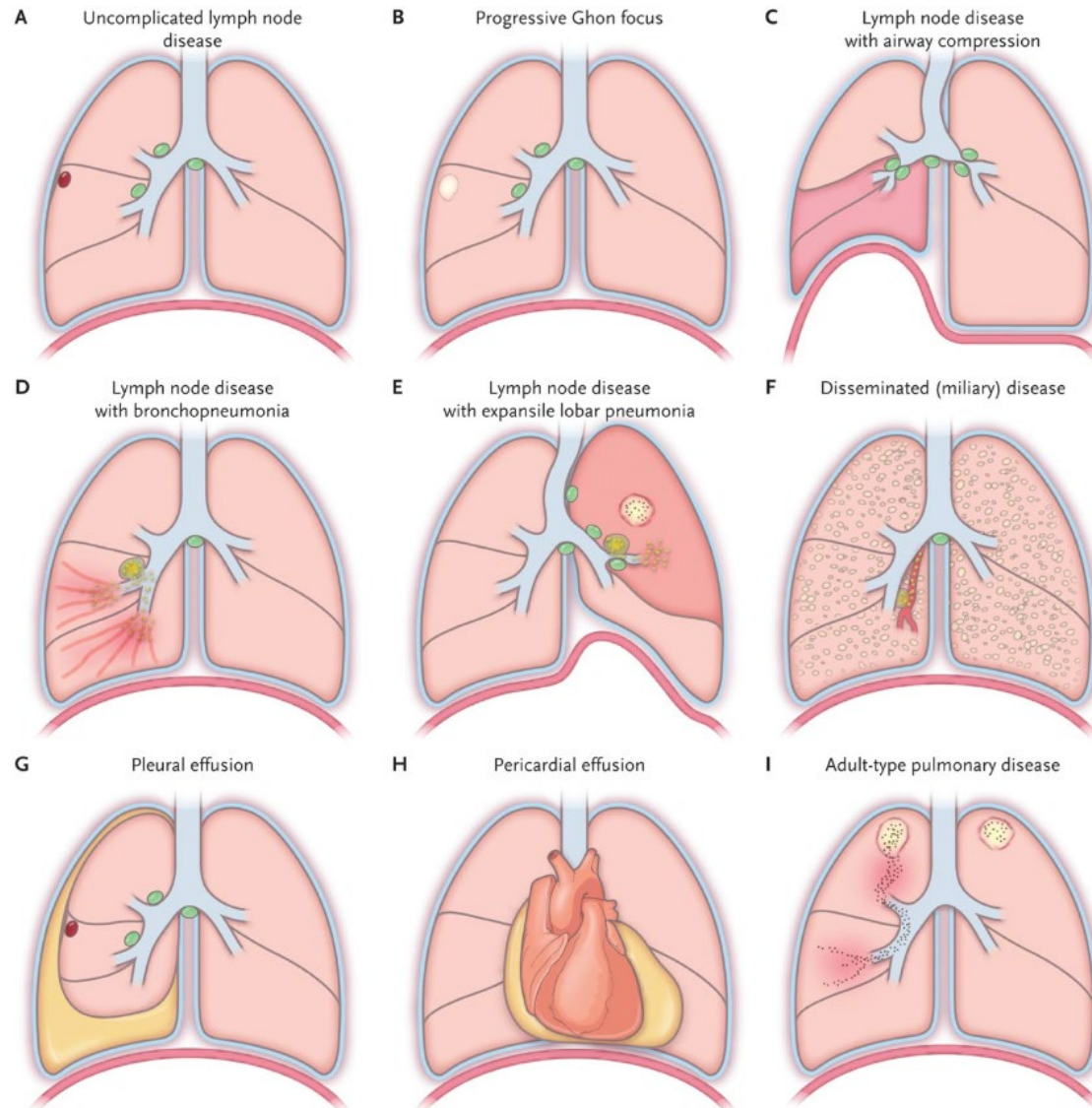


Weight Loss



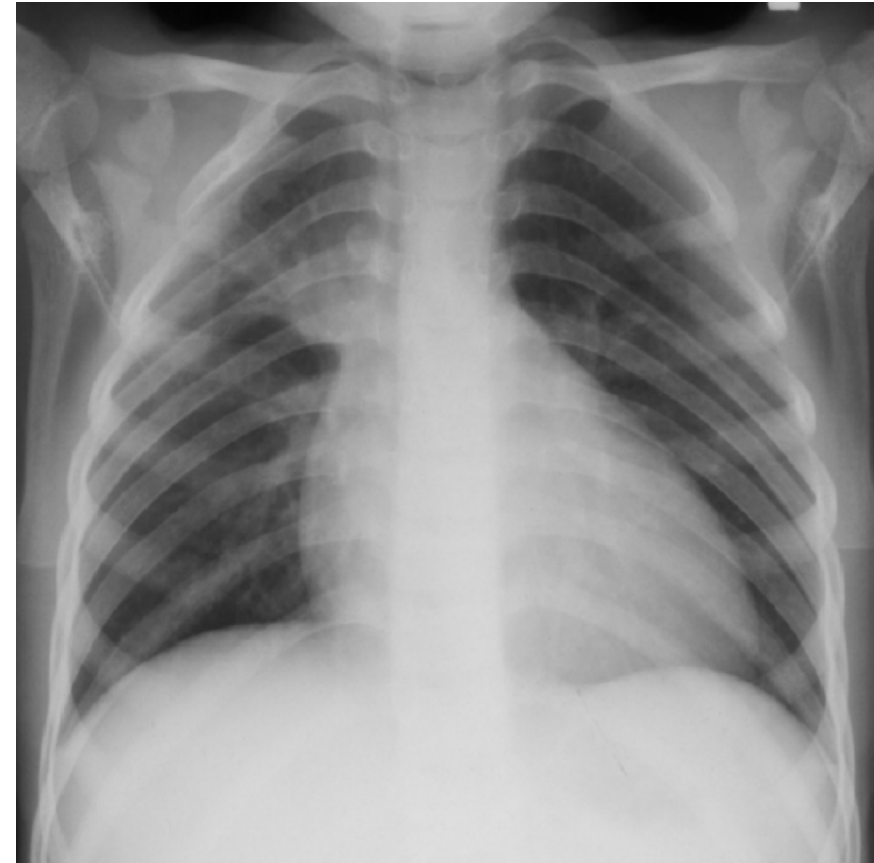
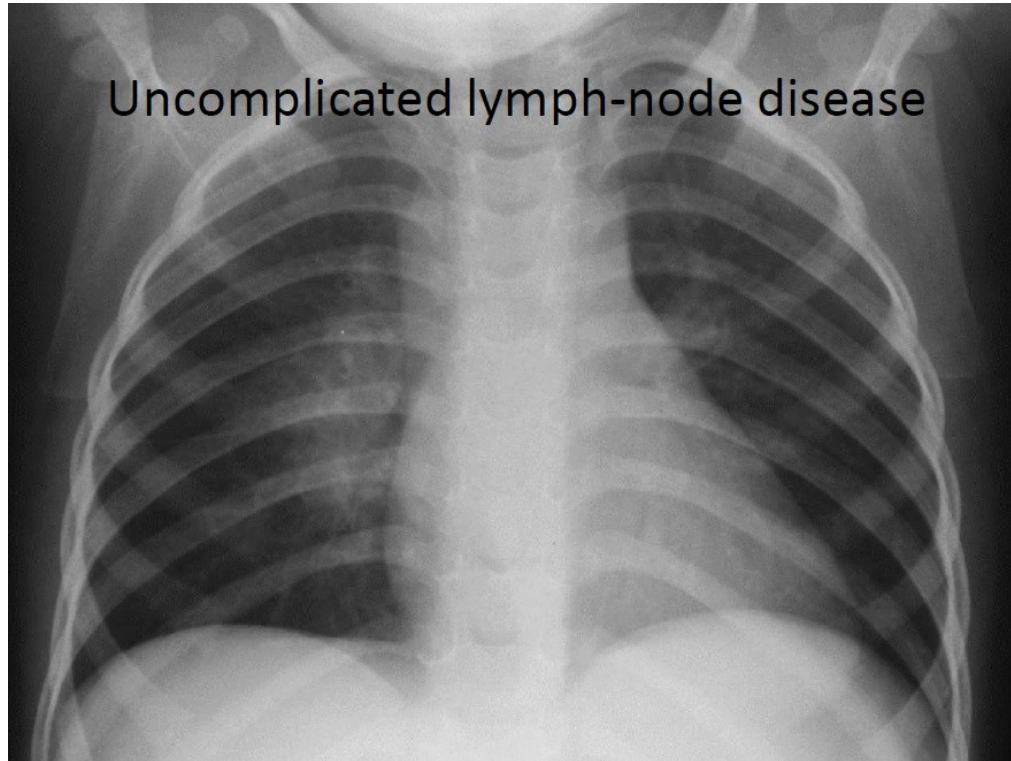
Failure to Thrive

Pediatric Intrathoracic TB Disease

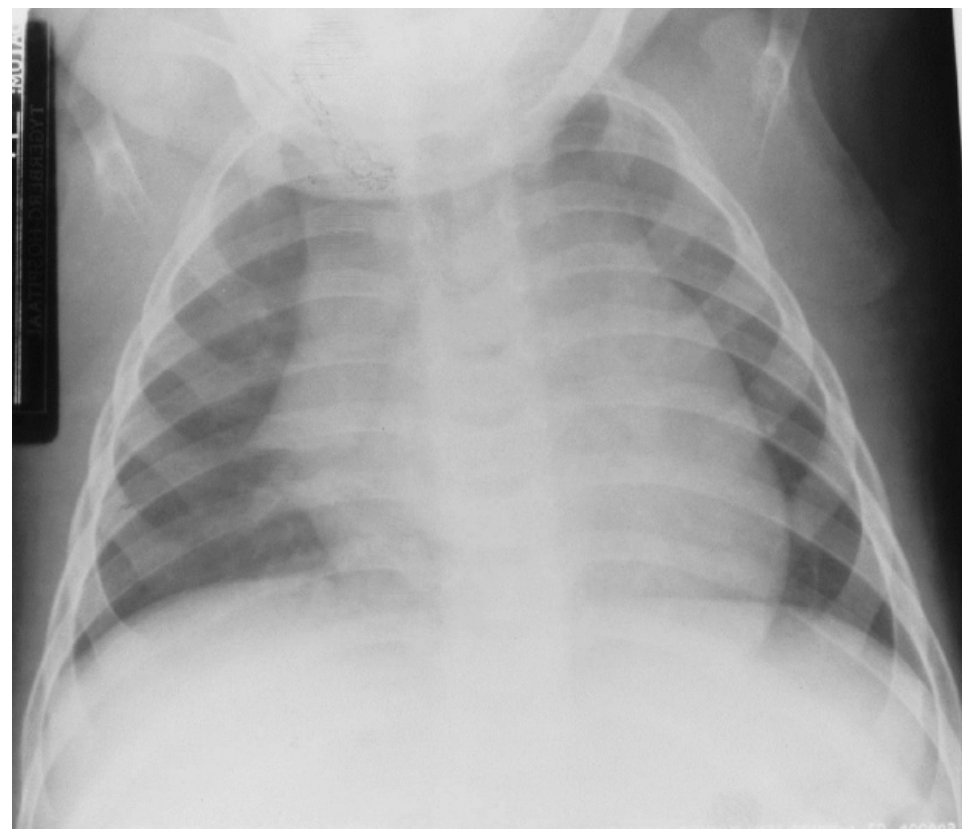
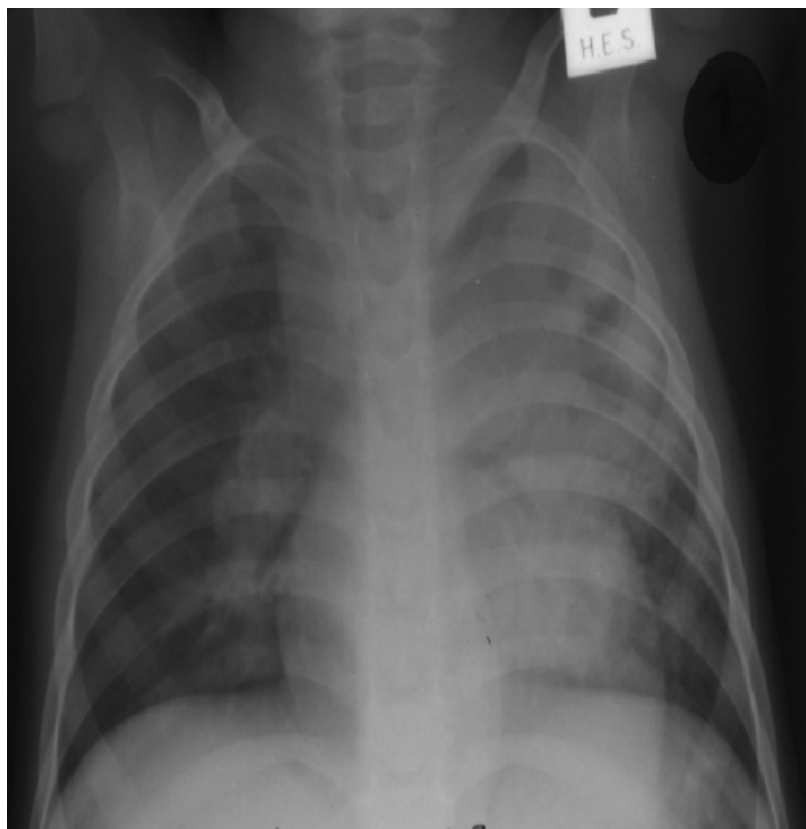


Marais, et al. NEJM 2012

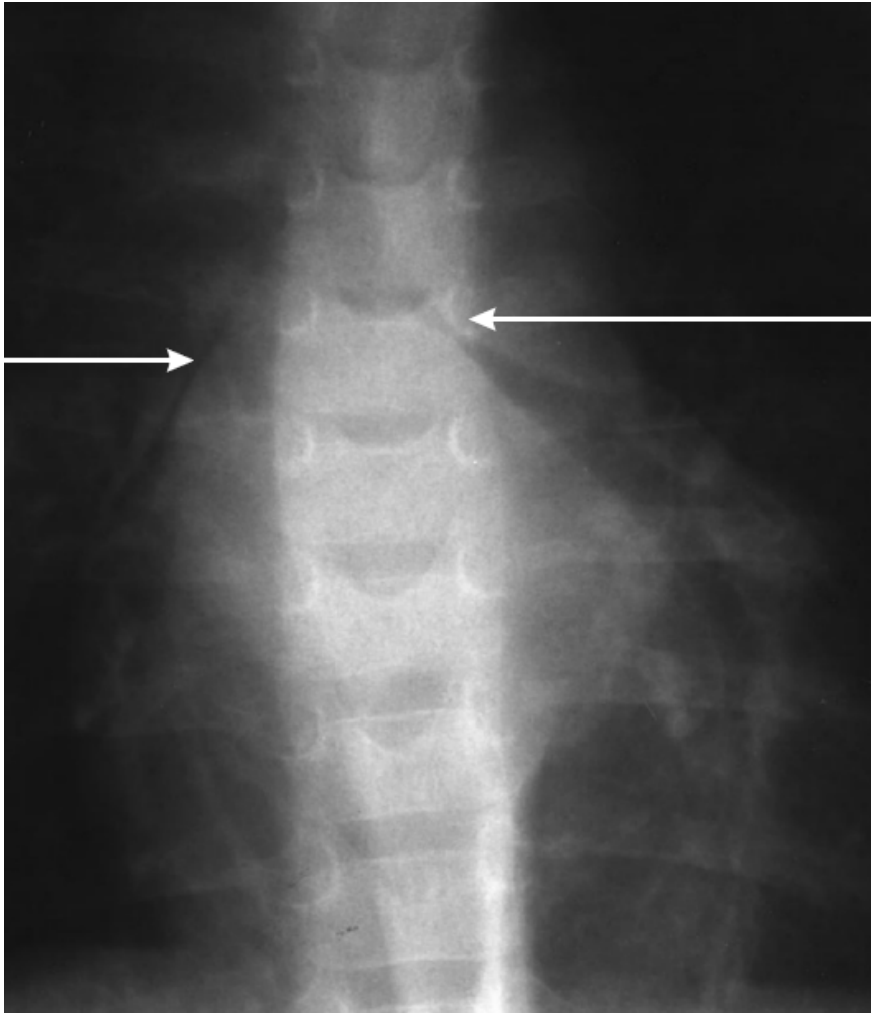
Hilar and Mediastinal Adenopathy



Hilar and Mediastinal Adenopathy

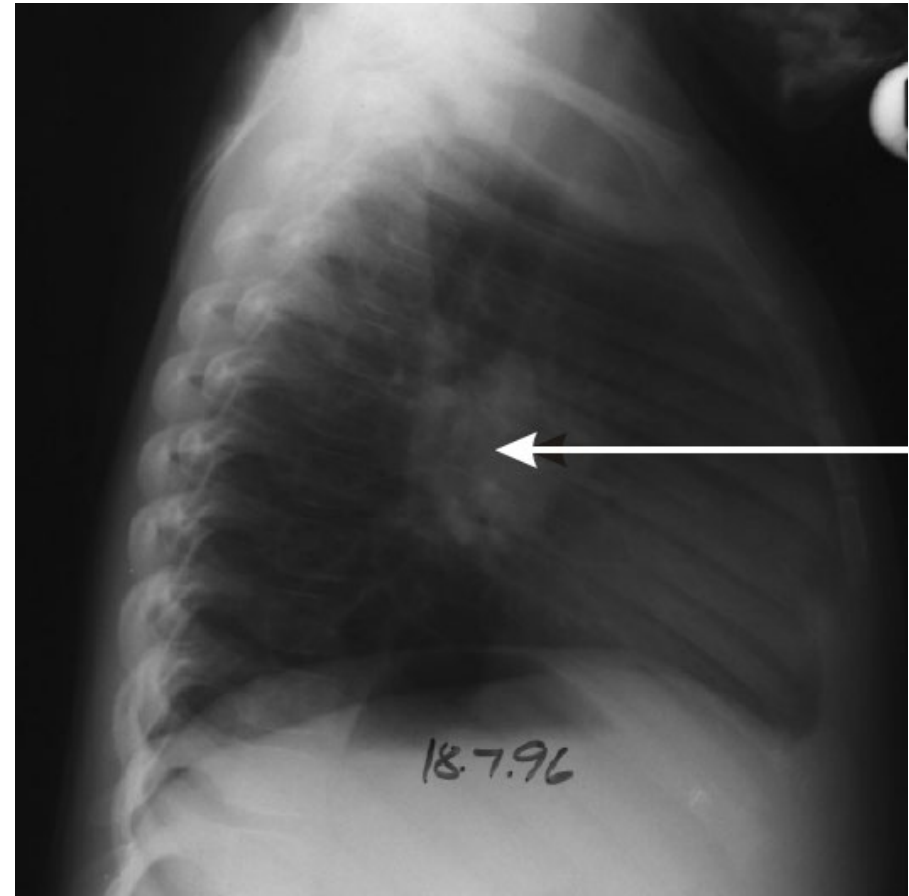
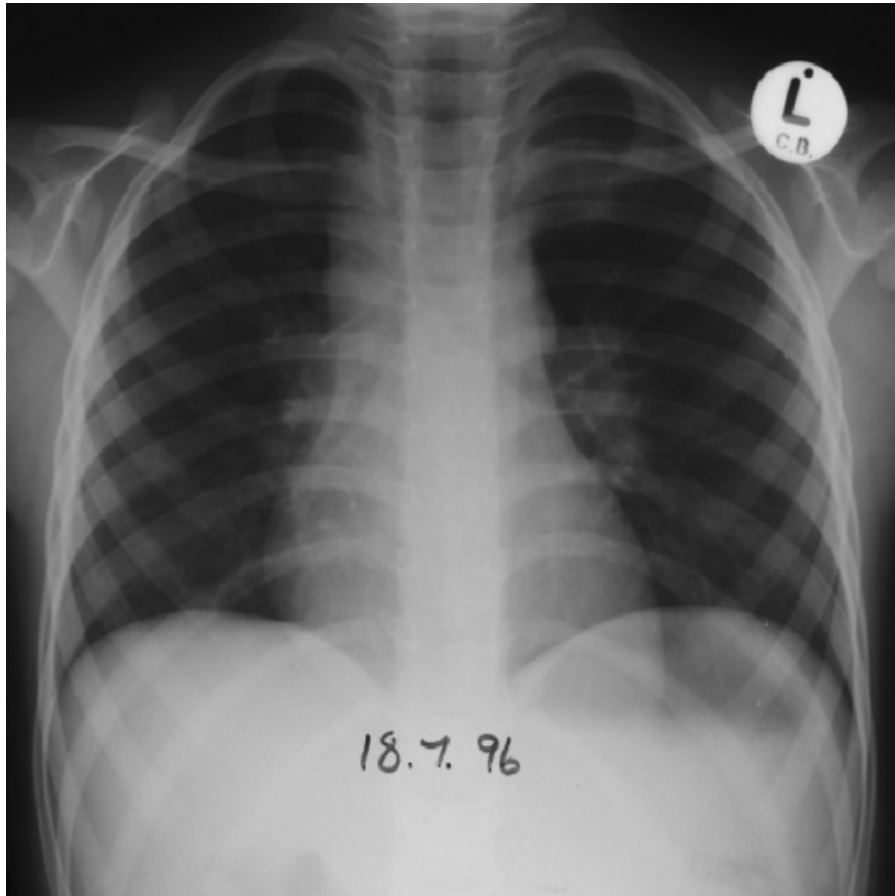


Clues to Hilar and Mediastinal Adenopathy



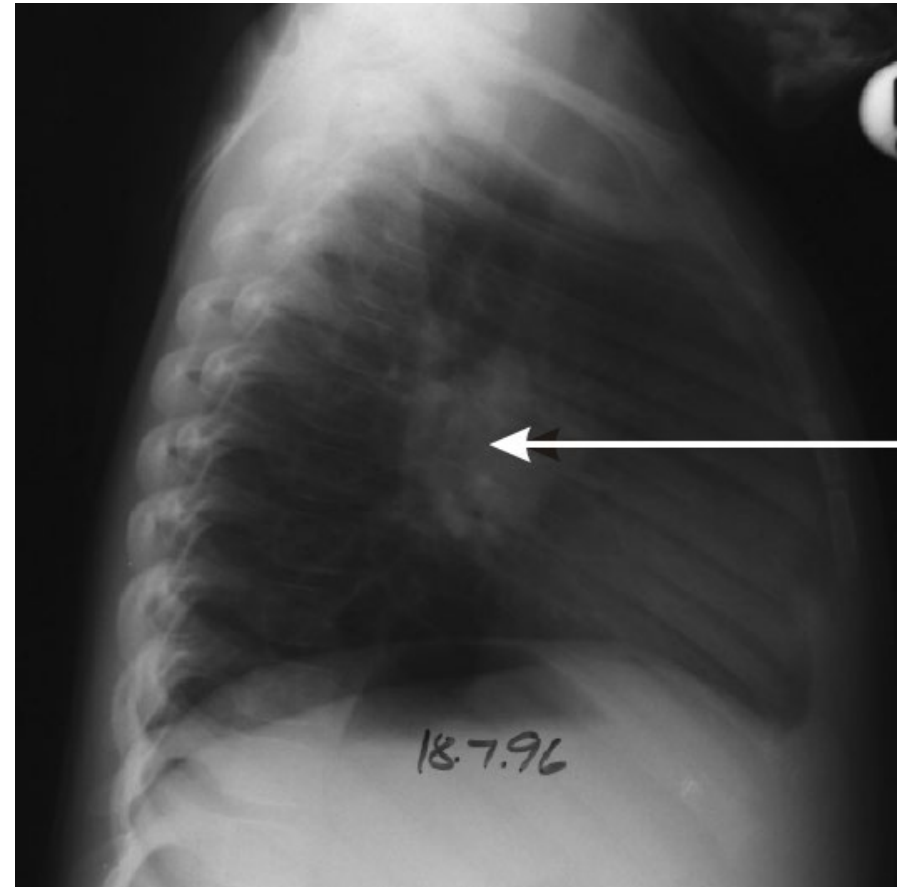
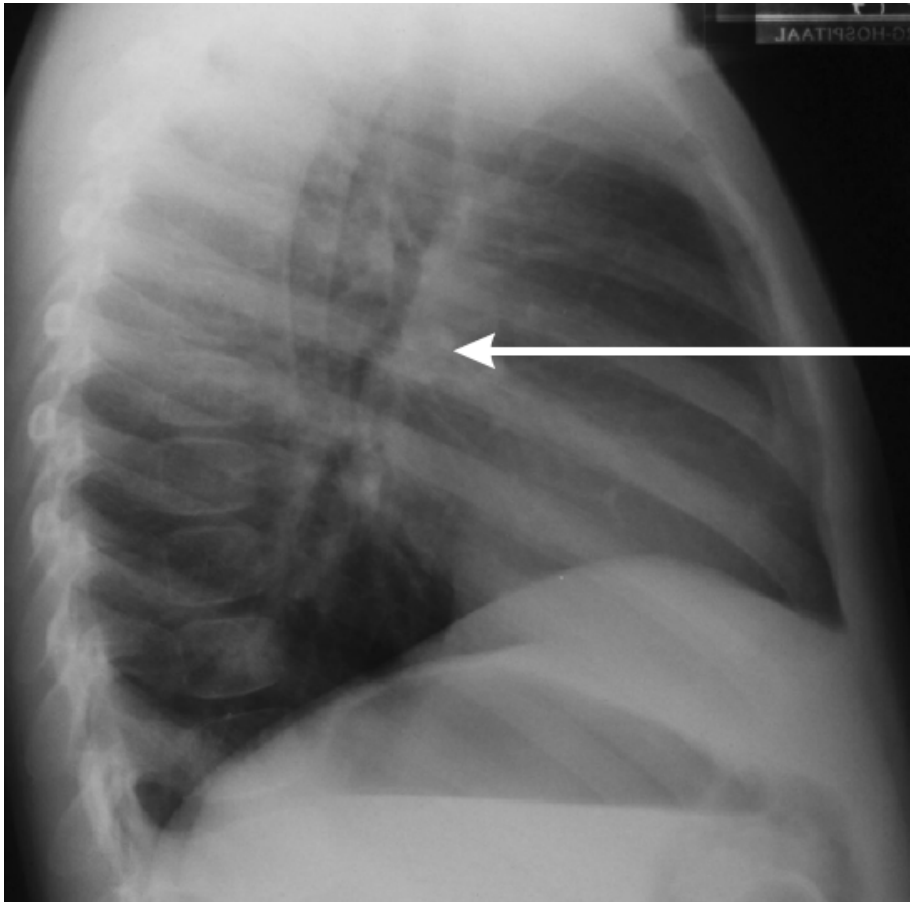
**Indirect visualization of adenopathy
through the compression of large
airways**

More Clues to Hilar and Mediastinal Adenopathy



Lateral Chest X-ray can better define hilar adenopathy!

How to Interpret a Lateral Film for Hilar Adenopathy



Difficulties in the Diagnosis of TB in Children

- Chest radiograph: Any lobe of the lung may be involved
 - Good technique/experience with children
 - Two views required: PA **and lateral**
 - Careful interpretation

Difficulties in the Diagnosis of TB in Children

TST and IGRA

- TST may be negative (10-40%)
- IGRA may be negative
 - Sensitivity is ~85% for definitive/probable TB
- Does not distinguish between infection and TB disease

Limited Diagnostic Confirmation in Pediatric TB

- Pauci-bacillary disease
 - Tubercle bacilli are relatively few in number
- Extrapulmonary disease
- Expectoated sputum not easily obtained from children < 10 years old
 - Gastric aspirates: 3 early morning specimens; not typically performed as an outpatient, often requires hospitalization
 - Induced sputum – now doing in BCHD: bronchospasm (rare) and infection control concerns
 - Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates, invasive
 - Stool – stool Xpert not available in the US
 - Urine – urine LAM not available in the US

Current Diagnostics are Poorly Sensitive for Pediatric TB



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%

Mycobacteriologic Diagnosis of Tuberculosis

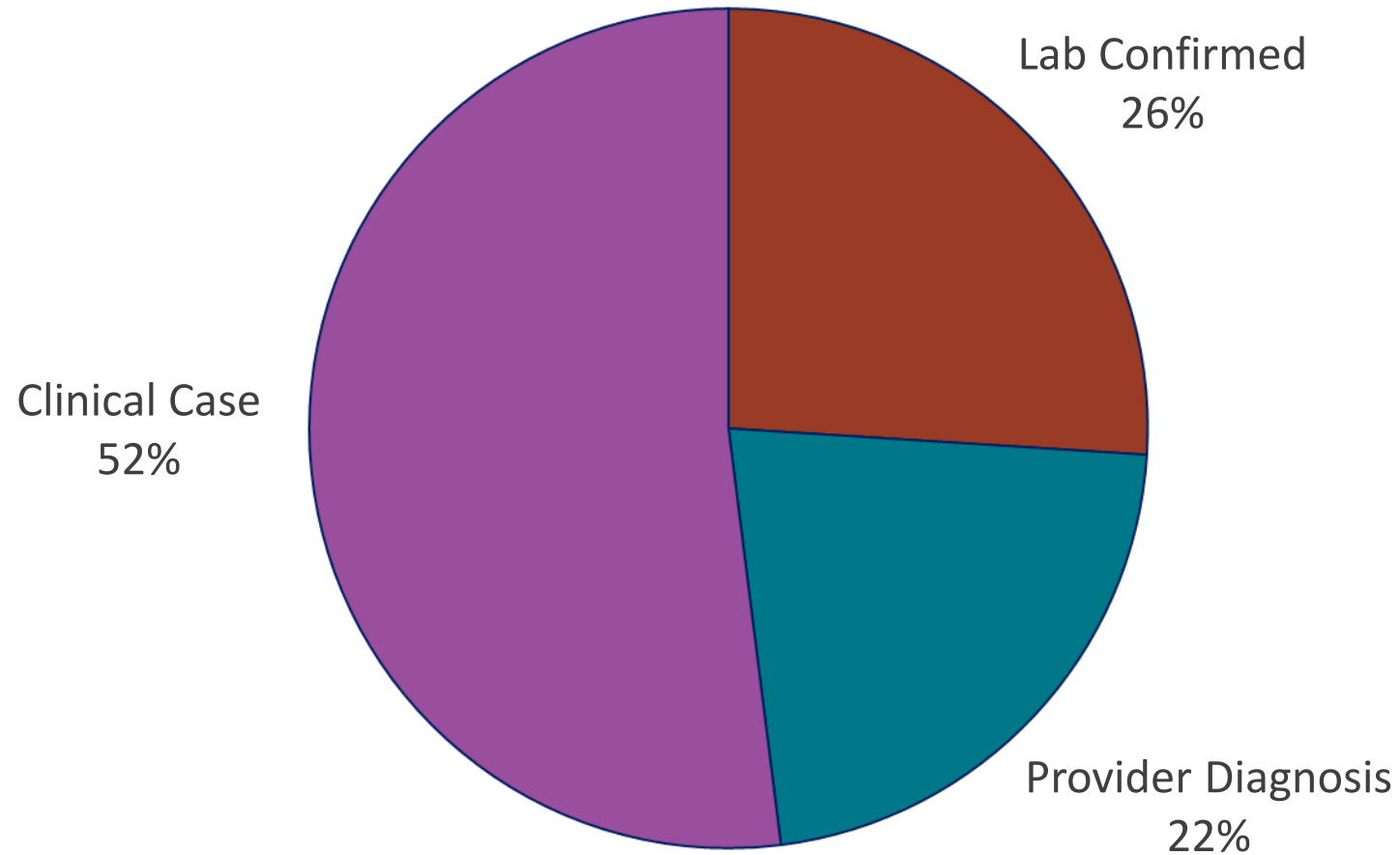
- Adults: 70-90% have a sputum that is (+) for *M. tuberculosis*
- Children: 30-40% have sputum that is (+) for *M. tuberculosis*
- Infants: 60-70% have “sputum” that is (+) for *M. tuberculosis*

- Collection of multiple specimens improves yield
- Collection of multiple specimens on day 1 as good as specimens collected on consecutive days

Xpert MTB/RIF (Ultra) for Pediatric TB

- Pooled sensitivity of Xpert Ultra was 73% compared with 65% for Xpert MTB/RIF for children with culture positive disease
- Sensitivity varied by specimen type
 - Gastric aspirate specimens had the highest sensitivity followed by sputum and stool
 - Pediatric specimens often not validated on Xpert in the USA
- Pediatric EPTB: Good sensitivity for culture-positive lymphadenitis but not for TB meningitis

Pediatric TB Cases by Case Verification Criteria* 1993–2015



N= 21,223

*Based on the public health surveillance definition for TB [MMWR 1997;46(No. RR-10):40-41]



TB Lymphadenitis



Extrapulmonary Tuberculosis



Pediatric TB Treatment

Principles of Regimen Development

- When culture results are not available (at least 60-70% of children):
 - Regimens are based on the source case susceptibilities, adherence, and treatment history
 - Local epidemiology
 - Prior episodes of TB
- When resistance is possible or suspected, a more aggressive diagnostic approach may be necessary
- Risk factors for drug resistance
 - Contacts of patients with known DR-TB
 - Prior TB treatment (unusual for young children)
 - Poor initial response to therapy
 - e.g., persistent smear positivity after appropriate treatment
 - Immigration from or travel to countries with a high prevalence of DR-TB

First-Line TB Therapy

Drug	Dose	Formulations	Notes	Adverse events
Rifampin	15 mg/kg (10-20 mg/kg)	Oral capsule (150 and 300 mg) Oral solution (10mg/mL)	CYP3A4 inducer (OCP, seizure meds, etc.)	Hepatotoxicity, Hypersensitivity
Isoniazid	10 mg/kg (10-15 mg/kg)	Oral tab (100 and 300 mg) Oral solution (50mg/5mL) IM solution (100mg/mL)	Crushed tabs are better tolerated than liquid solution	Hepatotoxicity, Peripheral neuropathy, Hypersensitivity
Pyrazinamide	35 mg/kg (30-40 mg/kg)	Oral tab 500mg Oral solution (100mg/mL)*	*requires compounding pharmacy	Hepatotoxicity, Hyperuricemia
Ethambutol	20 mg/kg (15-25 mg/kg)	Oral tab 100mg, 400mg Oral suspension (50mg/mL)		Optic neuritis, Hypersensitivity

Typical First-Line Regimen: 2RHZ + 4RH *or* 2RHZE + 4RH

Doses should be weight-adjusted as children grow during the 6+ month course of therapy

doses are increased but never decreased. Weight loss is very concerning in a child!

Practical Administration of TB Drugs to Children

- 1st-line TB medications can be crushed and mixed with food
 - Good stability in sugar-free chocolate pudding or grape jelly
 - Practically any food the child prefers to mask the taste of the medications can be used to enhance acceptability as long as the medication is taken quickly after crushing and mixing with food
- Rifampin and pyrazinamide can be compounded into suspensions
 - Often needed in young children for appropriate dose
- Crushed isoniazid tablets should be used whenever possible
 - Isoniazid solution causes significant GI upset (+/-50%)

Ethambutol

- Is ethambutol safe for use in Children?
 - Recent review suggests at this lower dose, ethambutol is safe in children, including infants for a 2-month period
 - Longer therapy may require ophthalmology follow up and should be discussed with a pediatric ID specialist
- When to use ethambutol in Children?
 1. Susceptibilities of the source case are unknown and significant risk of INH mono-resistance
 2. Extensive adult-type or smear-positive pulmonary TB disease
 3. Severe forms of extrapulmonary TB disease

Following Response to Therapy in Children

- Clinical response
 - Improving symptomatically, growth, development
- Microbiological response
 - Repeat sputa samples to assess for smear/culture conversion often unnecessary in children
- Radiologic response
 - Repeat CXR not mandatory
 - CXR findings often lag behind true improvement
 - Often helpful when a child has not shown significant clinical improvement
 - Hilar adenopathy can take 1-2 years to resolve and should not be considered a poor response to therapy

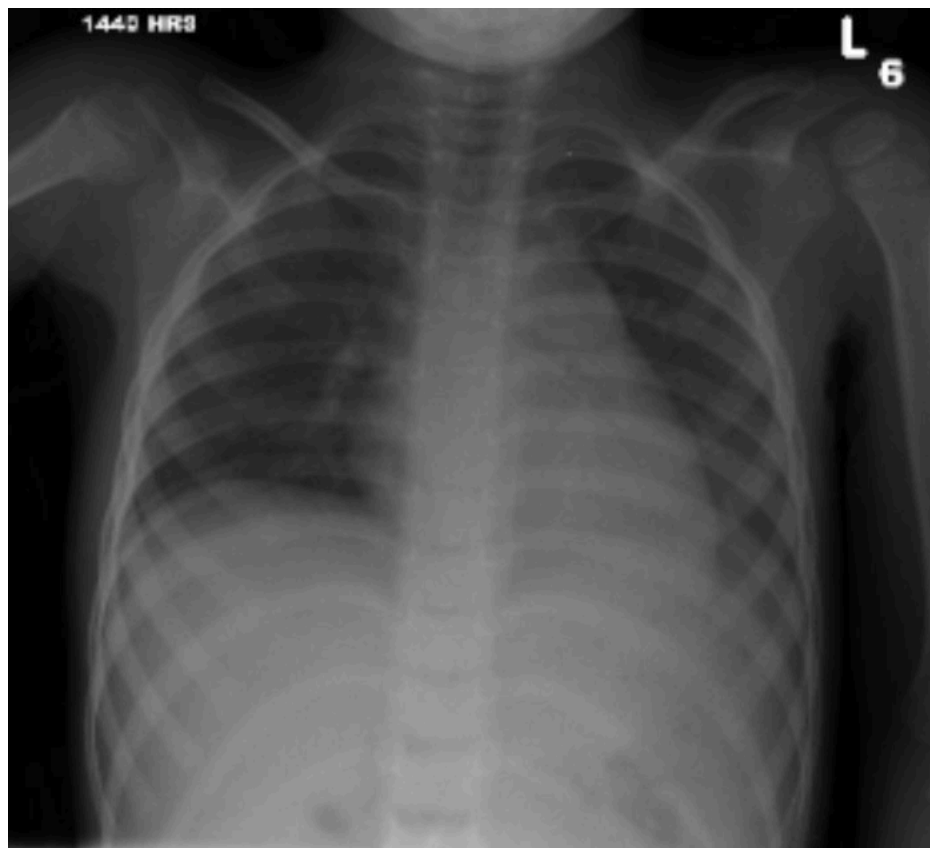
Following Response to Therapy in Children

- Directly observed therapy
- Follow monthly
 - Treatment response – symptoms, weight gain, developmental milestones
 - Drug toxicity (nausea, vomiting, abdominal pain)
 - Adherence
 - Weight adjust all medications
- Drug-related hepatotoxicity is rare
 - Liver function testing indicated when signs/symptoms of hepatitis develop, severe disease
- Treatment duration
 - 6 months for PTB, longer for TBM and TB osteomyelitis
 - Extend therapy: poor response to therapy, cavitation with persistently positive smears at 2 months, poor adherence

Clinical Case

- 2 year old presenting with 2 weeks of daily fever (40°C) after recent travel to India
- No known TB contacts
- Outpatient work up:
 - QFT positive, CXR: LLL pna
- Admitted to hospital
 - 3 consecutive early morning gastric aspirates and trial of antibiotics
 - No response to routine IV antibiotics for CAP (ampicillin)
 - Chest CT to better define extent of lesions and define adenopathy

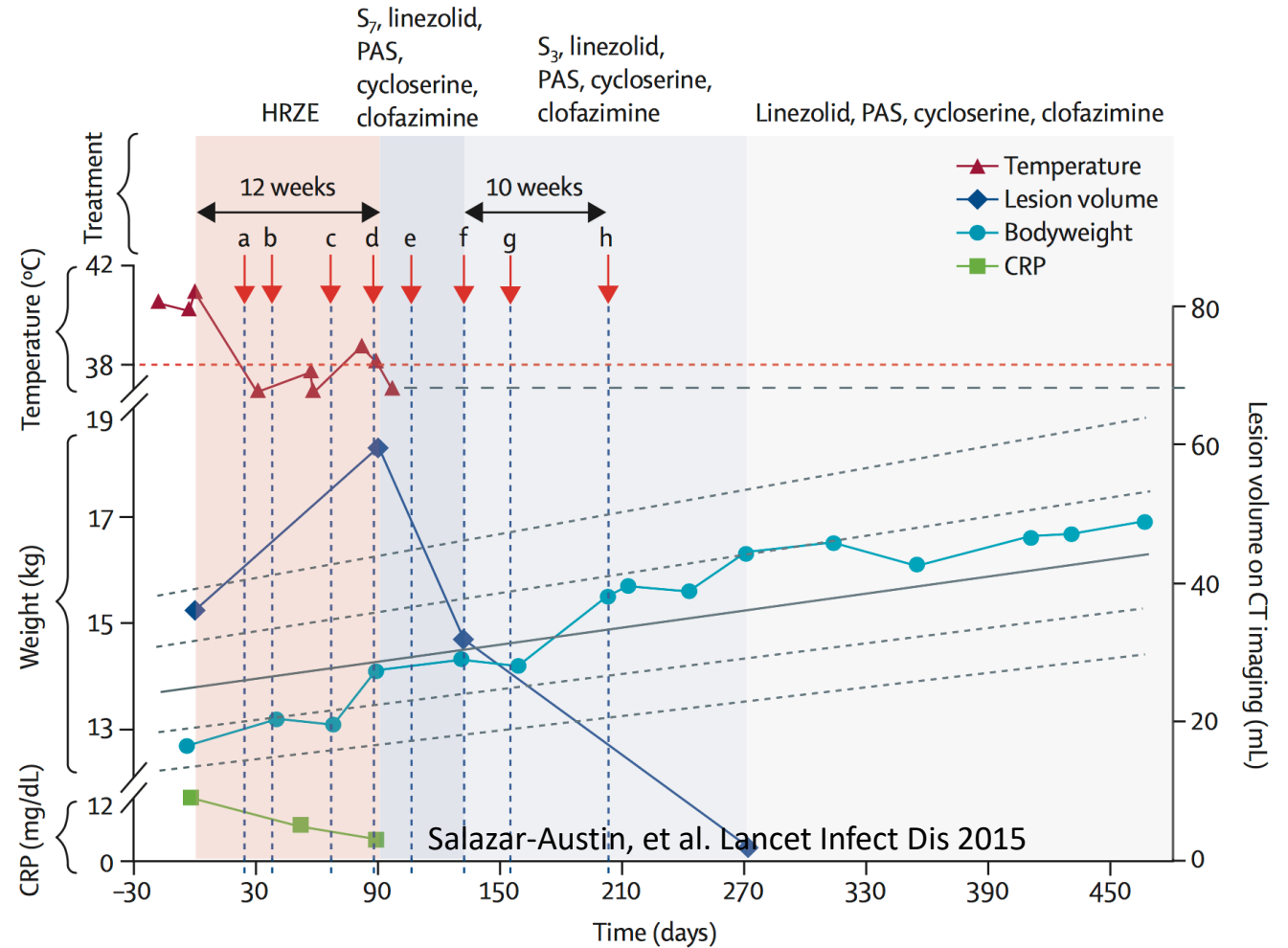
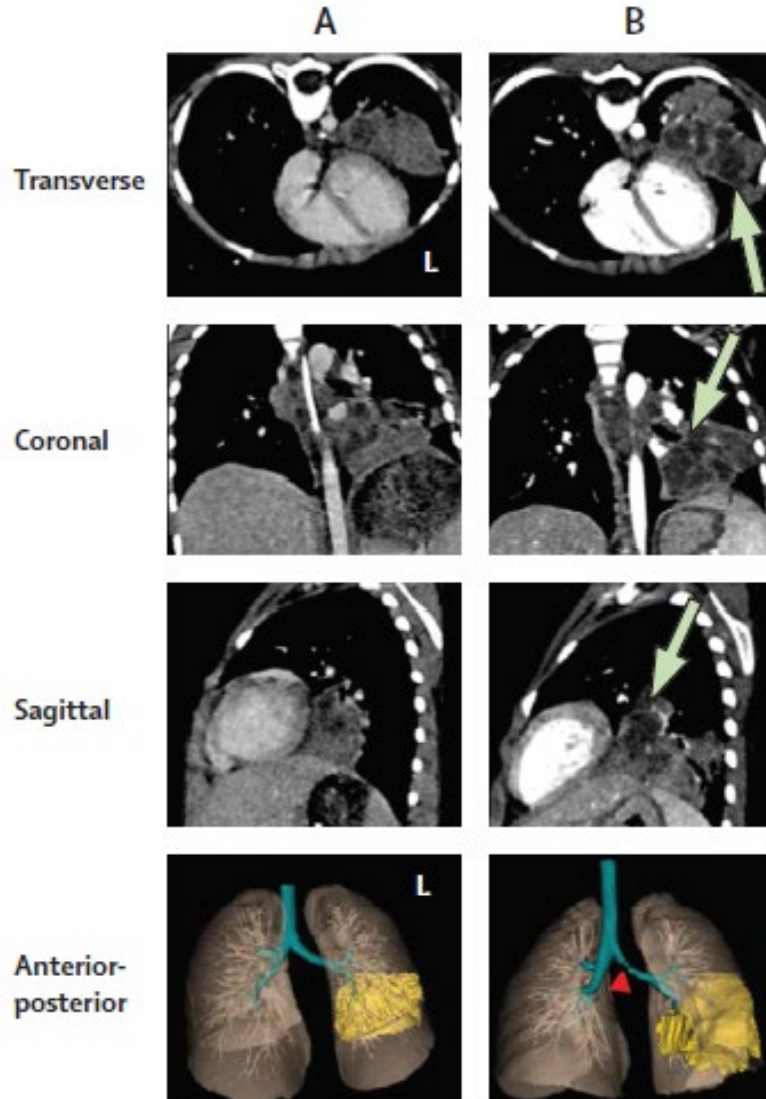
LLL on Lateral Film



Following Clinical Response to RHZE

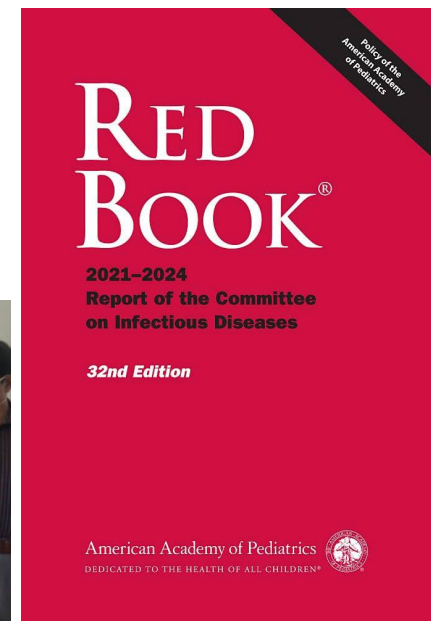
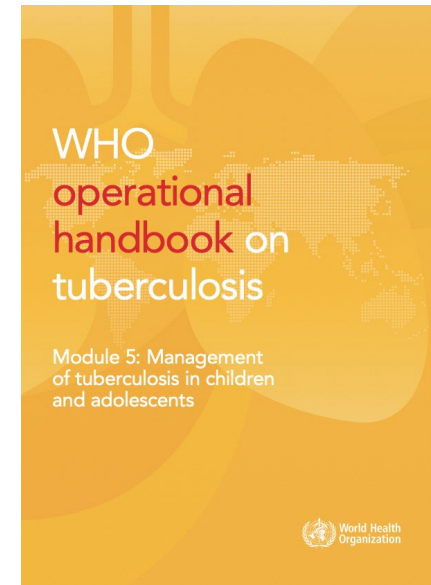
- Fever resolved, appropriate weight gain, down-trending CRP
- Continued low grade temperatures (<100.4°F) and tachycardia
- One of four gastric aspirate specimens was MGIT culture positive at 4 weeks
 - No growth on solid media, no susceptibilities available
- Thoughts?

Presentation of DR-TB After Treatment with RHZE: Subtle Findings



Treating Drug Resistant TB in Pediatrics

1. Limited PK and/or safety data for many drugs at younger ages
 - Dosing now available for BDQ and DLM down to 3kg (newborn)!
2. Limited availability of age-appropriate formulations in the US
3. Should be discussed with a pediatric infectious disease and/or

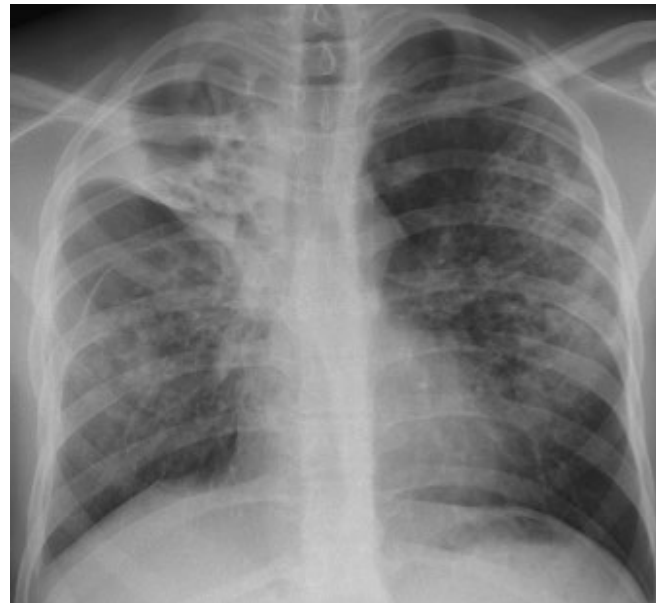


Tuberculosis in Adolescents

- Adolescents develop tuberculosis in one of two ways:
 - Reactivation of infection acquired during childhood
 - The closer to puberty at the time of infection the greater the risk of reactivation
 - Chronic pulmonary tuberculosis
 - Progression of infection acquired during adolescence to disease:
 - Classic primary disease
 - Progressive primary pulmonary tuberculosis
 - Chronic pulmonary tuberculosis

Adolescents: Reactivation Tuberculosis

- Constitutional symptoms often more prominent than respiratory symptoms
 - Weight loss and fever are very common
 - Drenching night sweats occur several times per week
 - Cough, chest pain, hemoptysis
- Cavitory lesions frequently seen



Another missed opportunity:
Just how bad can this get?

OR

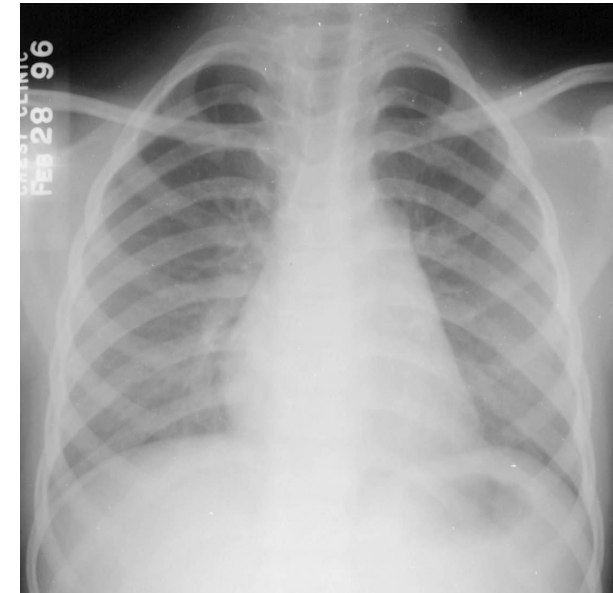
Can you die from TB if you are a
teenager?

AND

Why LTBI is important!

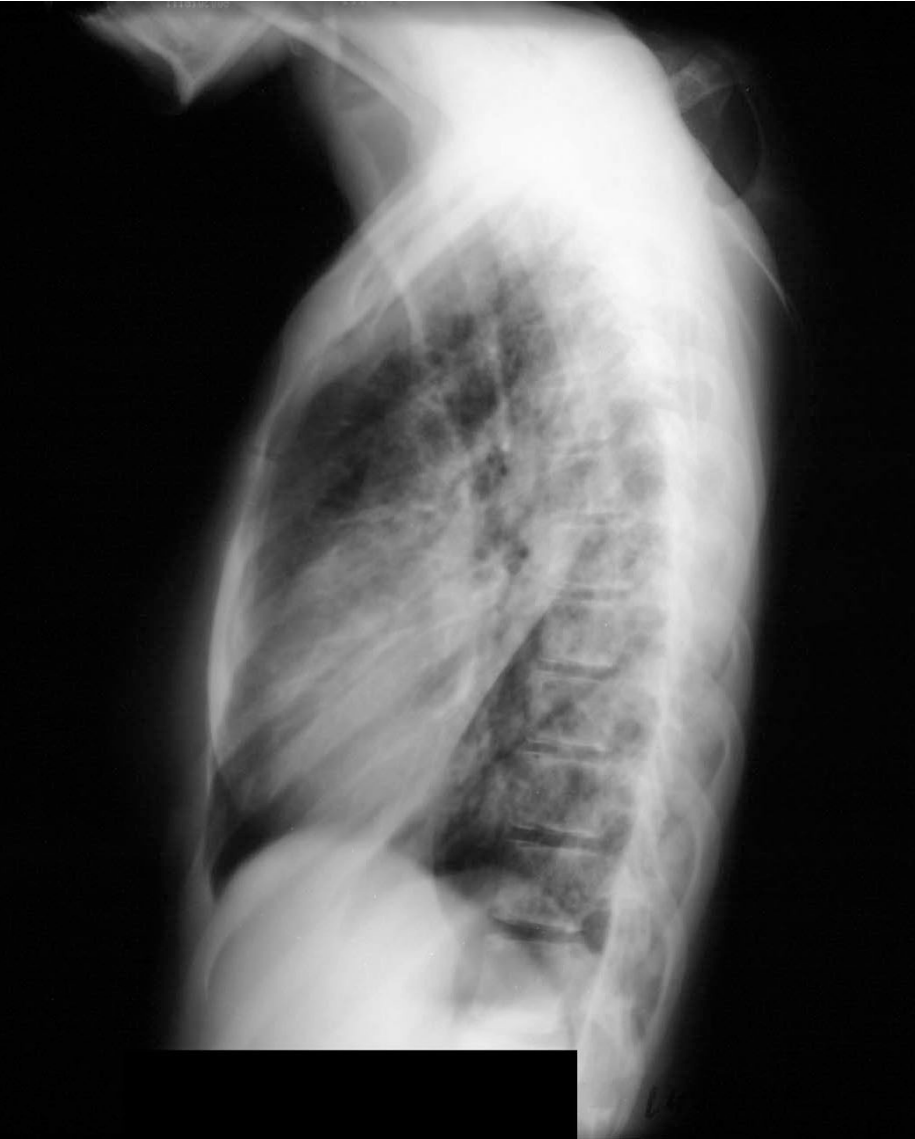
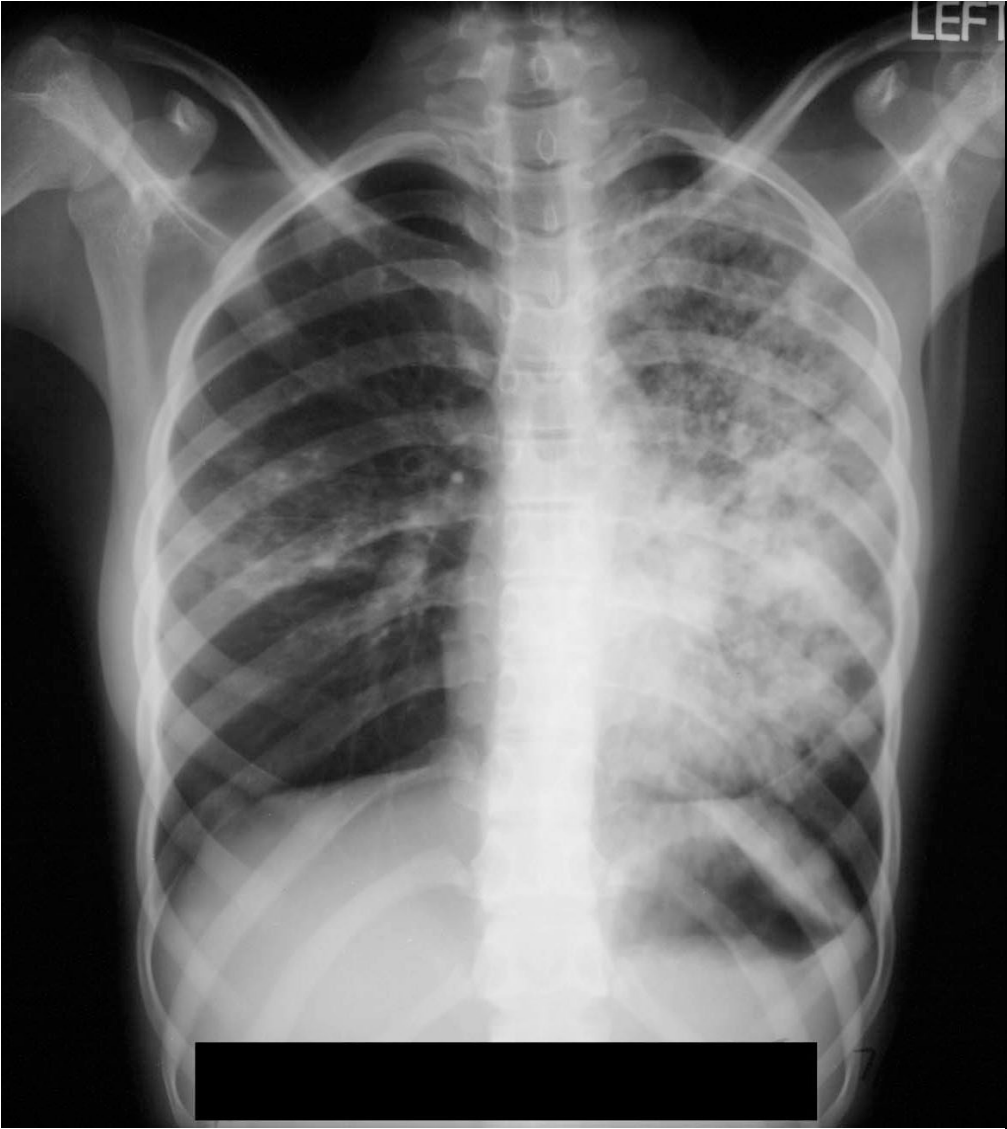
Adolescent TB Case

- 8-year old girl, recently arrived from Haiti was evaluated at the DOH for a 12 mm TST reaction
- There were no symptoms of TB disease and PE was normal
- A chest radiograph was done:
- INH 200 mg po once daily; #30 tabs dispensed
- 6 months later the chart reads: “Overdue for medication refill.”
- There were no further notes for 5 years



Hospital Admission

- The patient, now 13-years of age, was admitted to a local hospital with a 3 week history of fever, cough, increasing dyspnea, and weakness
- She had been sent home by the school nurse on 4 occasions over the previous 2 months for the fever and cough and then for weight loss and weakness
 - She was seen on 2 occasions by her PCP and was given antibiotics (azithromycin) and twice in EDs of local hospitals:
 - The last ED visit was 9 days PTA when chest radiographs were done and amoxicillin-clavulanate (Augmentin) was given
 - There was no improvement with antibiotic
 - A chest x-ray was done in the last ED

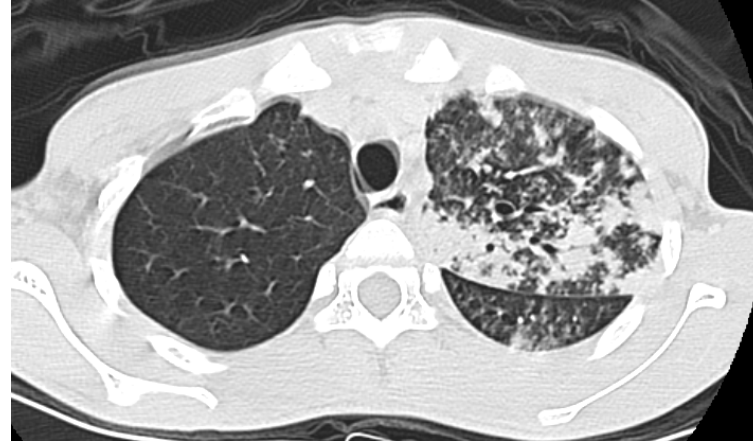


Case

- PE: Cachectic, weak appearing female with flat affect in mild respiratory distress
- T – 103.2⁰F HR – 160' RR – 22' O₂ sat = 92%
- Wt: 78.7 lbs UBWt.: 96.7 lbs
- Treatment IV ceftriaxone and oral azithromycin
- ID consultation:
 - Sputa: AFB smear: (+), few AFB; culture (+): pansensitive MTB
- Anti-TB medications started:
 - INH 300 mg po daily
 - RIF 600 mg po daily
 - PZA 500 mg po, three times a day (?)
 - Emb 400 mg po, twice daily (?)

Case

- 7/12: At hospital discharge
 - Remains febrile
 - Came directly to Chest Clinic with driven by her brother and sister with “TB escort”
 - Cachetic, weak with unsteady gate
 - Continued treatment added supplement, ibuprofen
 - DOT by RN
 - Home visit by CRNP (PED)
 - Weak, tires easily, bed ridden, bed-bathroom, bedroom had no windows, home was very warm (no AC)
 - Poor oral intake
 - Tachypneic, tachycardic



- Re-hospitalized 7/24-8/17: Weaker, hypoxemic, cachectic with weight down to 66 lbs
- RR - 40' O₂ sat 90%
- Continued TB meds; oxygen
- NGT placed for continuous nutritional supplementation

Case

- Gradually regained strength and began to walk
- Discharge: 8/17 RR – 20' on 1L oxygen; Wt 76 lbs
 - TB meds and supplement
 - AC purchased and placed in home
- 8/23: Wt. 88 lbs; RR = 18'
- 9/20: Wt. 97 lbs; RR = 18"
- 11/1: Wt. 99 lbs
- 12/13: Wt 102 lbs
- 12/13 CXR:

