Tuberculosis in Children

Lisa Y. Armitige, MD, PhD

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Comprehensive TB Nurse Case Management
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Lisa Y. Armitige, MD, PhD, has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Tuberculosis in Children

Lisa Y Armitige, MD, PhD
Professor, Medicine and Pediatrics
Division of Adult Infectious Diseases

Co-Medical Director
Heartland National TB Center

Lisa Armitige, MD, PhD has the following disclosures to make:

- Consultant for Oak Therapeutics SBIR

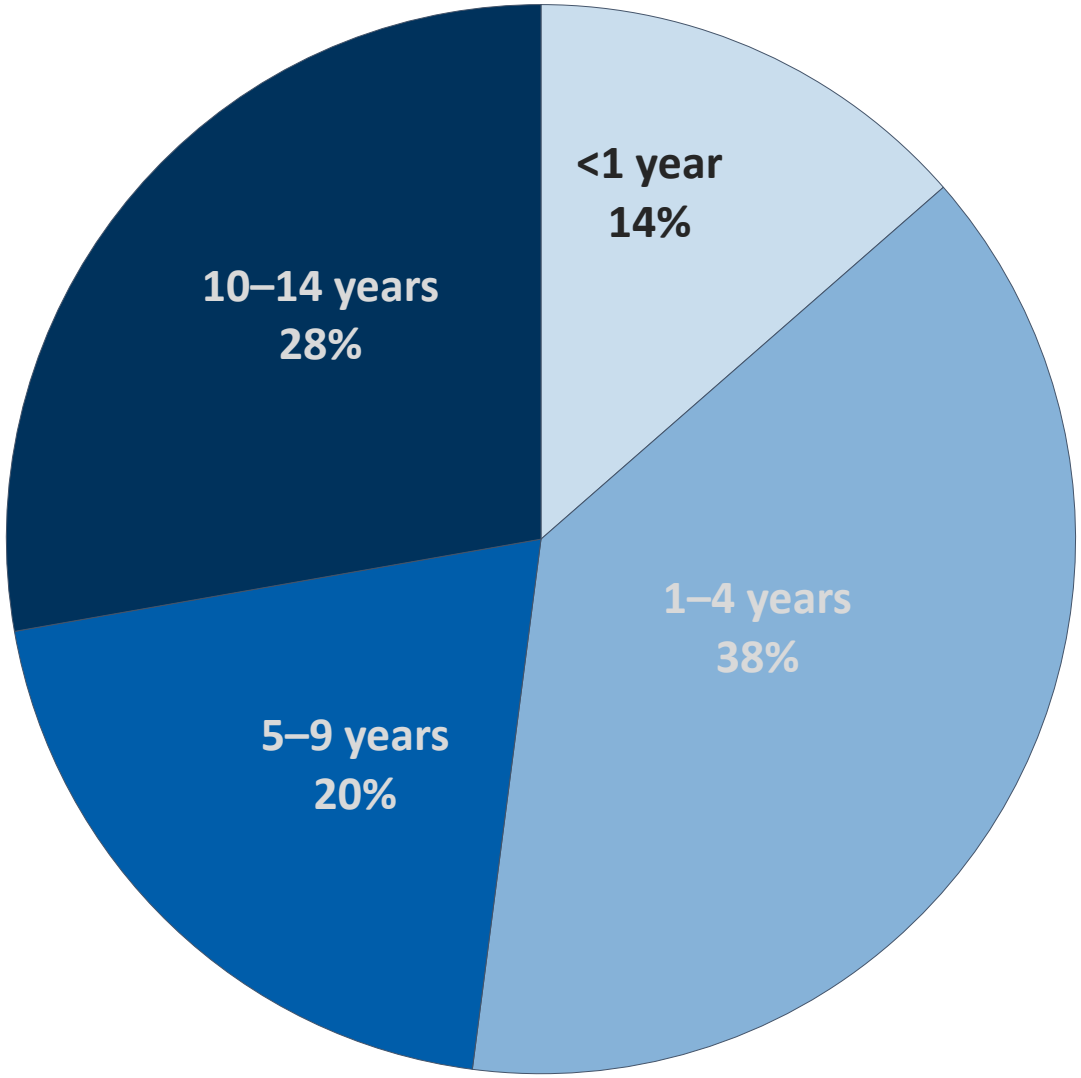
Epidemiology of Pediatric TB

US Pediatric Tuberculosis

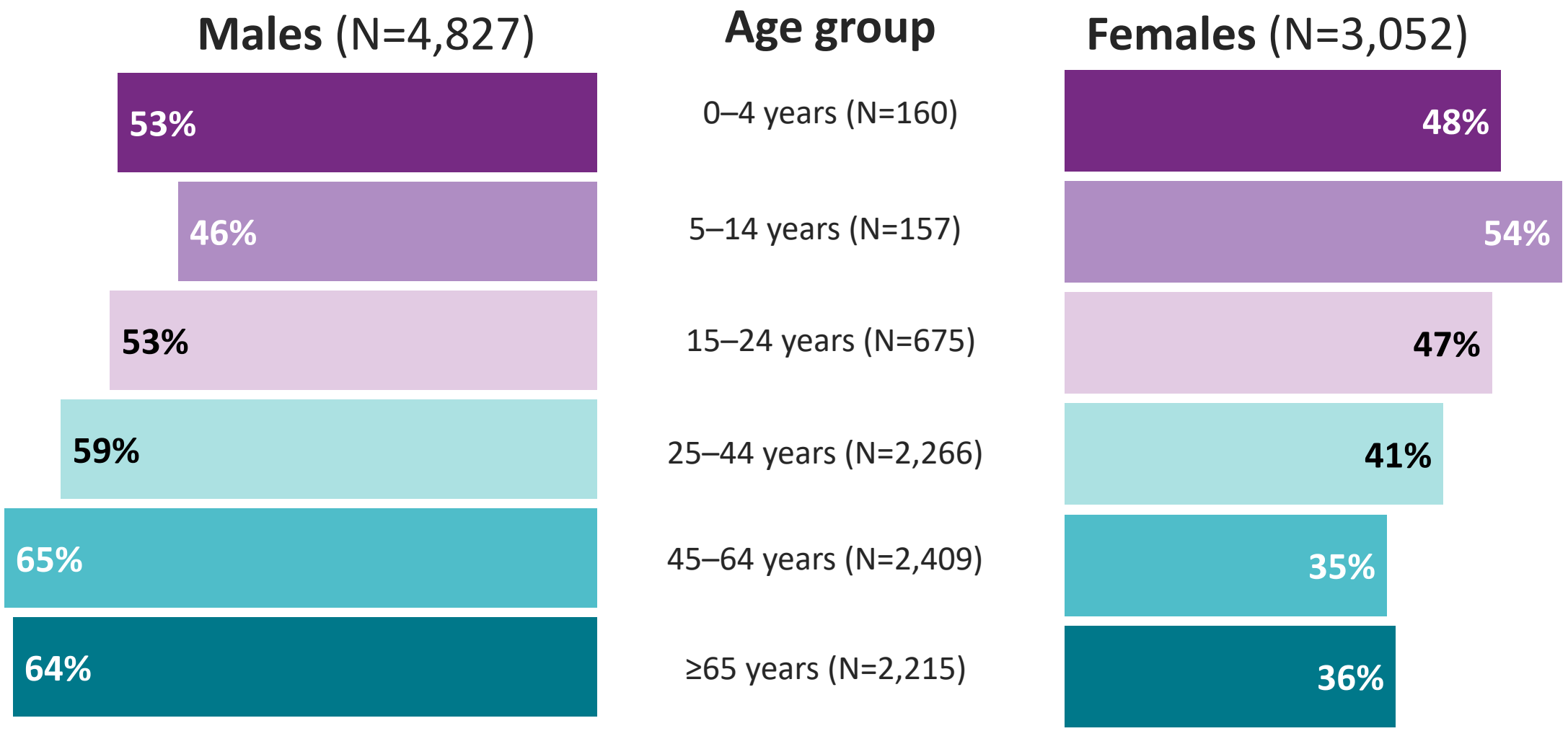
- Definition of pediatric tuberculosis (TB):
  - TB disease in a person <15 years old
- In 2021:
  - 7,882 TB cases were reported among all age groups
  - 317 (4.4%) were pediatric
    - same as 2020
    - 18% decrease from 2019 (365 pediatric cases)

Age group	N	Percentage of all cases
0–4 years	160	2.0%
5–14 years	157	2.0%

Percentage of Pediatric TB Cases by Age Group, United States, 2020 (N=317)



Percentage of TB Cases by Sex and Age Group, United States, 2021



Percent Risk of Disease by Age

Age at Infection	Risk of Active TB
Birth – 1 year*	43%
1 – 5 years*	24%
6 – 10 years*	2%
11 – 15 years*	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults+	30-50% lifetime

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

+WHO, 2004

Risk of Progression to TB Disease by Age

Age @ primary infection	Risk of Disease	
• Birth - 12months	Disease	50%
	Pulmonary Dis	30-40%
	Miliary or TBM	10-20%
• 1-2 years	Disease	20-25%
	Pulmonary Dis	75%
	Miliary or TBM	2-5%

Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402

Risk of Progression from TB Infection to Disease by Age

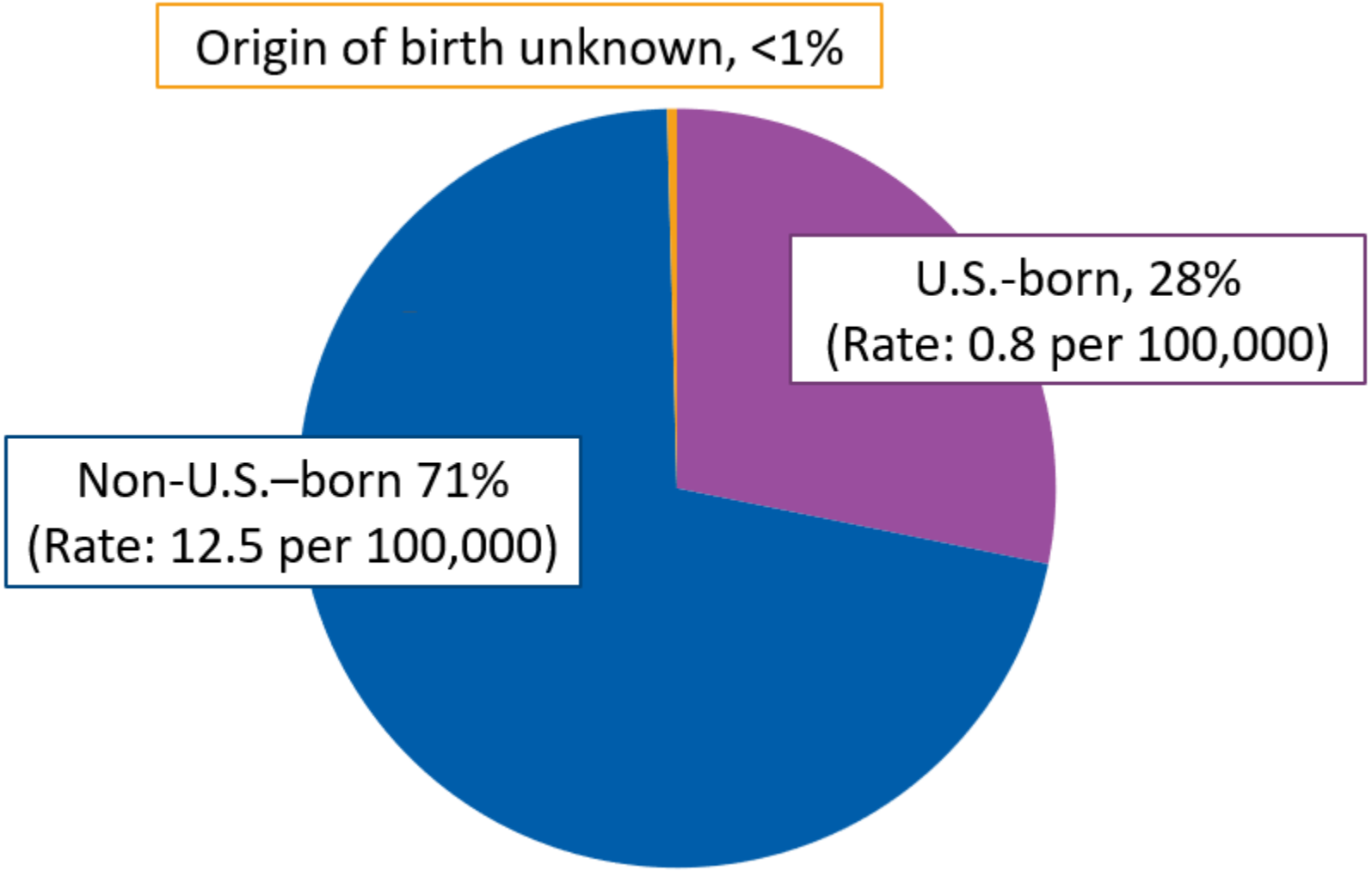
Age at Primary Infection (yr)	No Disease (%)	Pulmonary Disease (%)	Miliary or Central Nervous System TB (%)
<1	50	30 to 40	10 to 20
1 to 2	75 to 80	10 to 20	2.5
2 to 5	95	5	0.5
5 to 10	98	2	<0.5
>10	80 to 90	10 to 20	<0.5

Adapted from Marais, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Resp Crit Care Med*. 2006;173:1078–1090.

Peds in Review 2010;31:13

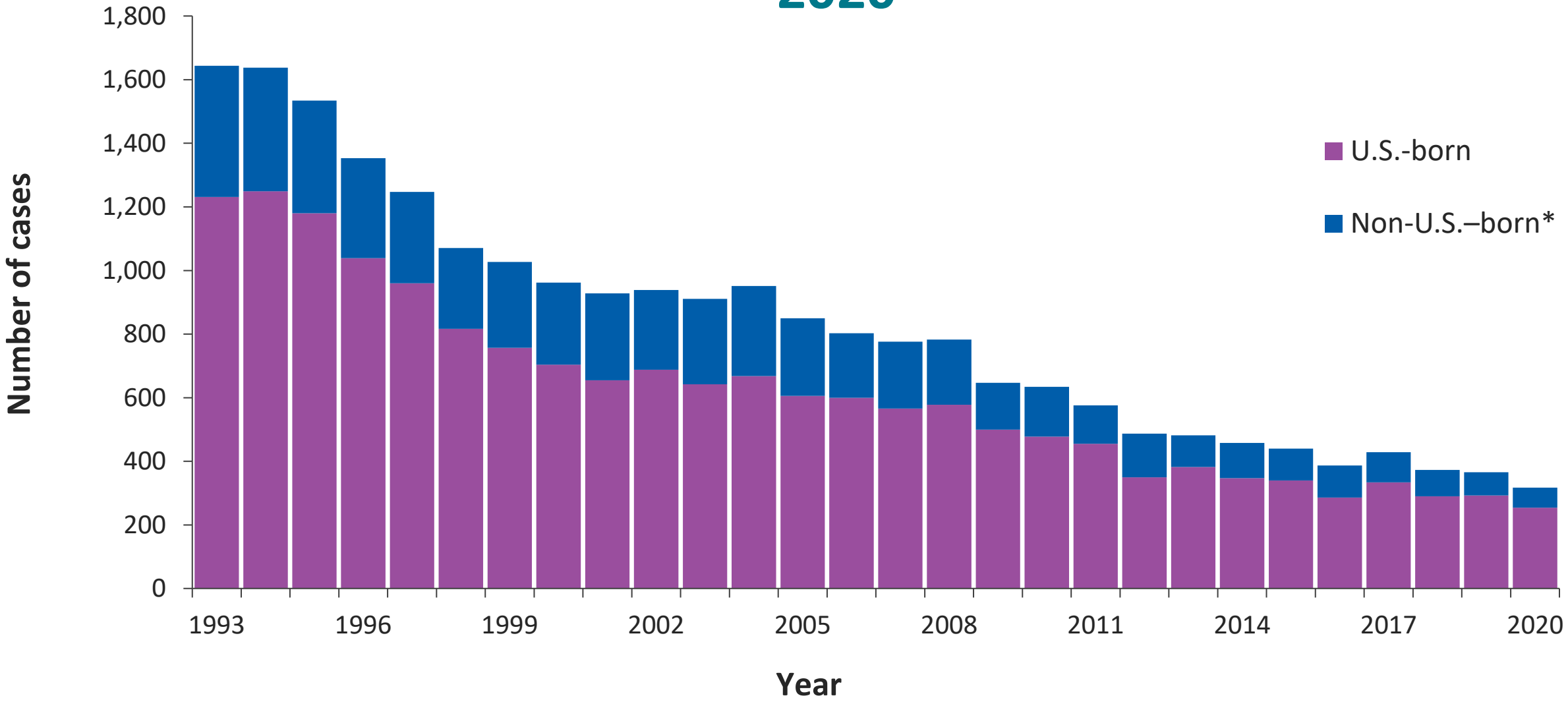
Differences In Adult and Pediatric TB

TB Incidence Rates and Percentages by Origin of Birth,* United States, 2021 (N=7,849)



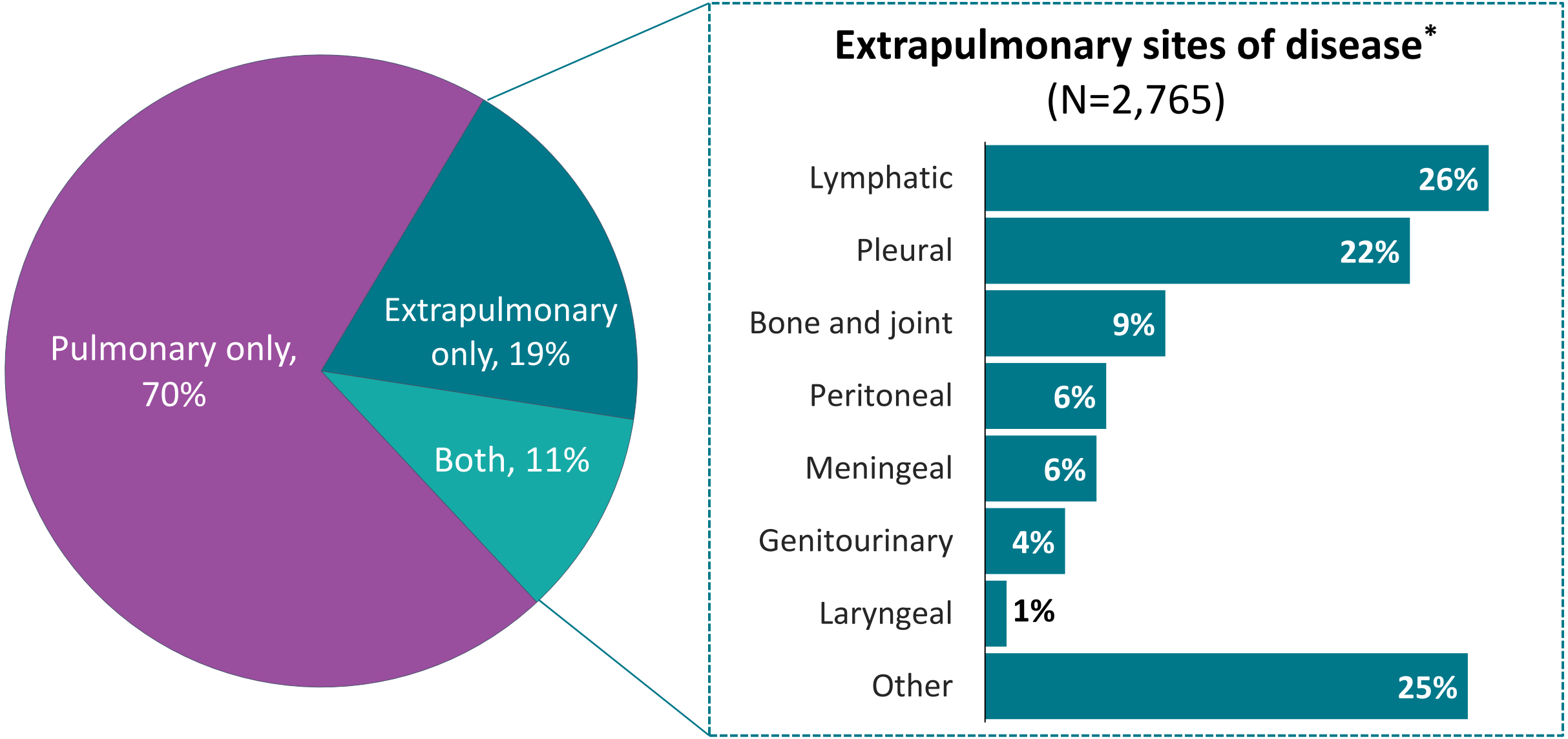
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

Pediatric TB Cases by Origin of Birth, United States, 1993–2020



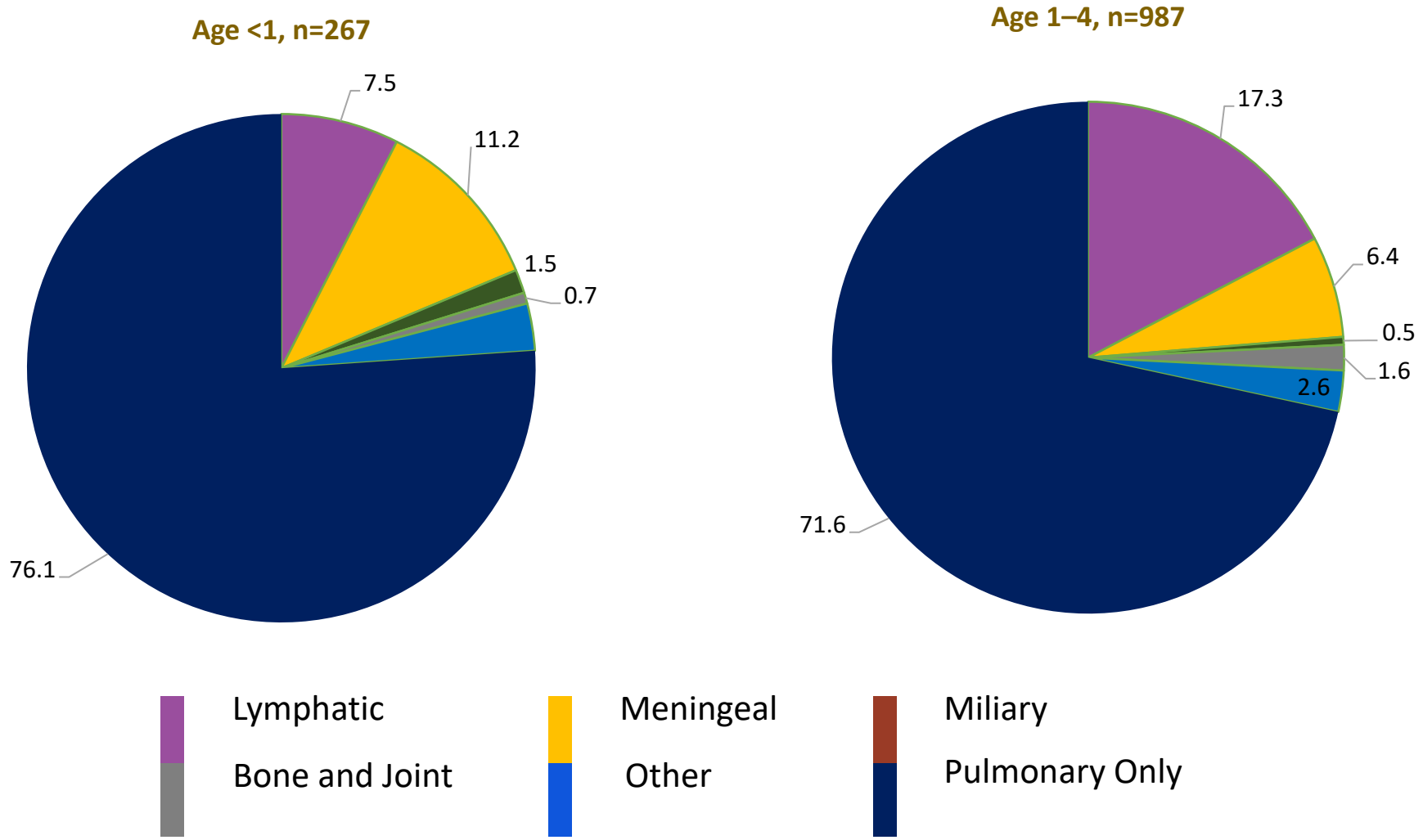
*Non-U.S.–born refers to persons born outside the United States or its territories or not born to a U.S. citizen

Percentage of TB Cases by Site of Disease, United States, 2022

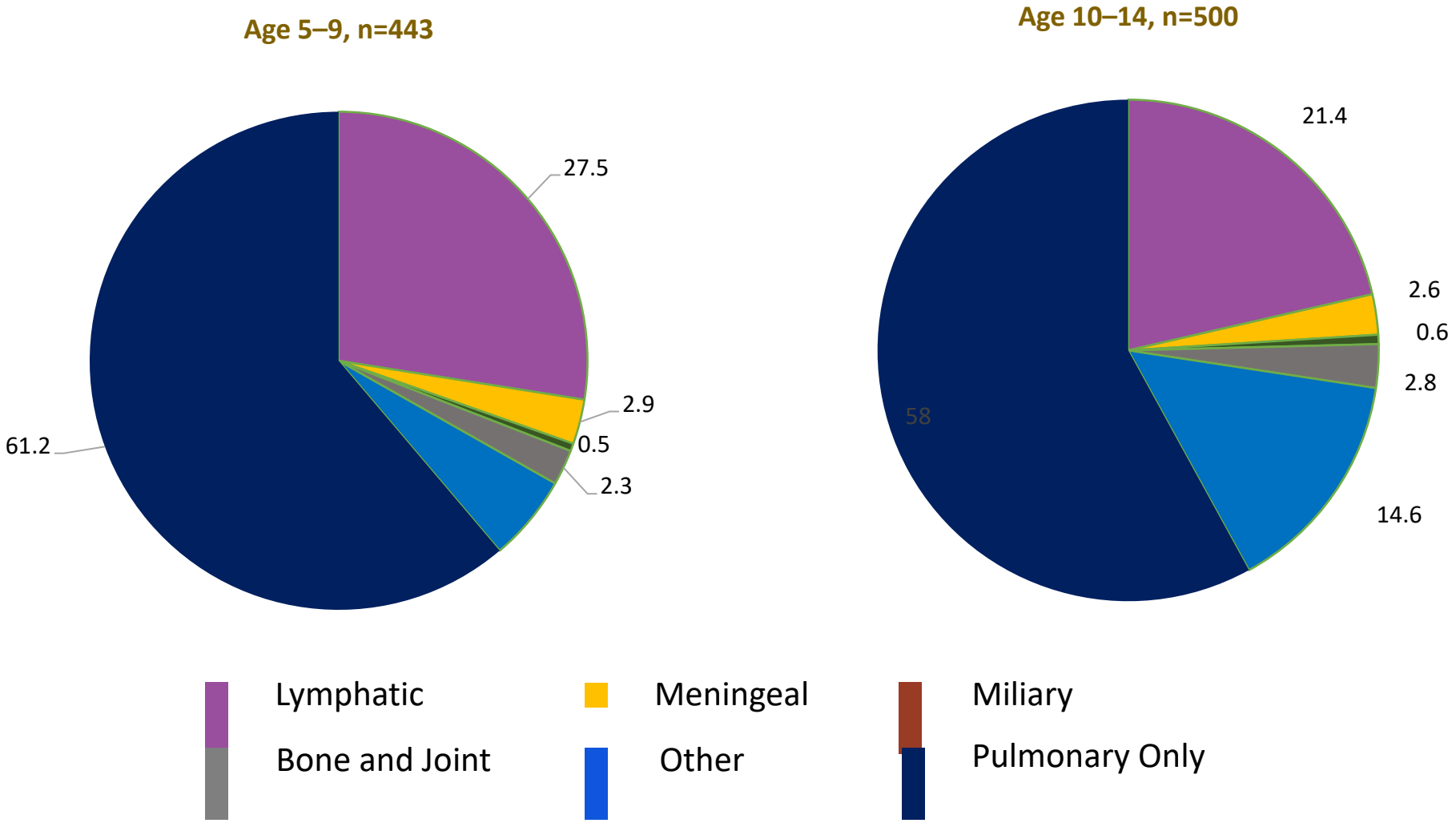


*Persons might have more than one extrapulmonary site of disease.

Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Age <5), Summed and Averaged Over 2013–2017



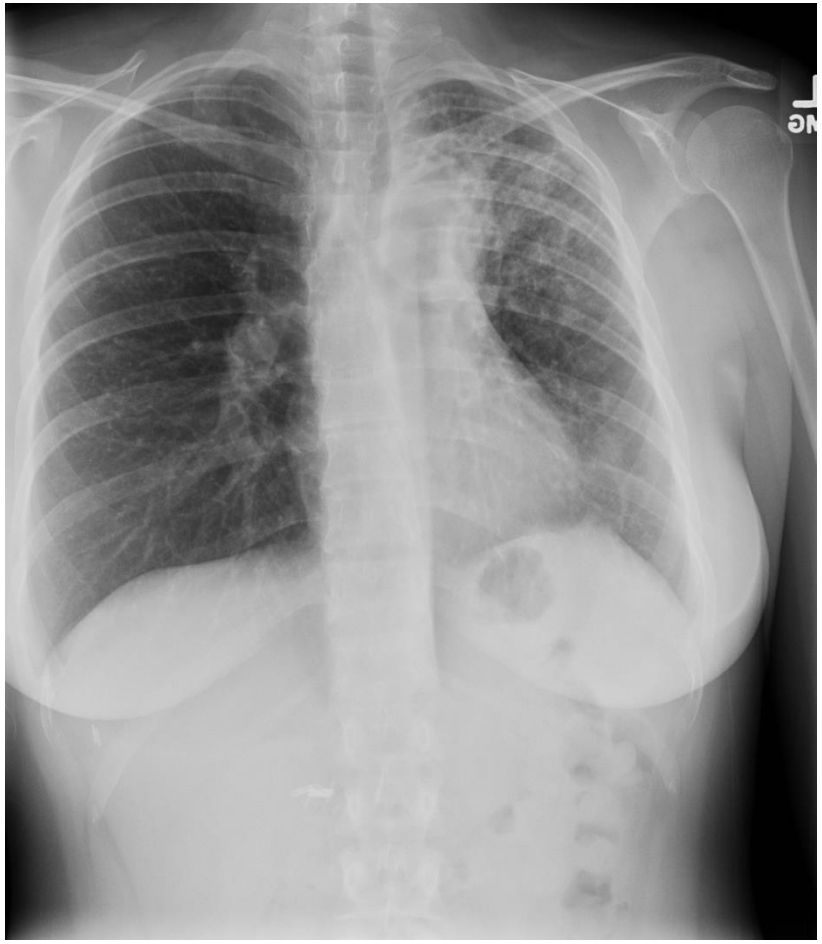
Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Ages 5–14), Summed and Averaged Over 2013–2017



Reactivation Disease

Adults and older children

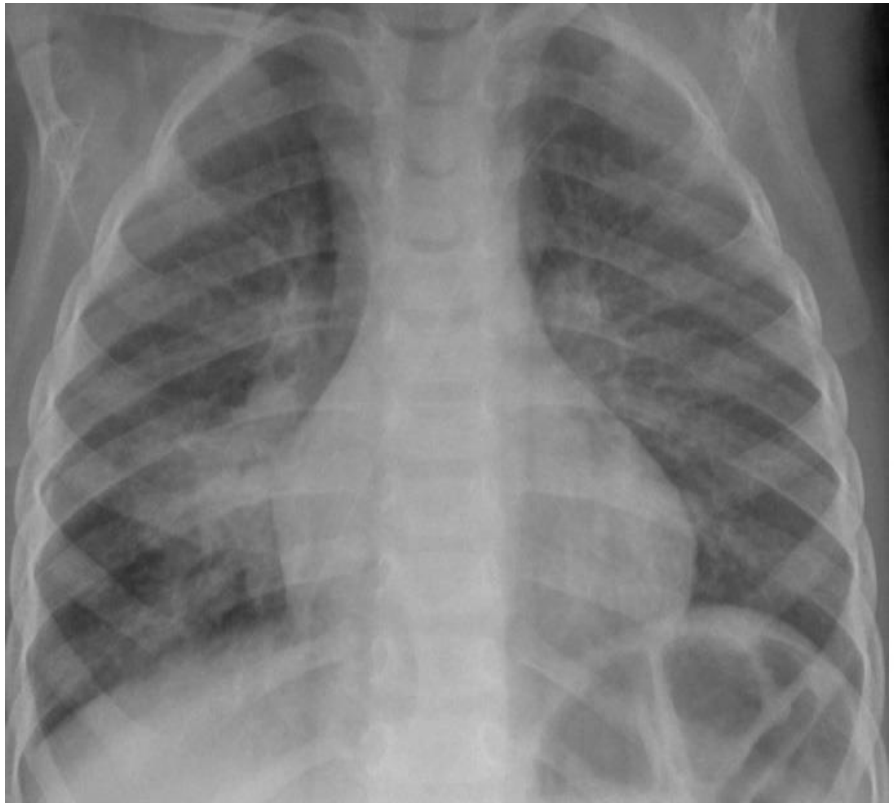
- Occurs years after infection
- Occasionally seen in teens
- May have cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious



Primary Disease

Small children and immunosuppressed

- Classic x-ray:
  - Lobar pulmonary infiltrates
  - **Hilar lymphadenopathy or**
  - Miliary infiltrates
- Low numbers of organisms
  - AFB smears negative in 95% of pedi cases
  - Culture negative in 60% of cases
- Most children <12 yrs not contagious
- Often asymptomatic (50%)



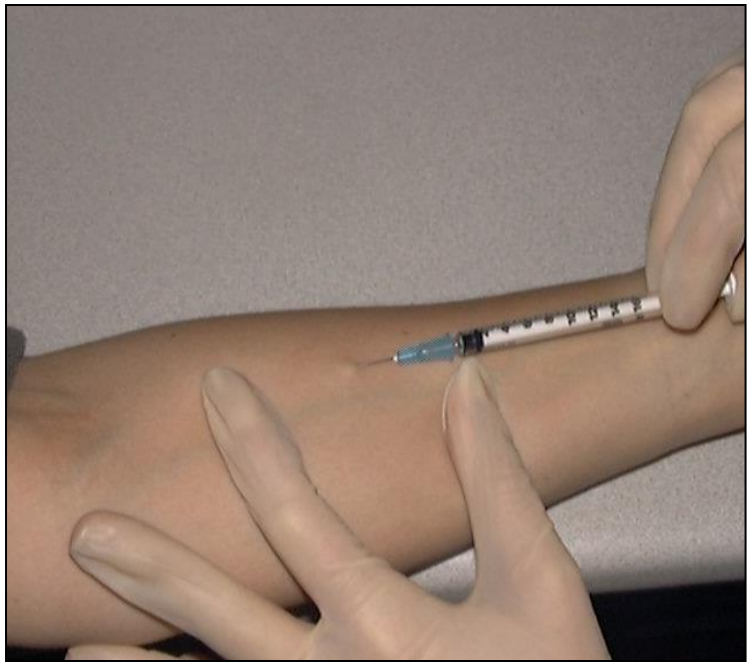
Diagnosing Tuberculosis in Children

TB Infection Diagnostics

- TB Skin Test (TST)
- Interferon Gamma Release Assays (IGRA)

The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- Induration in millimeters read 48-72 hours after injection



QuantiFERON®-TB Gold Plus

Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

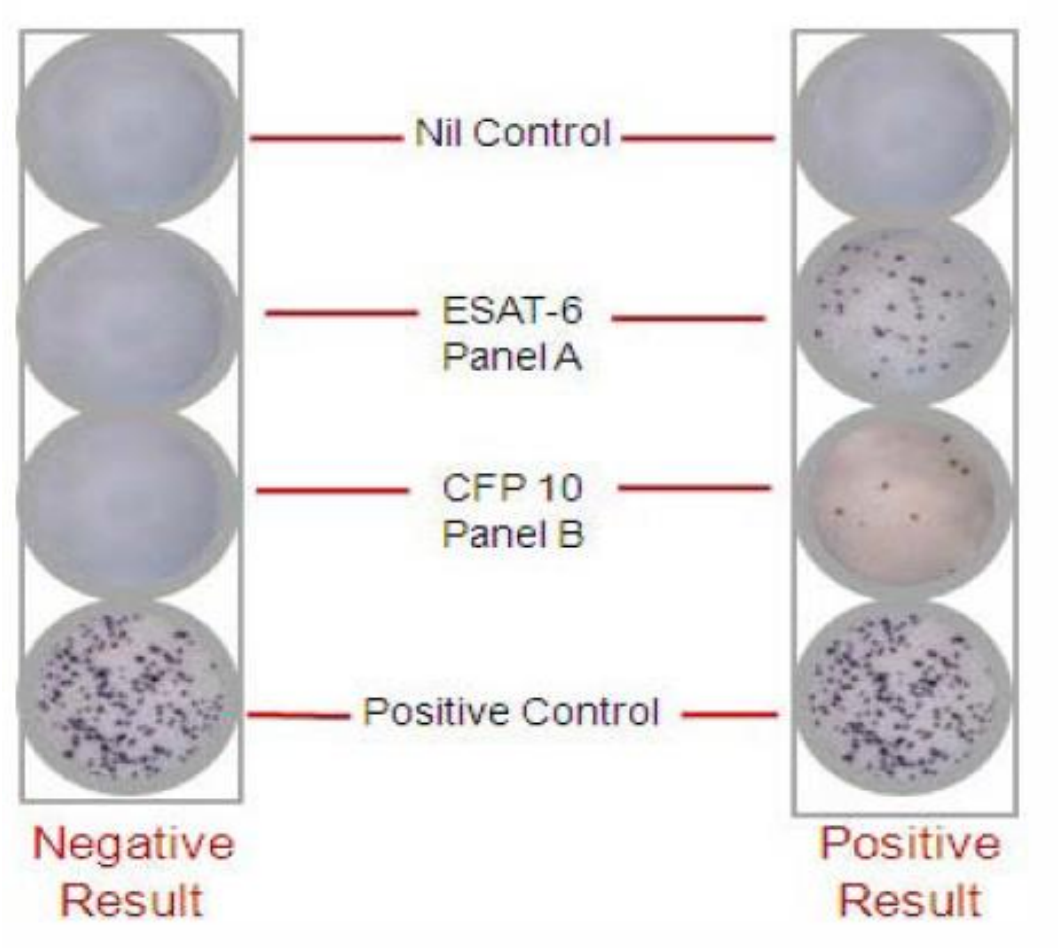
Nil – Negative Control
Adjusts for background IFN-γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value

T-Spot.*TB*


Nil Control
ESAT-6
Panel A
CFP 10
Panel B
Positive Control
Negative
Result
Positive
Result

IGRAs

2024-2027 American Academy of Pediatrics REDBOOK

- Either TST or IGRA testing is acceptable for children of any age
- IGRA is preferred for children who have received a BCG vaccine or who are unlikely to return for the TST reading
- For children without specific TB risk factors other than foreign birth or travel who have an unexpected low-level positive IGRA result, a second diagnostic test should be performed; the child is considered infected only if both tests are positive

Table 3.80. Tuberculin Skin Test (TST) and IGRA Recommendations for Infants, Children, and Adolescents[a]

Children for whom immediate TST or IGRA is indicated[b]:

- Contacts of people with confirmed or suspected contagious tuberculosis (contact tracing)
- Children with radiographic or clinical findings suggesting TB disease
- Children immigrating from countries with endemic infection (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees
- Children with history of significant[c] travel to countries with endemic infection who have substantial contact with the resident population[d]

Children who should have annual TST or IGRA:

- Children living with HIV

Children at increased risk of progression of TB infection to TB disease: Infants (age <1 year) and children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists, deserve special consideration. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for rapid progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered.

A TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy in any child requiring these treatments.

Take Home for Testing for TB in Children

- IGRAs are the better choice for children who have had BCG
- TB screening tests are especially unreliable in:
  - Very young infants
  - Very sick infants
  - Immune suppressed children
- No test overrides clinical and epidemiologic data

Clinical Presentation of TB in children

Common symptoms of TB disease in children

- Cough and/or respiratory distress
- Pulmonary findings on examination
- Lymphadenopathy or lymphadenitis
- S/Sx of meningitis including seizures
- Persistent fever (FUO)
- Weight loss or failure to thrive
- Up to 50% of children with TB disease have no symptoms

Signs and Symptoms of Pulmonary TB

Clinical Feature or Disease Type	Infants	Children	Adolescents
Symptom			
Fever	Common	Uncommon	Common
Night sweats	Rare	Rare	Uncommon
Cough	Common	Common	Common
Productive cough	Rare	Rare	Common
Hemoptysis	Never	Rare	Rare
Dyspnea	Common	Rare	Rare
Sign			
Rales	Common	Uncommon	Rare
Wheezing	Common	Uncommon	Uncommon
Decreased breath sounds	Common	Rare	Uncommon
Location of Disease			
Pulmonary	Common	Common	Common
Pulmonary + Extrapulmonary	Common	Uncommon	Uncommon

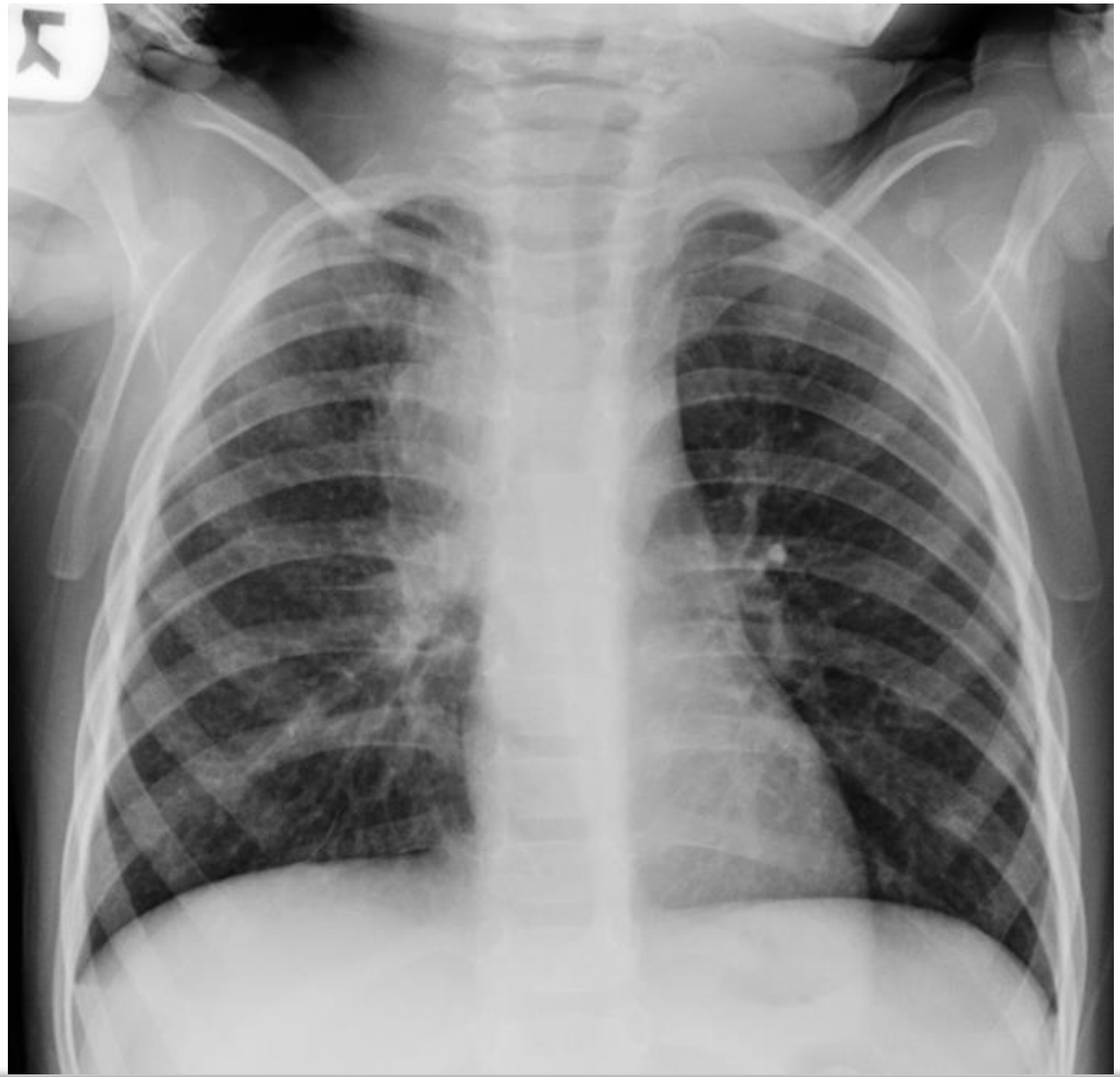
Peds in Review 2010;31:13

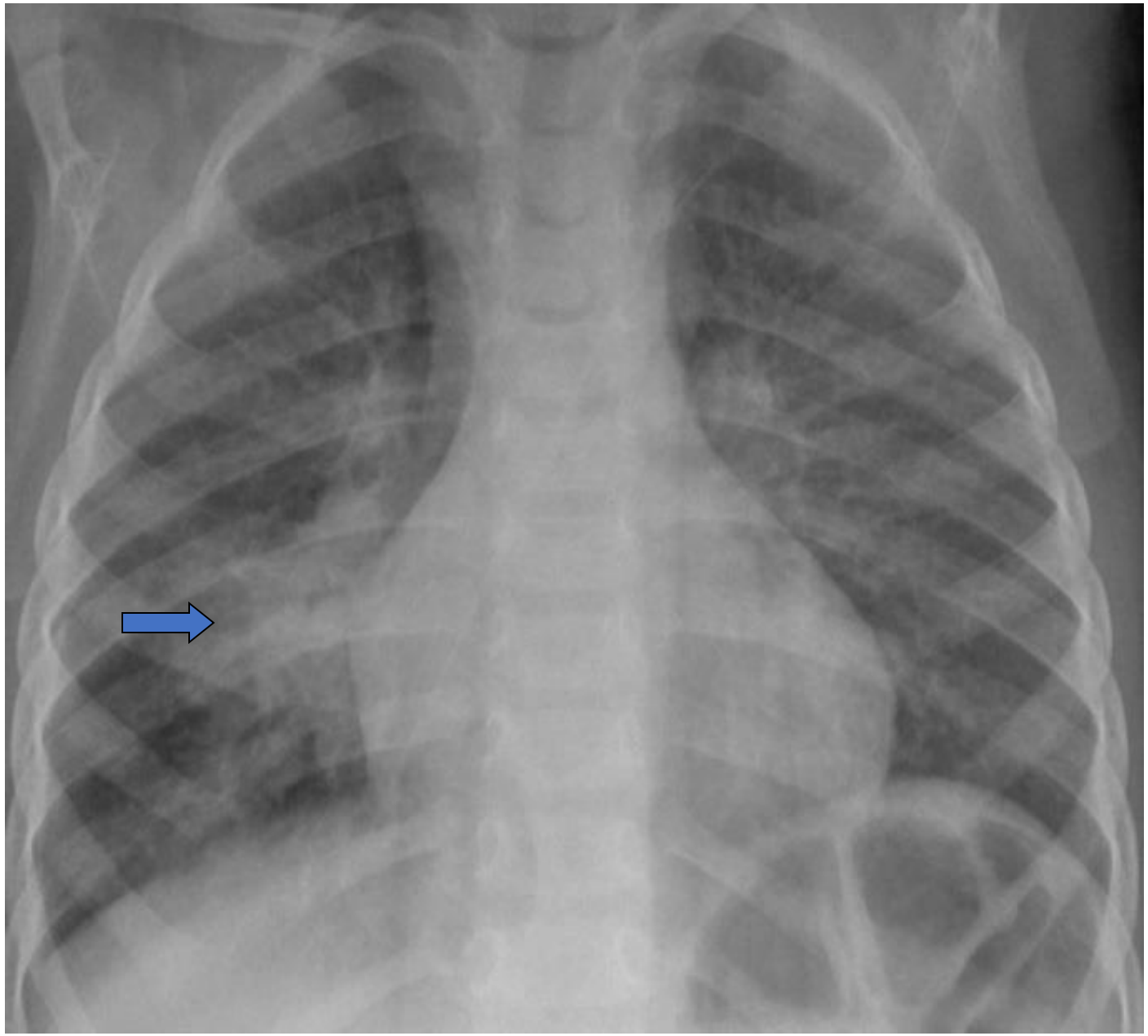
CXR Findings in Pediatric TB

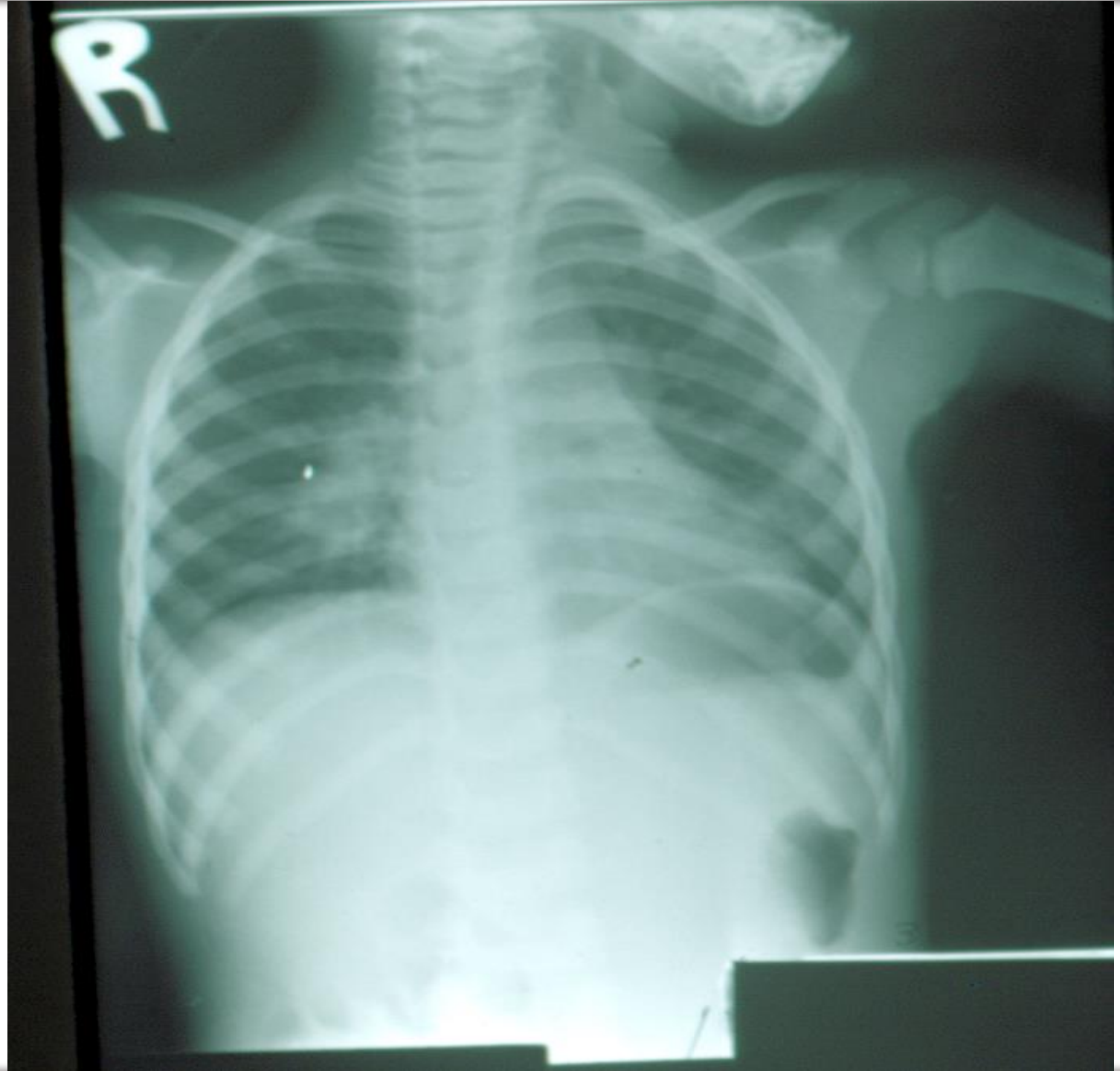
- Hilar or mediastinal adenopathy
- Segmental/lobar infiltrates
- Calcifications
- Miliary disease
- Pleural effusions

15% of patients with TB disease will have normal CXRs

Intrathoracic Lymphadenopathy



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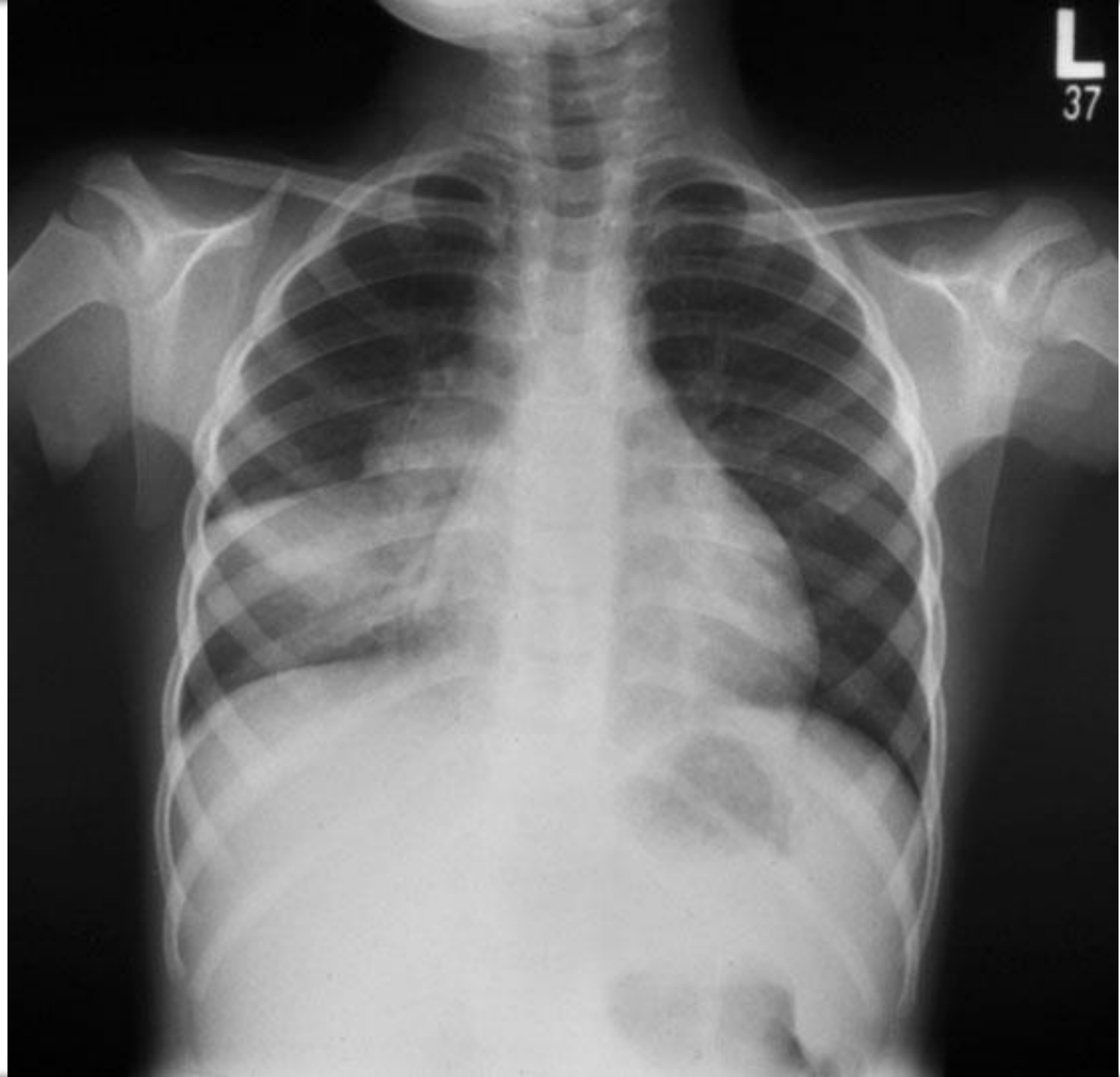
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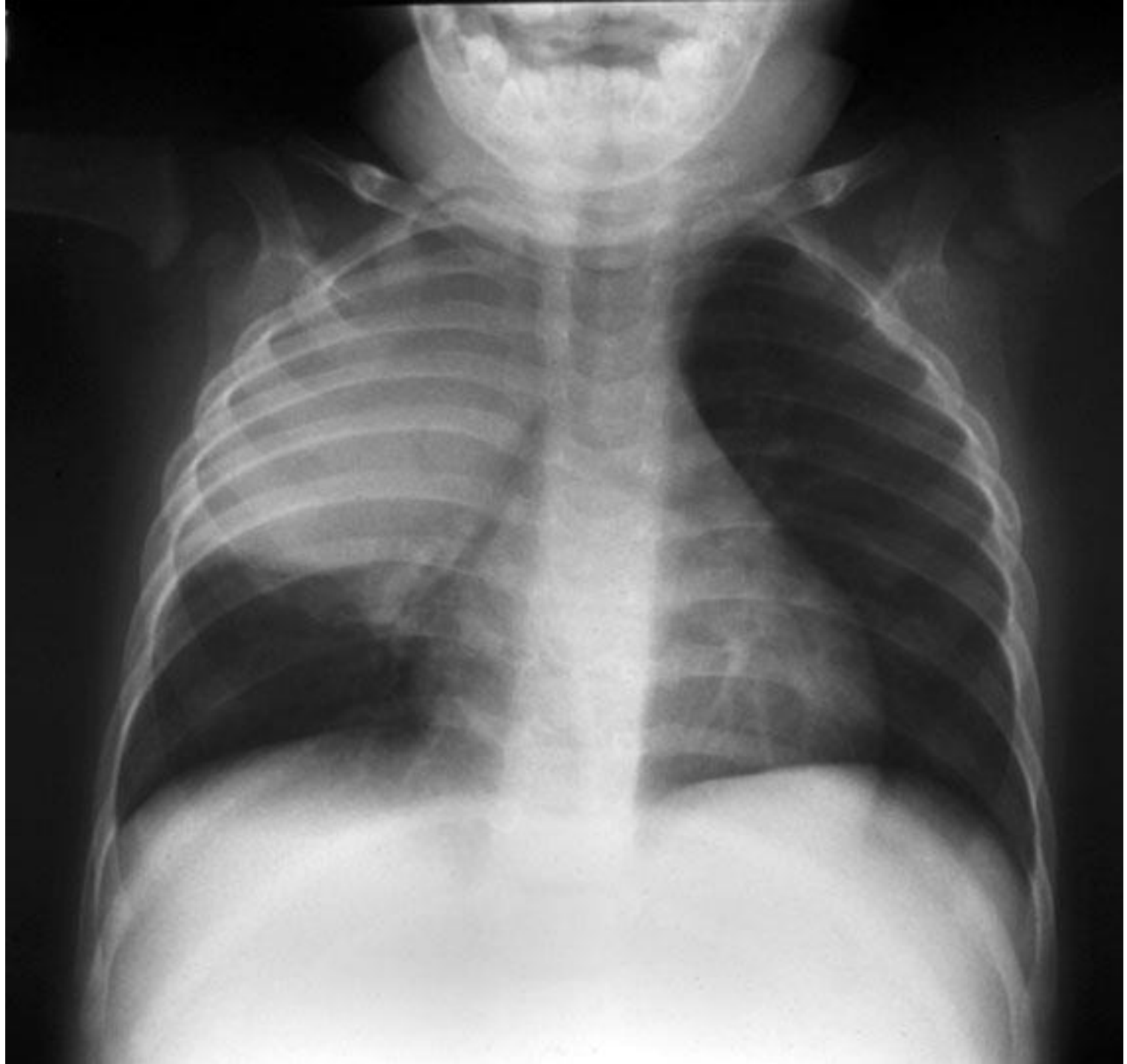
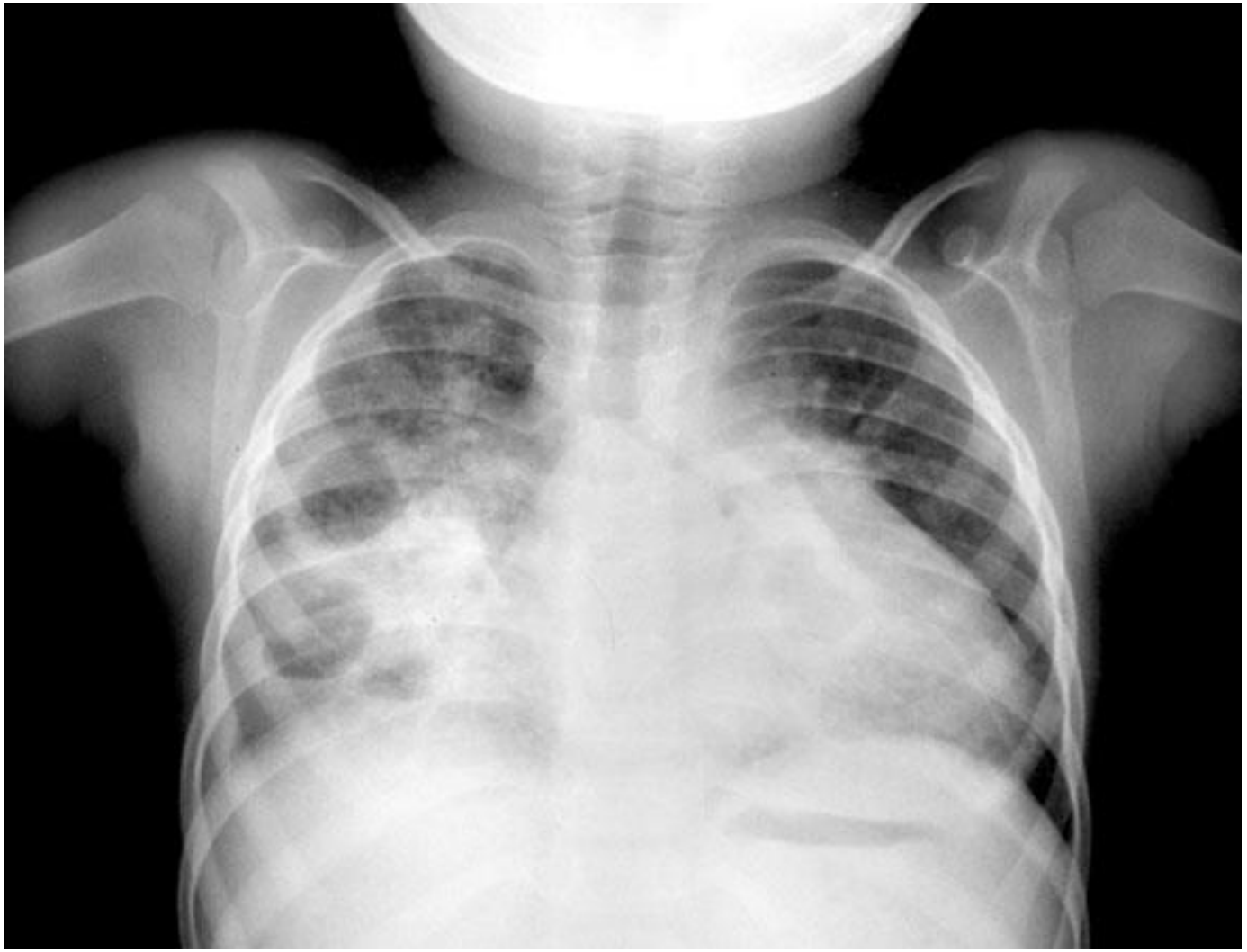
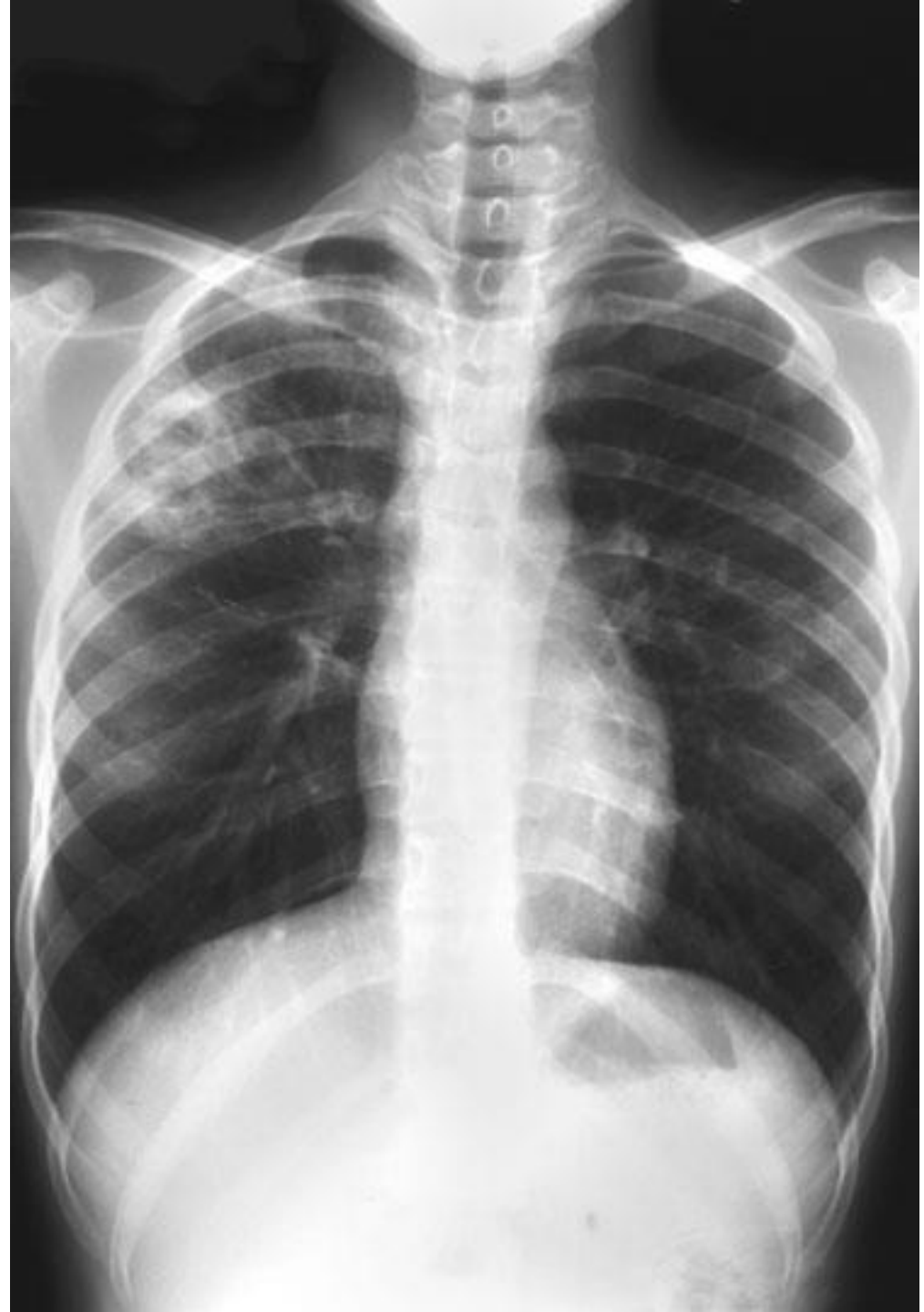


Cavitary Lesions





Unique Diagnostic Challenges of TB in Children

- More difficult diagnosis
- Nonspecific signs and symptoms
- Fewer mycobacteria
- Fewer positive bacteriologic tests
- Increases risk of progression to disease
- Higher risk of extrapulmonary and TB meningitis

Tuberculosis diagnosis – Adults vs Children

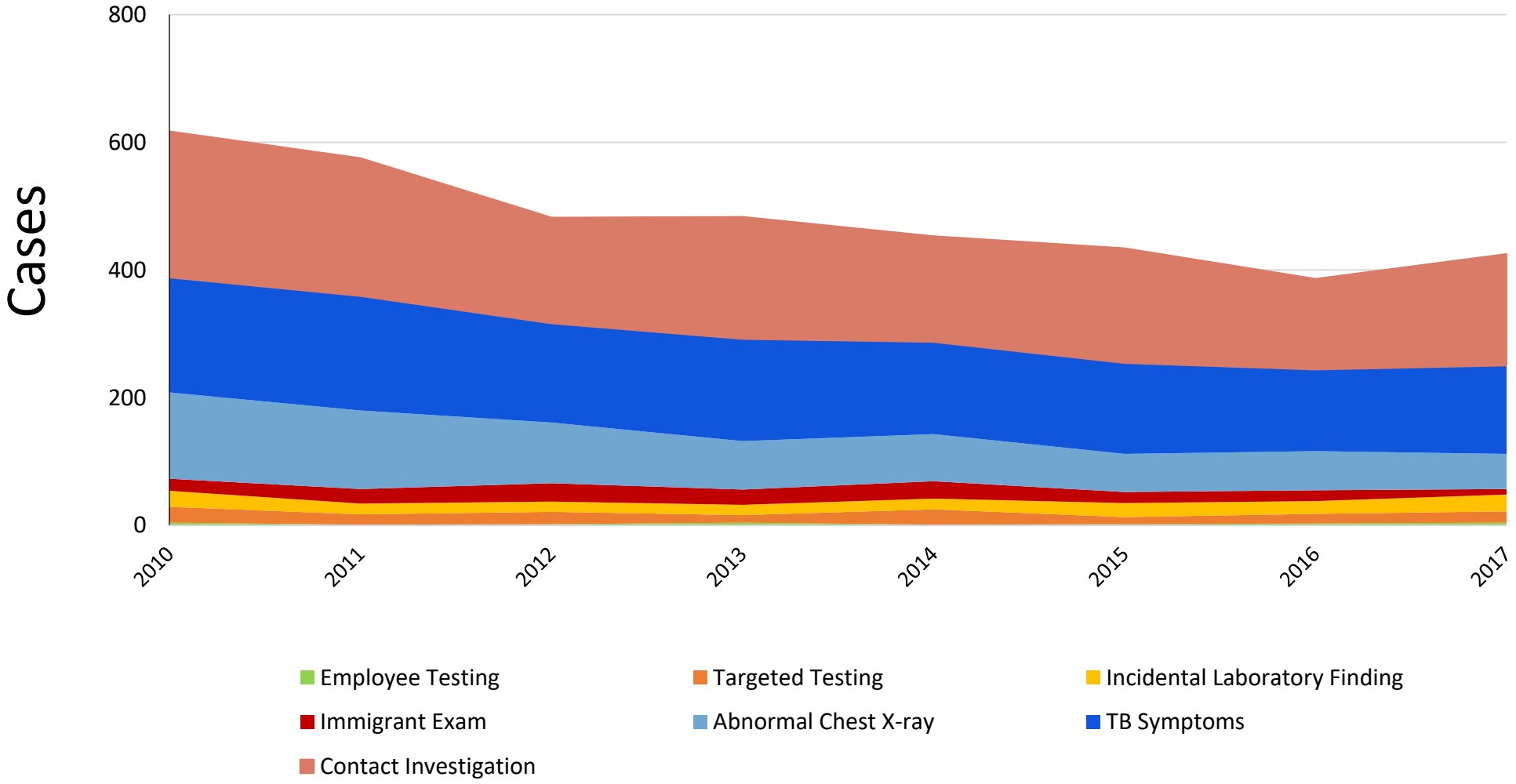
Adults – Mycobacterial-based diagnosis

- positive sputum AFB smear 60% - 75%
- positive sputum culture 90%
- positive tuberculin skin test 80% [HIV < 50%]

Children

- positive sputum/gastric AFB smear 10%
- positive sputum/gastric culture 10% - 40%
- positive tuberculin skin test 50% - 80%

U.S. Pediatric TB Cases by Reason Evaluated, 2010*–2017



Treating Tuberculosis in Children

TB Prevention After Exposure

- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household receive isoniazid

- Children who should be considered for treatment after exposure:
  - Household contact with contagious person
  - Initial TST negative in the window period for conversion
  - CXR and physical exam normal

- **Window prophylaxis recommended:**
  - For children < 5 yrs of age
  - Immunosuppressed patients
  - Patients on tumor necrosis factor-alpha blockers
  - May prevent progression to disease during window period

3HP in children

- Approved for children ≥ 2 y/o

(new AAP recommendations soften this to ≥ 5 y/o)

- Dosing:

INH:

25 mg/kg ages 2-11 y/o
15 mg/kg ages 12 years and older

rounded up to the nearest 50 or 100 mg; 900 mg maximum

RPT:

10.0–14.0 kg 300 mg
14.1–25.0 kg 450 mg
25.1–32.0 kg 600 mg
32.1–49.9 kg 750 mg

≥50.0 kg 900 mg maximum

Treating TB Infection

- Rifampin x 4 months
  - 10-20 mg/kg daily
  - 20-30 mg/kg daily for infants and toddlers
  - Duration: 4 months
  - If person around child with TB is known to have INH-resistant disease or if child is INH-intolerant
- Isoniazid (INH) x 6-9 months
  - 10-15 mg/kg single daily dose if given by family
  - 20-30 mg/kg twice weekly if given by health department
  - Duration: 9 months
- Isoniazid + rifampin daily x 3 months

Duration of Therapy

- INH 9
- Rifampin
- INH + rifampin
- INH +RPT

- 9 months (270 doses)
- 4 months (120 doses)
- 3 months (90 doses)
- 12 weeks (12 doses)

The longer the duration/more doses, the less likely your patient is to complete Rx!

Fewer than 60% complete 9 months of INH!

Therapy for TB Disease

- Start 4-drug therapy (a change from 2006 Red Book)
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
- Use PZA only during 1st 2 months for susceptible TB
  - This is your 'shortening agent': consolidate from 9 to 6 months of therapy
- Stop EMB once culture results known, if have pan-susceptible TB
  - This is your insurance in case you have drug-resistant TB
- Anticipate minimum 4-6 month therapy, may need to extend it to longer periods, especially for extrapulmonary disease
- Patience is the best thing you can have as a TB nurse dealing with children
  - Start the negotiations early, try to take a breath when you are frustrated, phone your friends
- ***Always*** administered by directly observed therapy (DOT)

2024 Red Book

SHINE Trial

Shorter Treatment for Minimal Tuberculosis (TB) in Children

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

Trial Design

- Multicenter, open-label, parallel-group, non-inferiority, randomized controlled, two-arm trial
- Comparing a 4-month vs the standard 6-month regimen
- Used fixed-dose, combination dispersible tablets
  - mg/kg: INH 10 (7-15), rifampin 15 (10-20), EMB 20 (15-25), PZA 35 (30-40)
- Endpoint: favorable outcome; TB-free survival at 72 weeks
- Margin of Inferiority set at 6%

Inclusion Criterion

- Age 0-16 years
- Weight ≥ 3kg.
- Clinician has decided to treat with standard first-line regimen
- Symptomatic but non-severe TB including:
  - extrathoracic lymph node TB; intra-thoracic uncomplicated (hilar) lymph node TB
  - minimal or no parenchymal abnormality on CXR
  - smear negative on gastric aspirate/other respiratory sample

Note: GeneXpert may be positive or negative and a negative GeneXpert can be used as a substitute for a negative smear;

culture of respiratory sample may be positive or negative;

lymph node aspirate may be smear/culture/GeneXpert positive or negative)

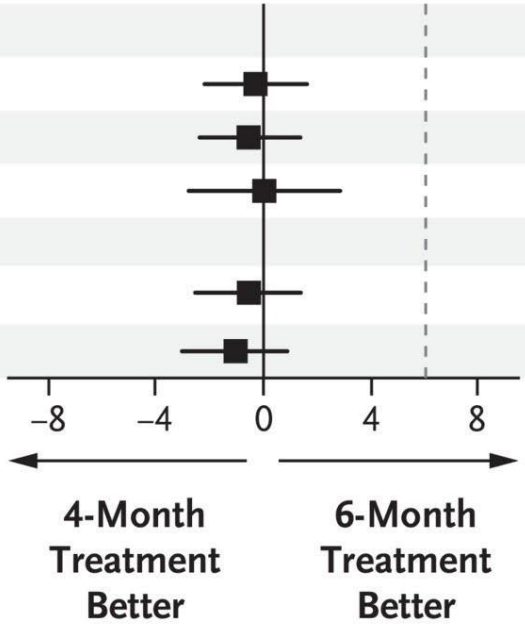
- Not treated for previous TB unless successfully treated > 2 years since last completed treatment
- Known (or pending confirmation of) HIV status; HIV-infected or HIV-uninfected
- Willing and likely to adhere to 72 weeks follow up
- Informed written consent from the parent/legal caregiver(s) and assent in children
- Home address accessible for visiting and intending to remain within the recruitment area

Exclusion Criterion

1. Smear-positive respiratory sample TB
   (note: smear-positive peripheral lymph node sample is allowed)
2. Premature (<37 weeks) **and** aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with drug resistant adult source case (including mono- resistant TB)
7. Known drug resistance in the child
8. Severely sick
9. Pregnancy

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

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		6% *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)



Primary Efficacy Analysis (Modified Intention-to-Treat Population).

Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

The NEW ENGLAND JOURNAL of MEDICINE

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

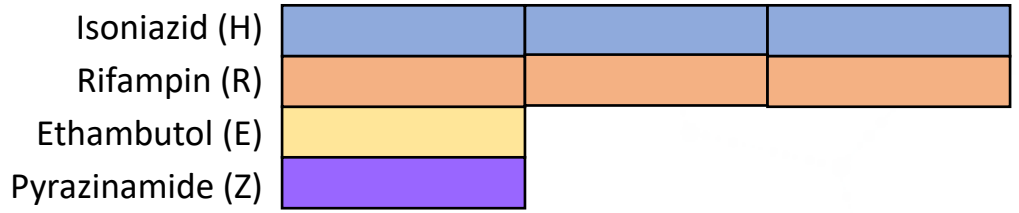
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

2234 participants (194 PLHIV, 1703 with cavity on CXR)
Randomized 1:1:1 to 3 arms
Noninferiority study

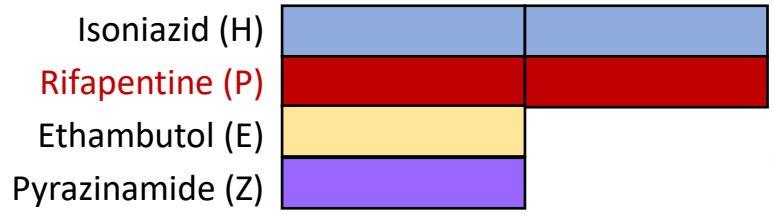
N Engl J Med 2021;384:1705-18.

Study 31/A5349

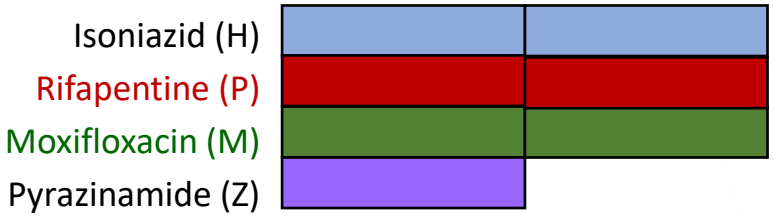
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)



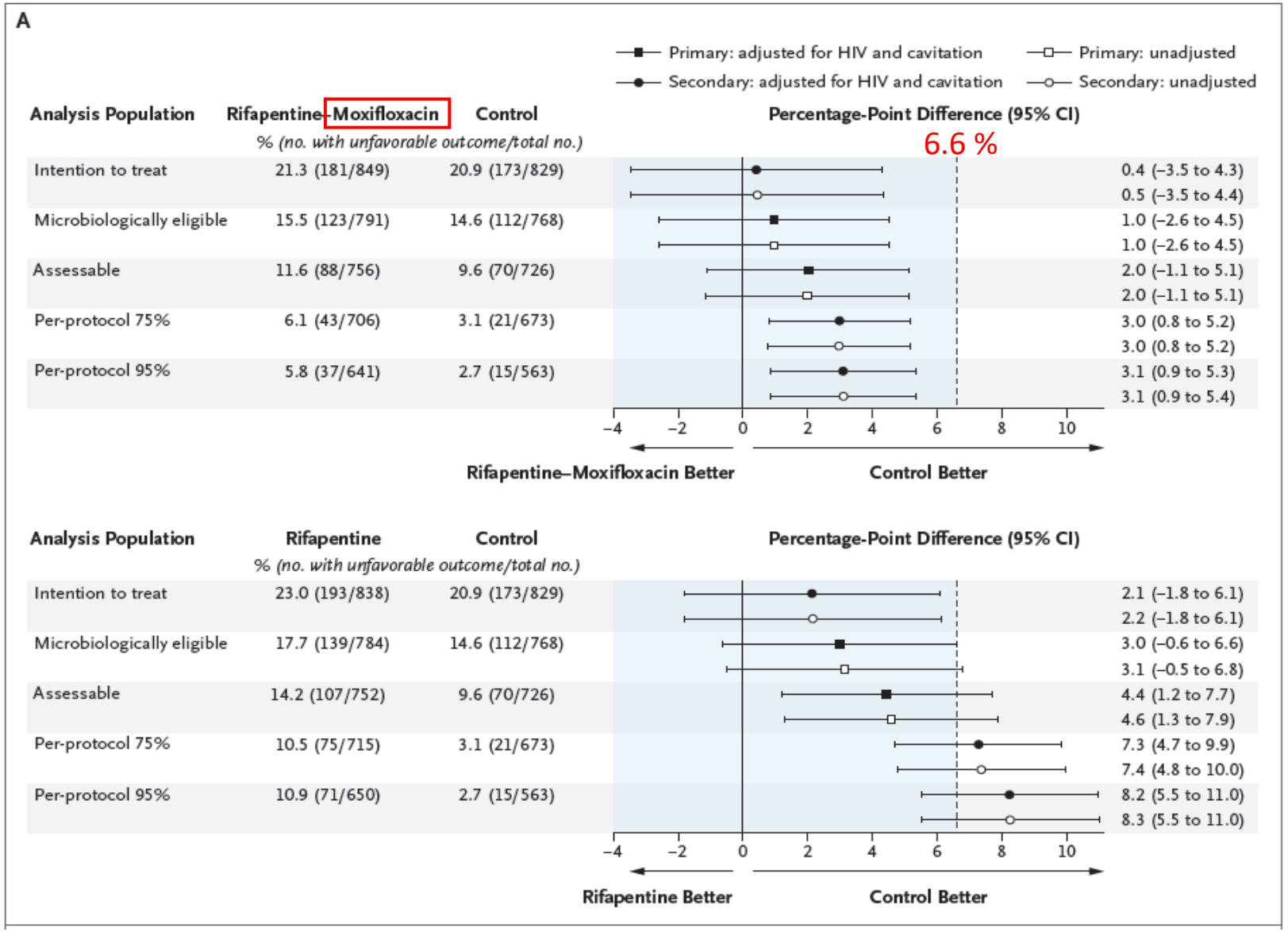
RPT/Moxi
(2HPZM/4HPM)



Notes:

- HRZE dosed at standard doses
- Dosed daily, 7 days/week, observed 5 days/week
- Rifapentine 1200 mg (8 tablets)
- Moxifloxacin 400 mg

Study 31 - Results



N Engl J Med 2021;384:1705-18.

Safety and Efficacy Study 31/A5349

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

	EFFICACY		SAFETY	
Regimen	**Favorable outcomes**	**Unfavorable outcomes**	**Grade 3 or higher AEs**	**All-cause mortality**
Control (2HRZE/4HR)	90.4% (656/726)	9.6% (70/726)	19.3% (159/825)	0.8% (7/825)
RPT-MOX (2HPZM/2HPM)	88.4% (668/756)	11.6% (88/756)	18.8% (159/846)	0.4% (3/846)

TABLE 2. EFFICACY AND SAFETY OUTCOMES IN S31/A5349 AMONG PLHIV

	EFFICACY				SAFETY			
Regimen	**Favorable outcomes**		**Unfavorable outcomes**		**Grade 3 or higher AEs**		**All-cause mortality**	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Control (2HRZE/4HR)	84.7% (50/59)	90.8% (605/666)	15.3% (9/59)	9.2% (61/666)	21.4% (15/70)	19.1% (144/755)	2.9% (2/70)	0.7% (5/755)
RPT-MOX (2HPZM/2HPM)	91.4% (53/58)	88.1% (615/698)	8.6% (5/58)	11.9% (83/698)	13.9% (10/72)	19.3% (149/774)	0% (0/72)	0.4% (3/774)

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

Challenges

- Pill burden
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
- Drug shortages

Take Home Points

- TB can present very differently in adults and children with more severe forms in younger children
- Contact investigation around individuals with infectious TB plays a big role in identifying children with tuberculosis
- Diagnostics for TB are frequently not adequate, an astute pediatrician is invaluable to TB diagnosis in children
- Treatment shortening studies are showing success in children with TB

Thank you for your attention

Questions?

Lisa.Armitige@dshs.texas.gov

1-800-TEX-LUNG

www.HeartlandNTBC.org