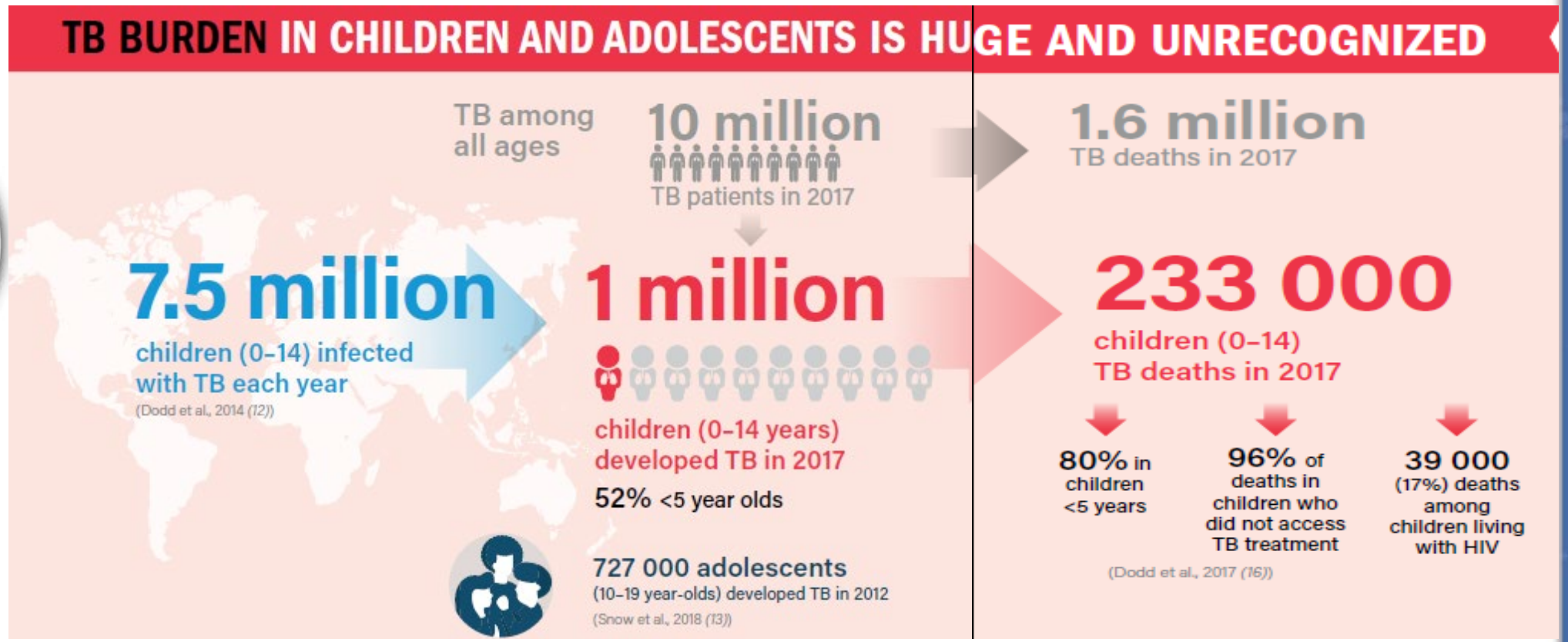
TB in Special Populations

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

Co-Medical Director
Heartland National TB Center

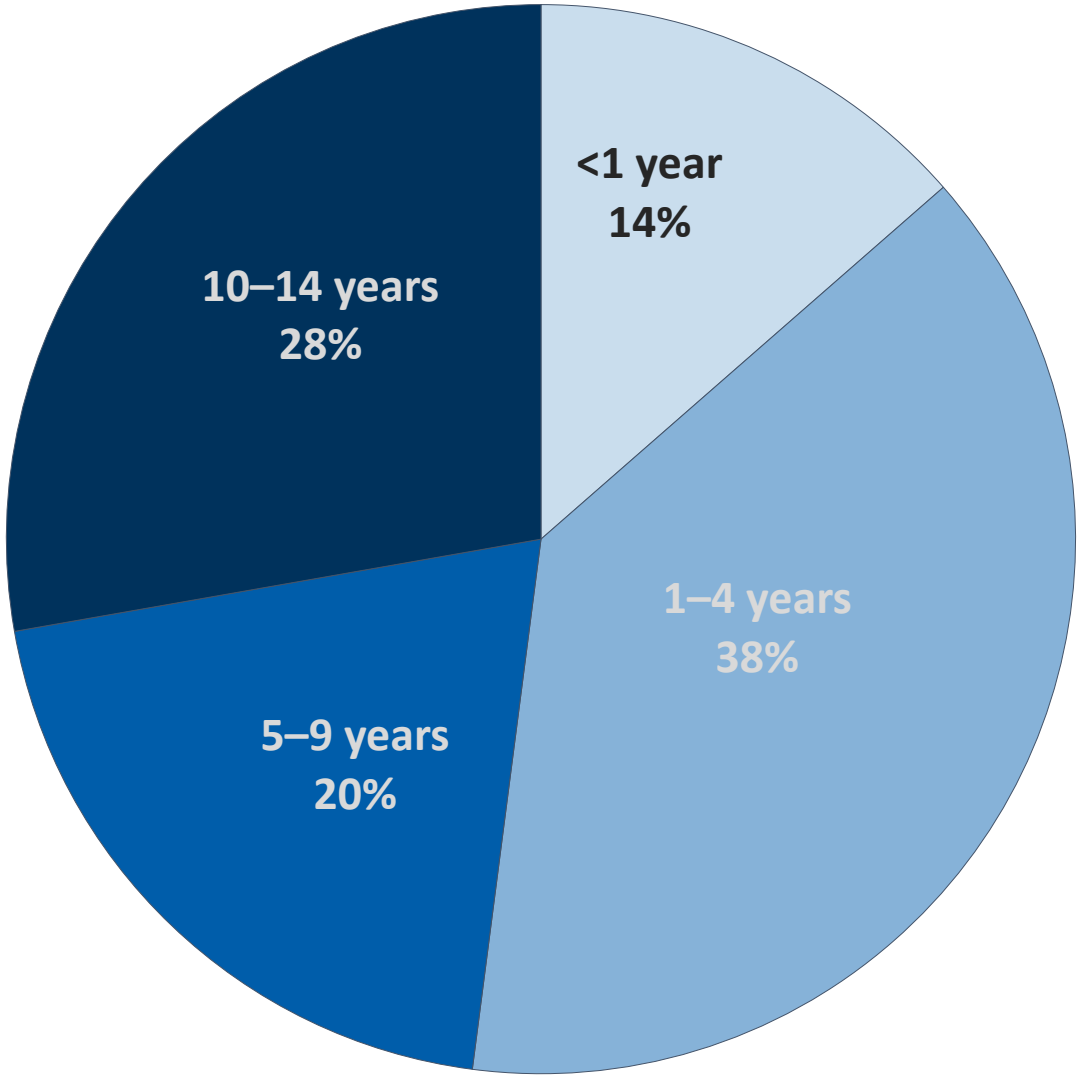
Pediatric TB

Global Pediatric TB

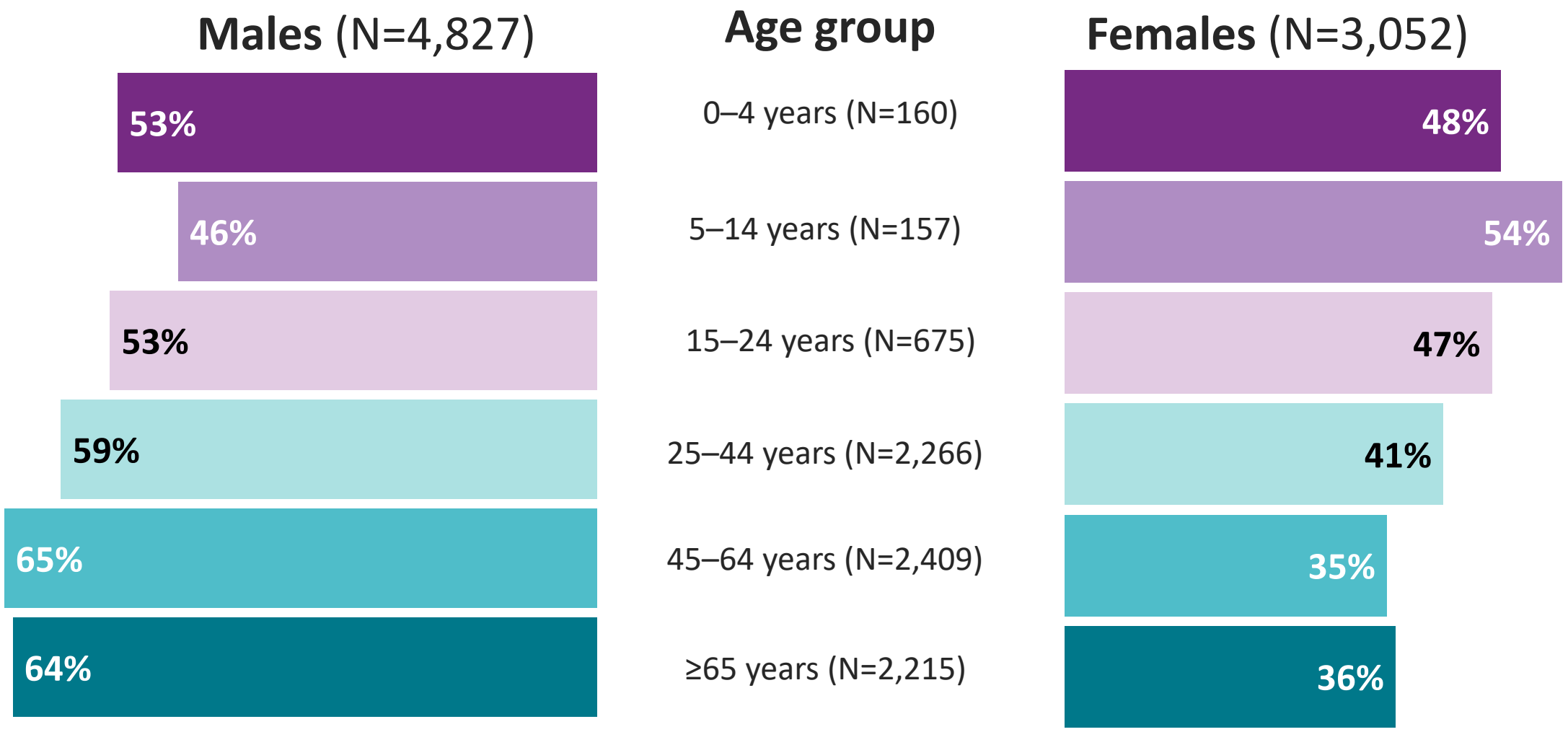


https://www.who.int/tb/cHILD2.jpg

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

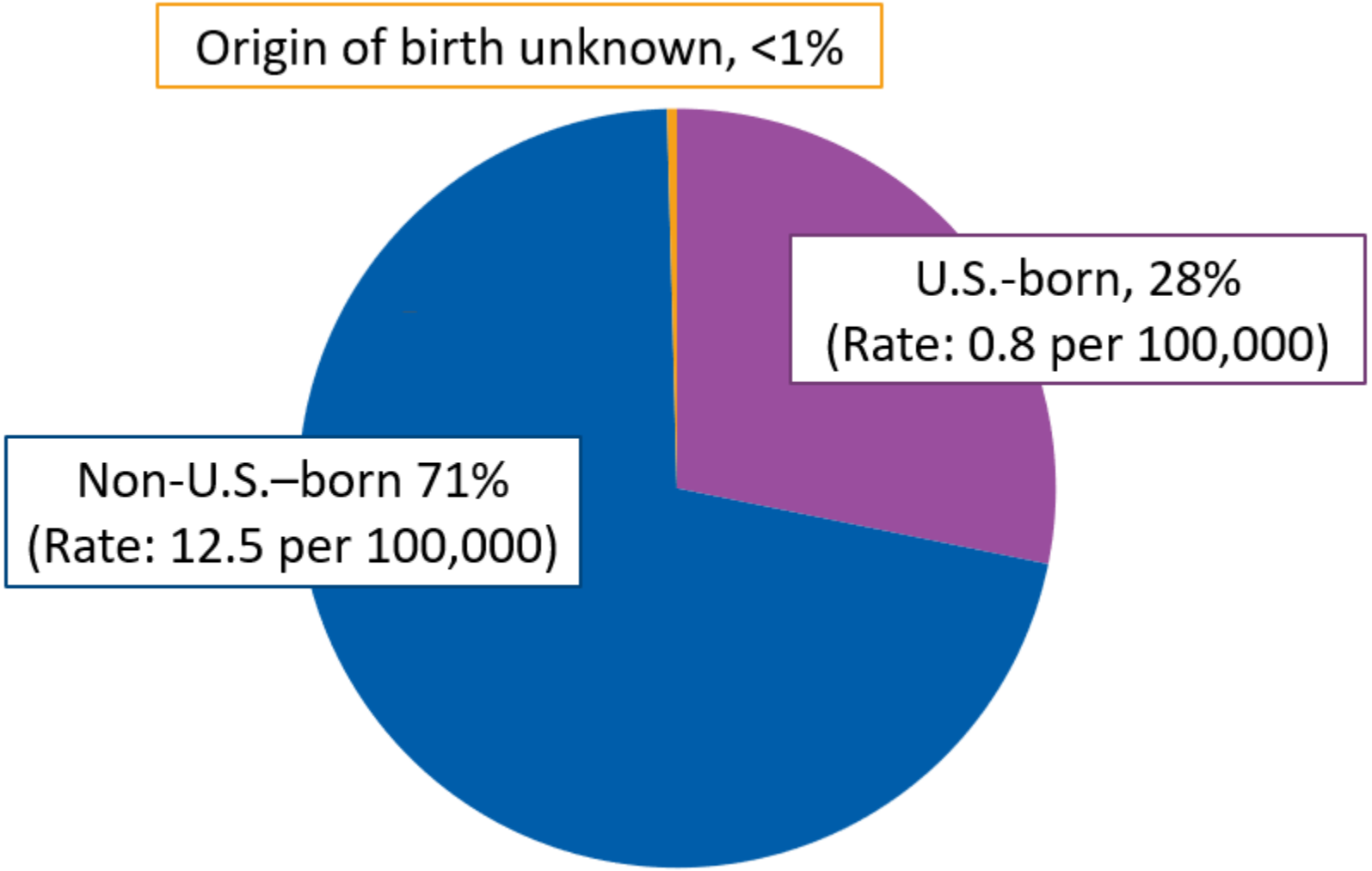
Risk of Progression to TB Disease by Age

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

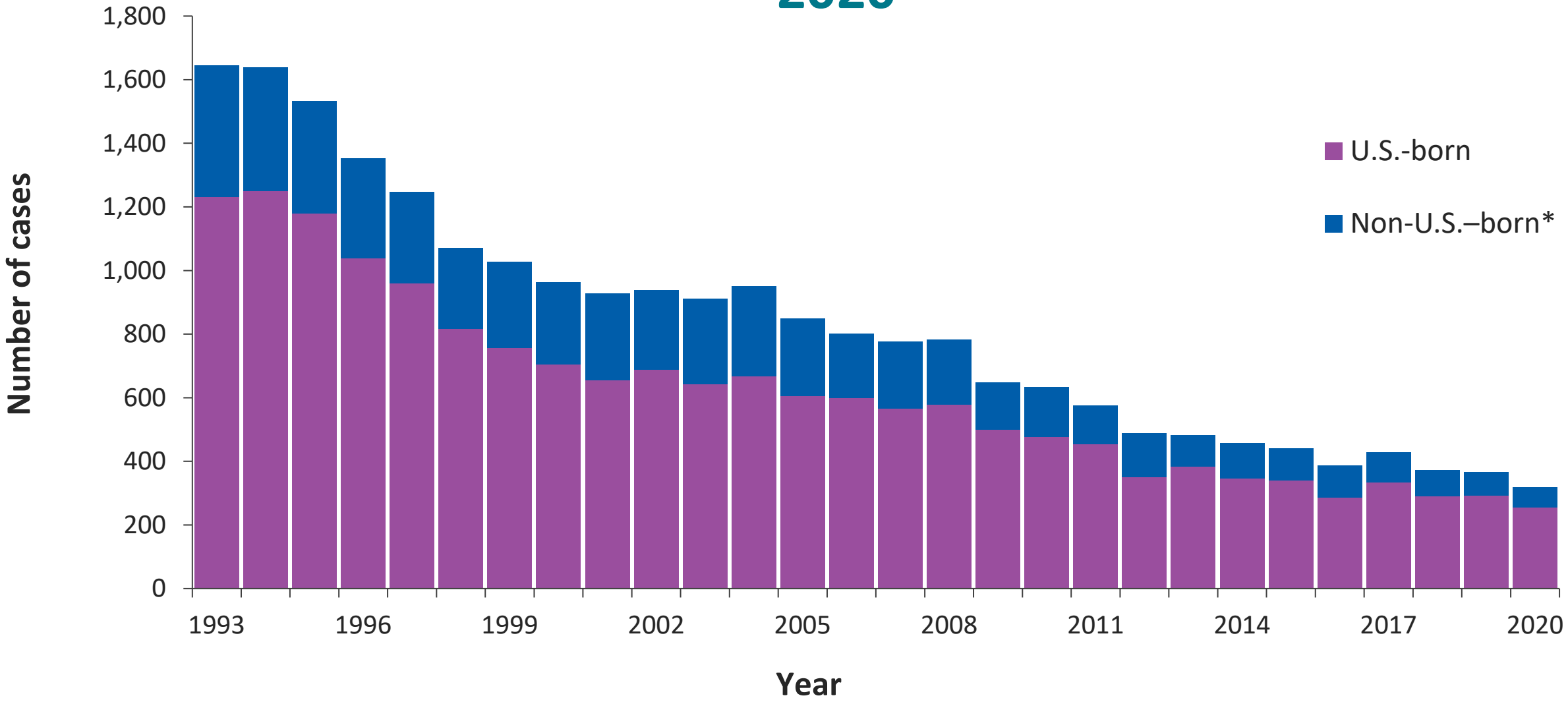
Differences In Adult and Pediatric TB

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



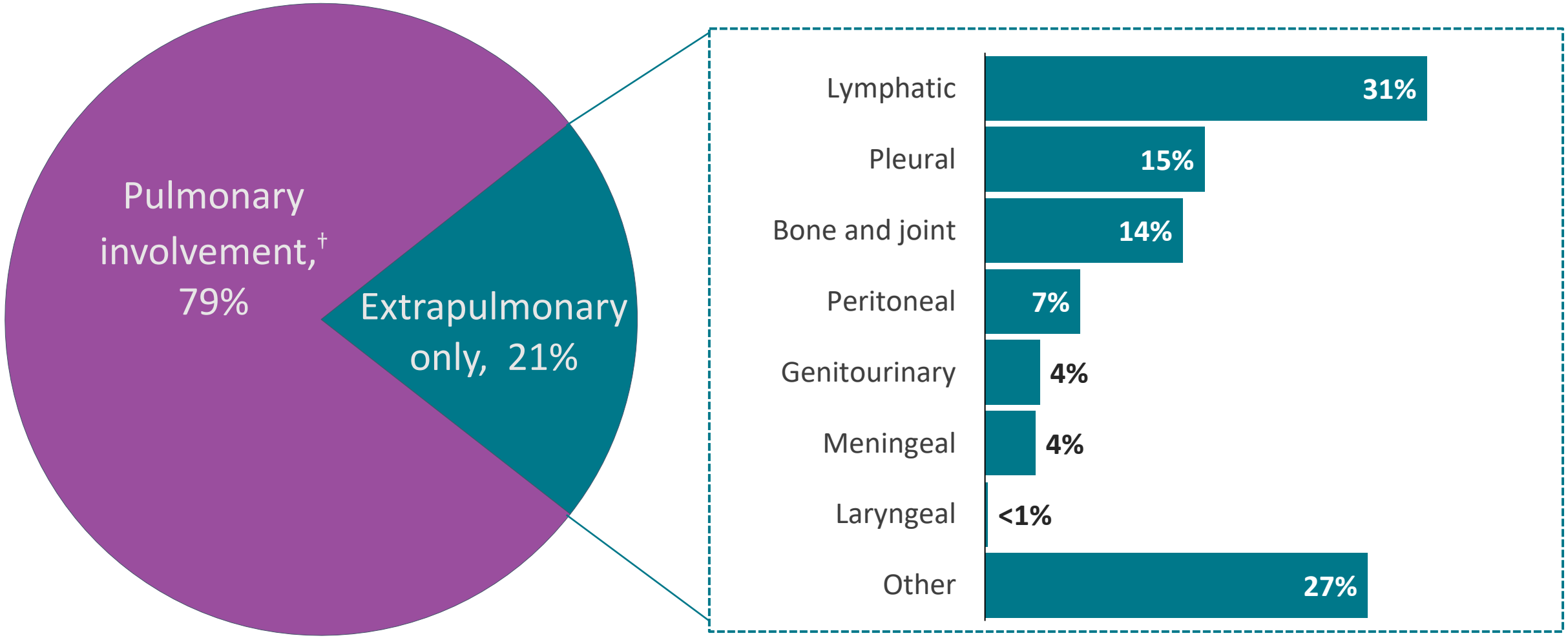
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

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



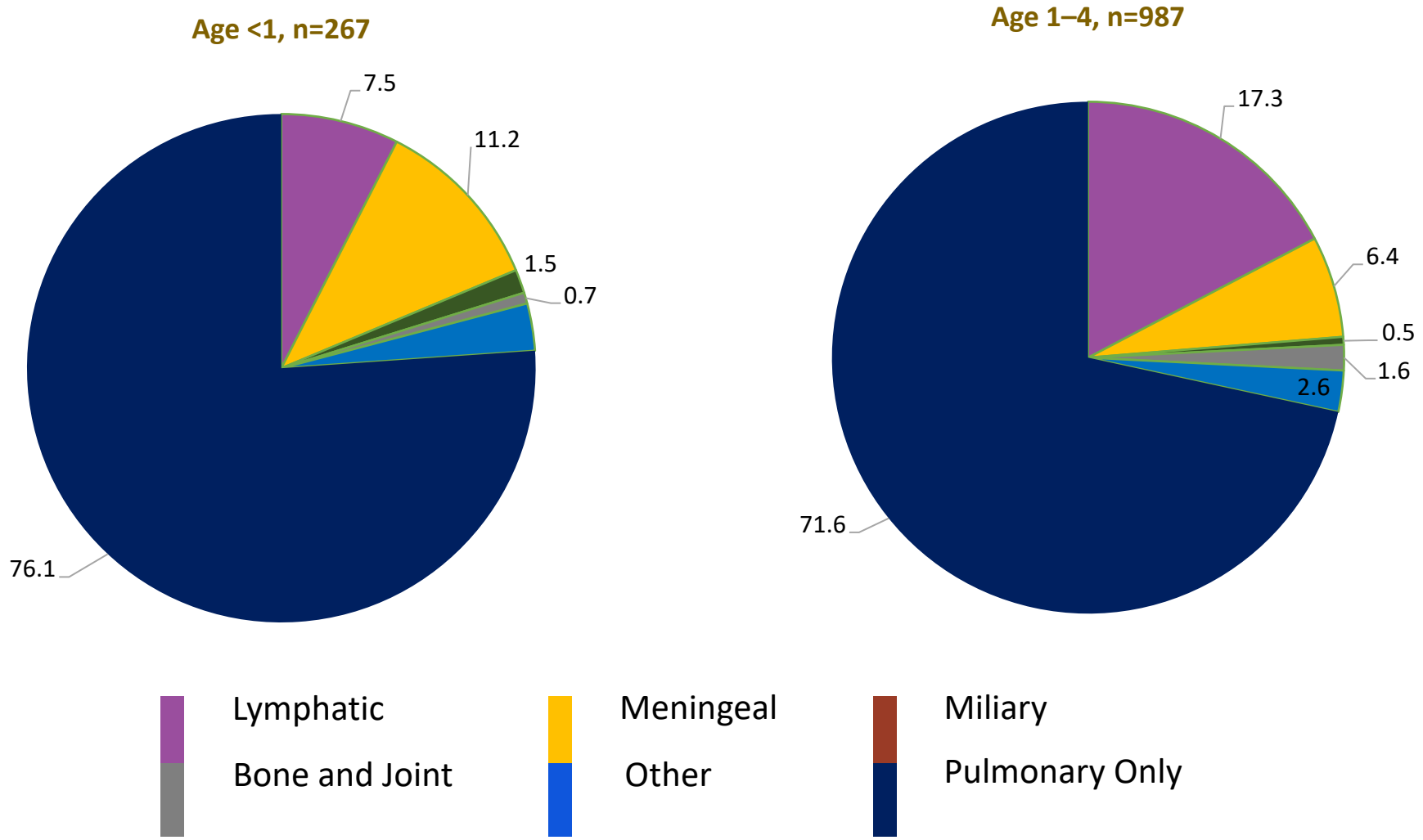
*Non-U.S.–born refers to persons born outside the United States or its territories or not born to a U.S. citizen

Percentage of TB Cases by Site of Disease,* United States, 2021

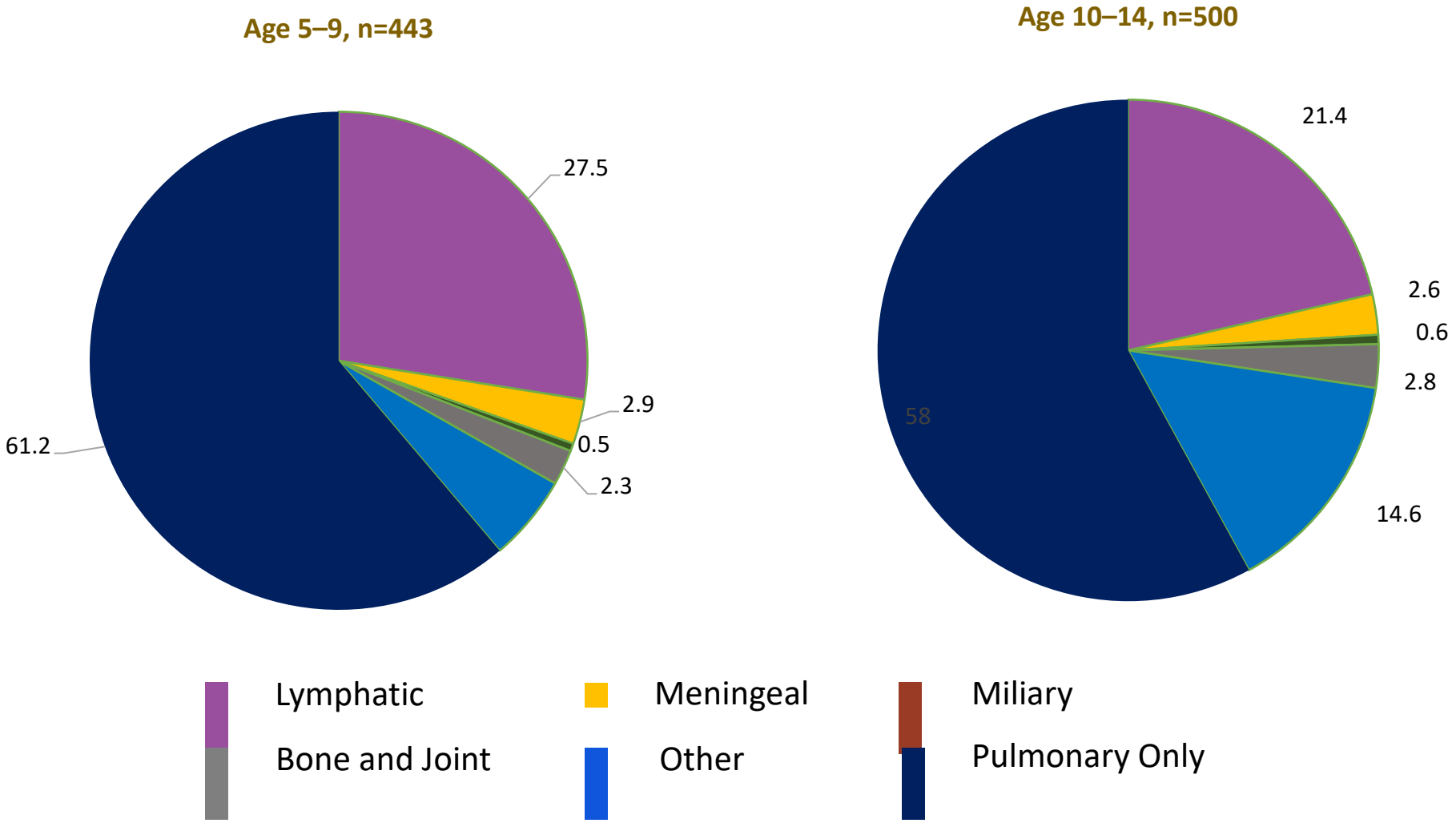


*Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.
†Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

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



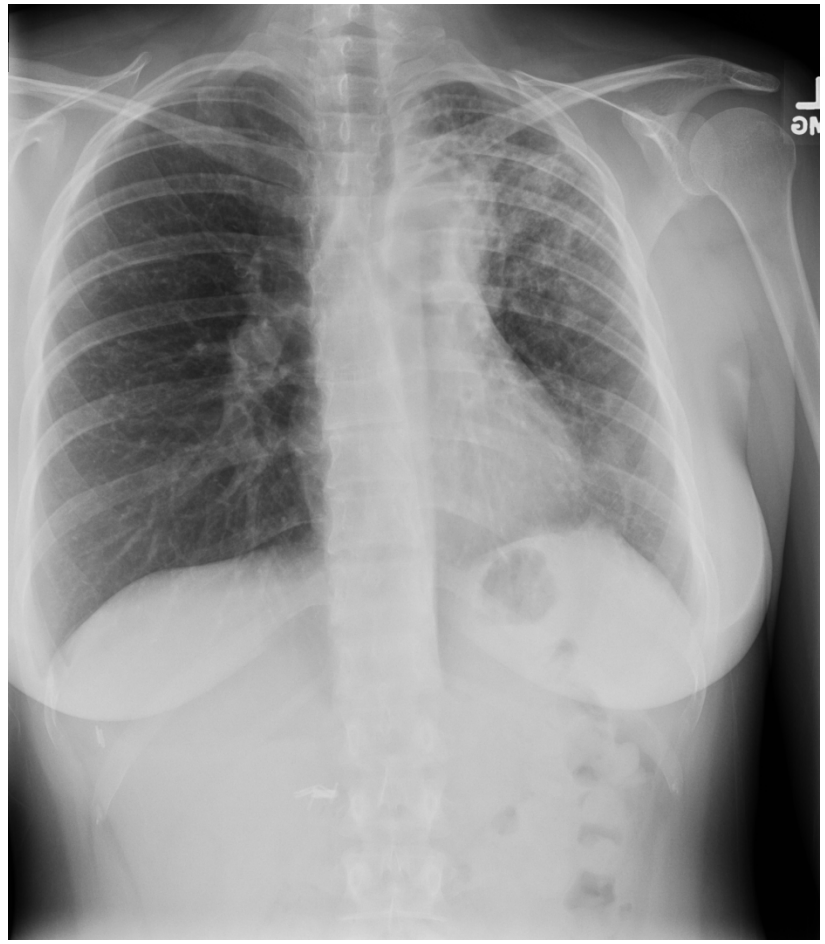
Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Ages 5–14), Summed and Averaged Over 2013–2017



Reactivation Disease

Adults and older children

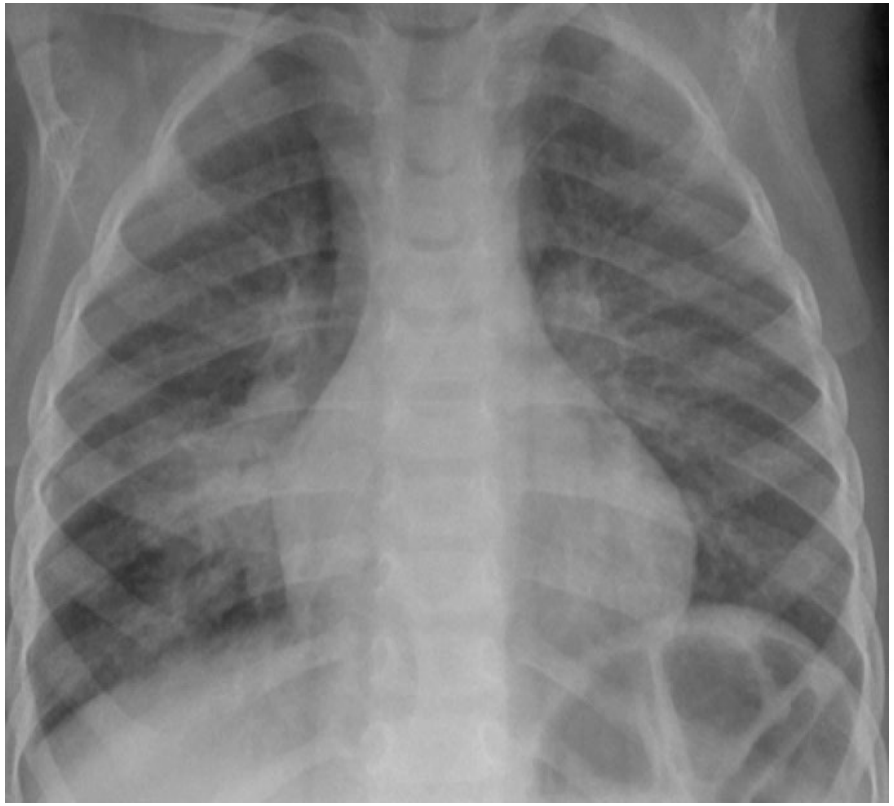
- Occurs years after infection
- Occasionally seen in teens
- May have cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious



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

IGRAs American Academy of Pediatrics REDBOOK

- IGRAs can be used in immunocompetent children of ages in all situations when a TST would be used
- IGRAs are the preferred test for children who have received a BCG vaccination
- Neither IGRAs nor the TST are perfect; always need clinical judgment, especially in very sick children and children < 6 months

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

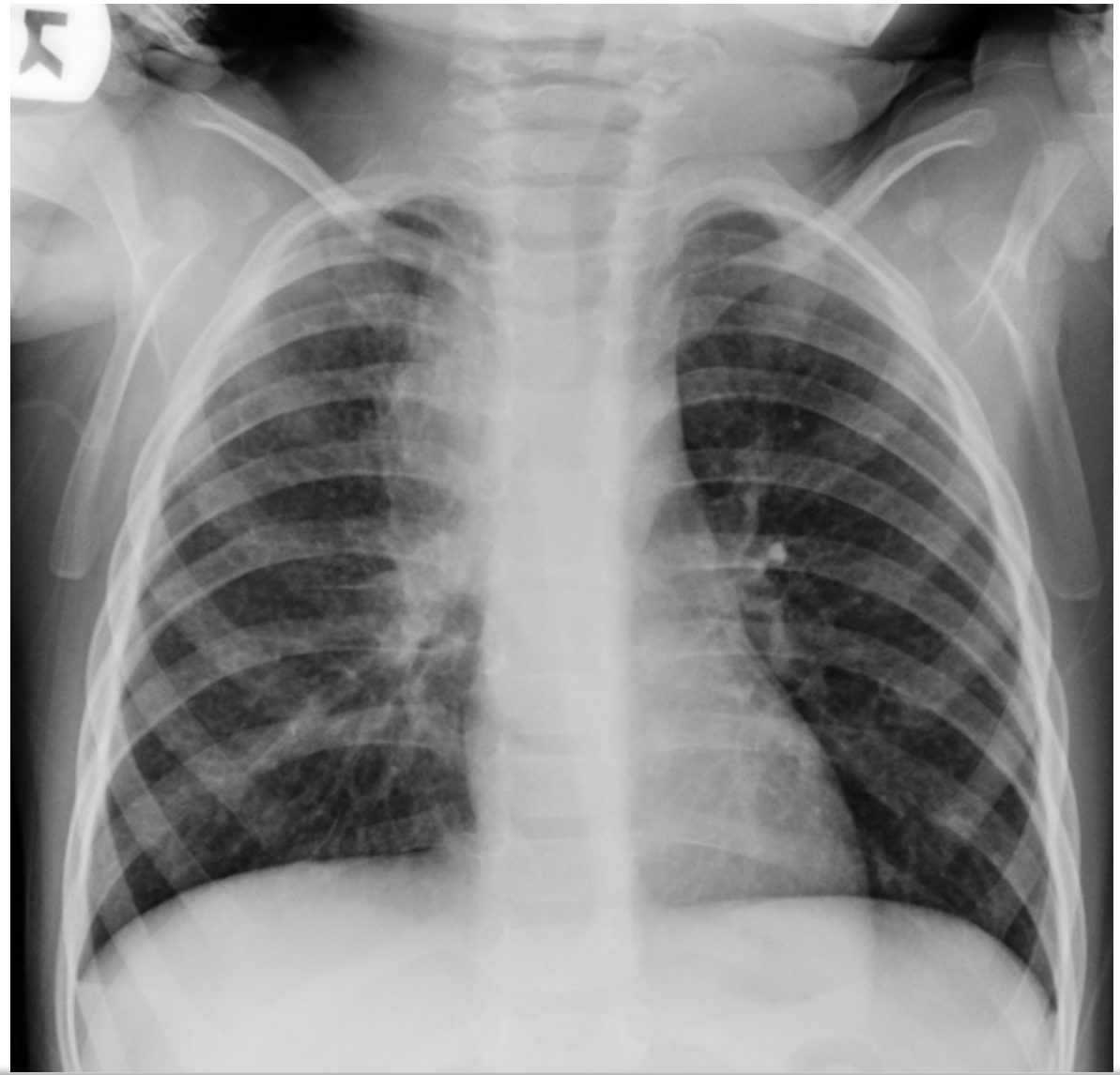
Peds in Review 2010;31:13

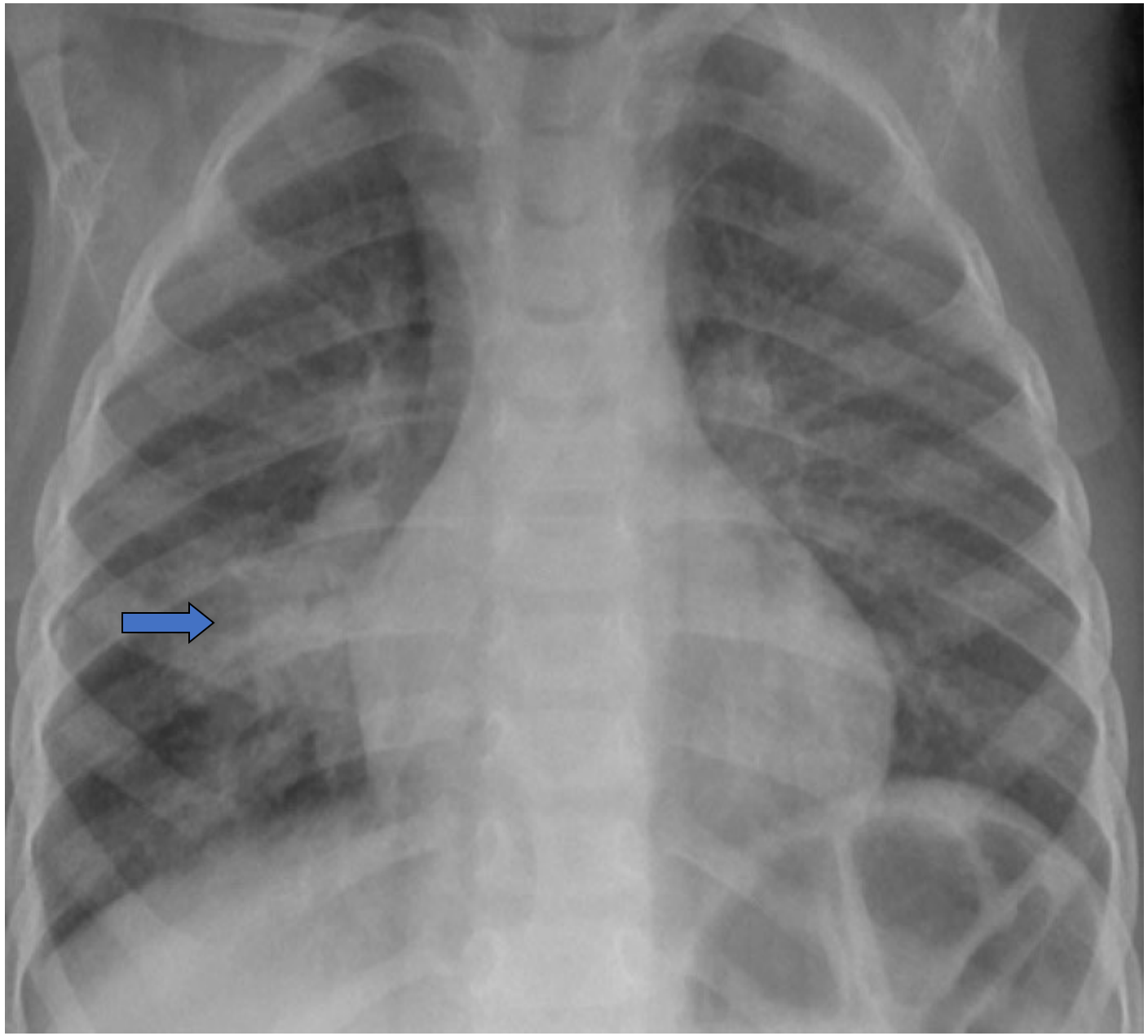
CXR Findings in Pediatric TB

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

15% of children with TB disease will have normal CXRs

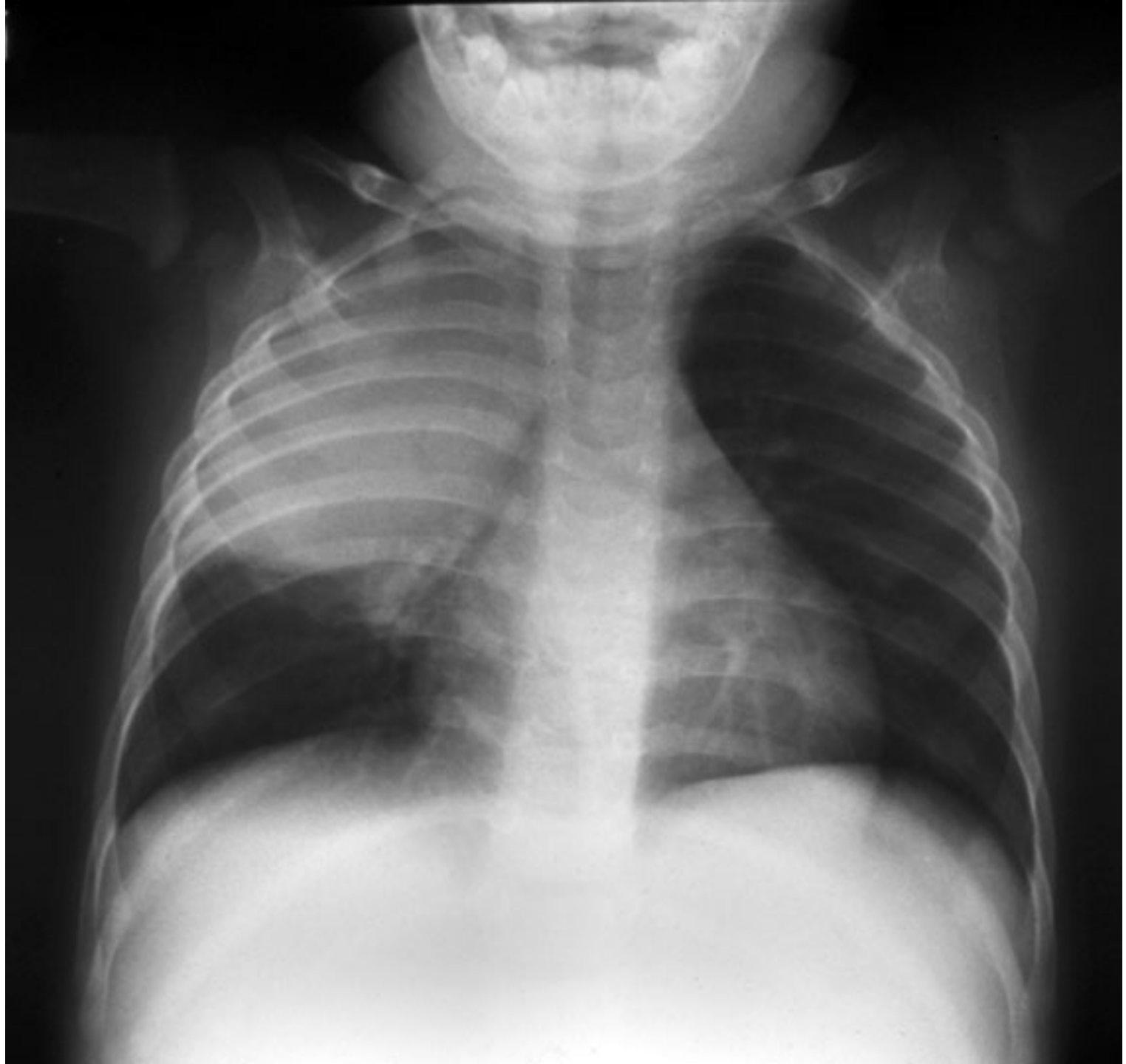
Intrathoracic Lymphadenopathy






R


L
37



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

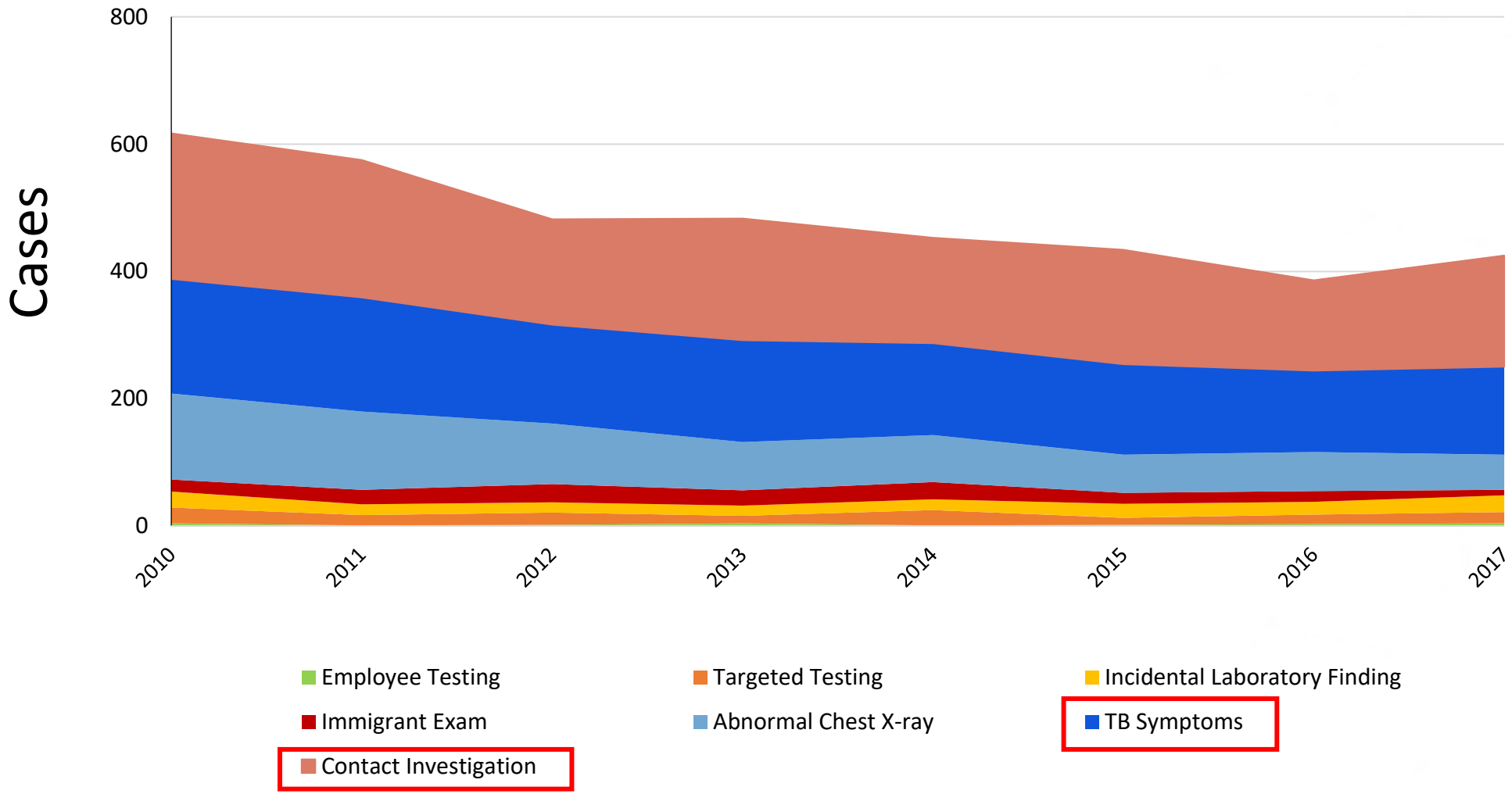
Adults – Mycobacterial-based diagnosis

- 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 WHO recommendations for infants and toddlers as well)

- 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

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
- Can dose BIW or TIW after first 2 weeks of daily dosing
- ***Always*** administered by directly observed therapy (DOT)

2021 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

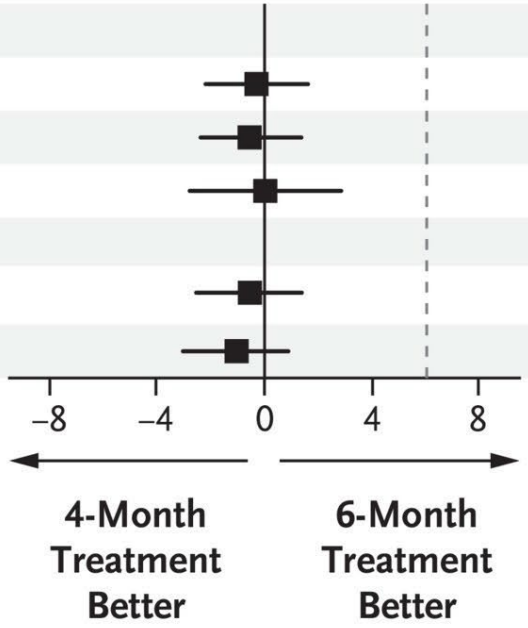
A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. 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%

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. (%)		*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)		

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

Enrolled 63 children ages 12-17

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

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

TB in Pregnancy

Caring for Two People in One Body

Implications of Delayed Screening/Diagnosis

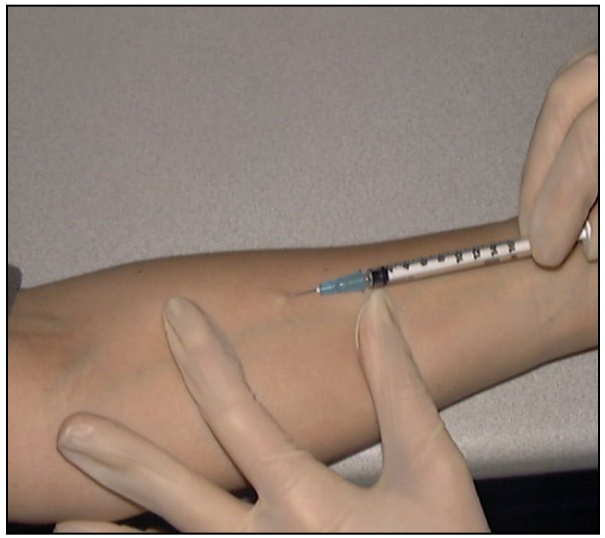
- Left untreated, a pregnant woman
  - May infect her infant
  - May infect her family
  - May pose an Infection Control threat during delivery

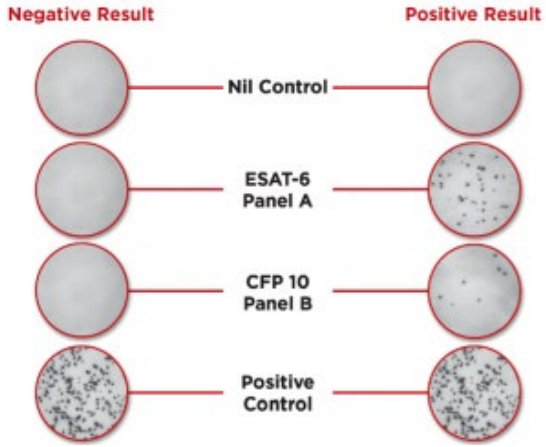
Reasons to Test a Pregnant Woman for TB

- The same reasons you test ANY person for TB
  - They have signs or symptoms of TB disease
  - They have contact with someone who has infectious TB
  - Work requirements
  - Recent immigration or immigration requirements

Is there anything different about testing pregnant women?

- Basically, no, there isn't





What if they screen TB test positive?

- Get a CXR
- Use a lead shield for the abdomen to protect the baby
- If they have symptoms, collect sputum and consider starting treatment for TB disease

Yes! You can X-ray a pregnant patient!

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017 (Replaces Committee Opinion Number 656, February 2016)

Committee on Obstetric Practice

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ⇦

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

†Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

TB Infection (LTBI) but not TB disease

- When to treat for LTBI
  - Determine why they were tested
  - Determine their risk of progression
    - If their risk is high, treat right away
      - Recent conversion
      - HIV positive
    - If their risk is lower, strongly consider treating

TB Infection (LTBI) but not TB disease

- Treatment options
  - Rifampin 600 mg daily for 4 months
  - Isoniazid 300 mg daily for 6 months
  - Not INH-rifapentine…….yet
- Treatment monitoring
  - Monthly labs and toxicity screening
  - Monitoring should extend at least 3 months postpartum

Treatment for TB disease

- A person diagnosed with or strongly suspected of having TB disease should be started on treatment without delay
- All first line drugs are generally considered safe in pregnancy
- Treatment regimen
  - PZA or no PZA?
  - Rifampin, INH, EMB for 9 months if PZA is excluded

PZA

- The WHO and IUATLD endorse use of PZA in the treatment of TB in pregnancy
- The CDC 2003 treatment guidelines did not endorse use of PZA in pregnancy due to lack of studies to show safety
- Current (2016) CDC/IDSA/ATS treatment guidelines state
  - Clinicians should evaluate risk/benefit of prescribing PZA, discuss with patient, informing patient that benefits may outweigh risk
  - Patients with HIV, extrapulmonary or severe disease should receive PZA in their treatment regimen

Suspected Active TB at Delivery

- Protect the delivery team
- Try to find a negative pressure room for delivery or perhaps a room further away from the general floor, like a surgical suite
- Delivery team should wear N95 masks

- Make arrangements to send placenta for pathologic evaluation and AFB culture

After-Delivery Concerns

- How do you evaluate the infant?
  - Evaluate for any signs of infection
  - CBC, blood culture for AFB, ultrasound of the liver/spleen
  - Consider gastric aspirates
  - CSF if evidence of disease

After-Delivery Concerns

- Should you separate the patient from their infant?
  - Only if the patient is suspected of having MDR TB
  - If patient is infectious, put the baby on INH or rifampin and have the patient wear a surgical mask while holding the baby until they are no longer infectious
- Can the patient breastfeed?
  - Yes
  - First line TB drugs all into the breastmilk in low but safe levels

Take Home Points

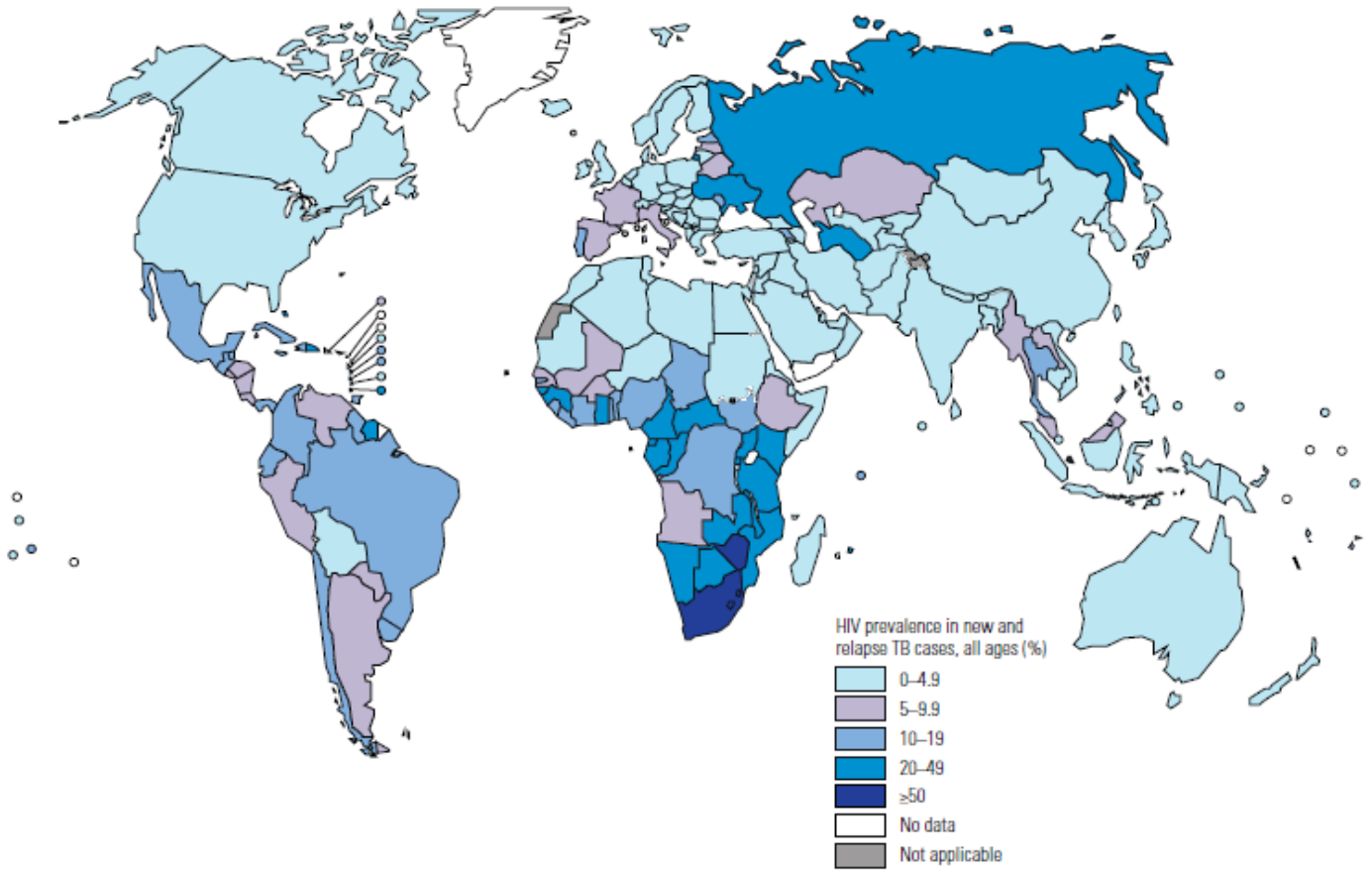
- Protecting a pregnant person also protects their baby, their family and their community
- If a CXR is warranted, it should be performed
- Pregnant persons can be safely treated for TB infection and TB disease
- PZA, though controversial, in most cases will add more benefit than harm to the treatment of TB in pregnancy

TB and HIV

Global Epidemiology of TB/HIV

FIG. 4.5

Estimated HIV prevalence in new and relapse TB cases, 2019



GLOBAL TUBERCULOSIS REPORT 2020

FIG. A3.1

The three global lists of high-burden countries for TB, HIV-associated TB and MDR/RR-TB to be used by WHO in the period 2021–2025, and their areas of overlap

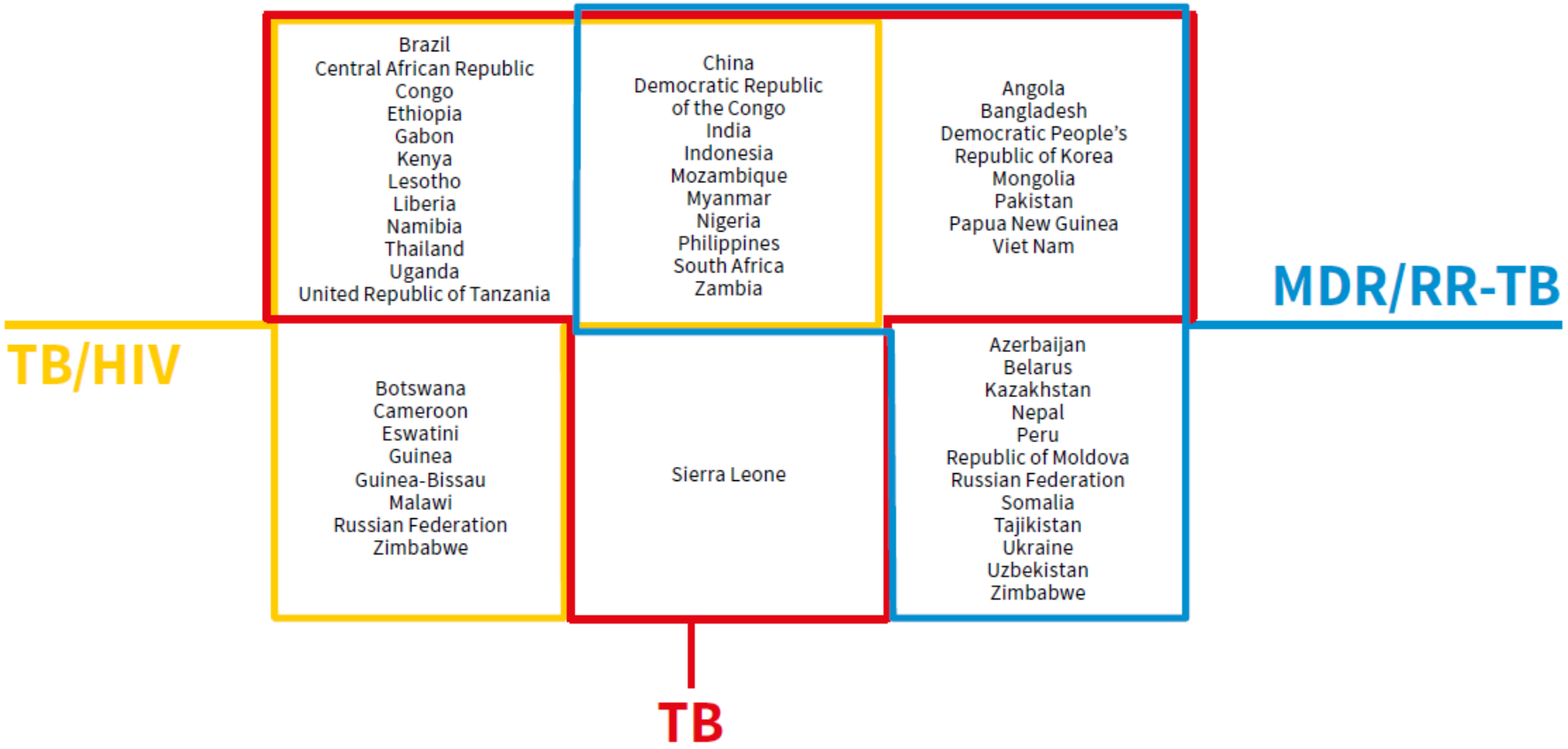
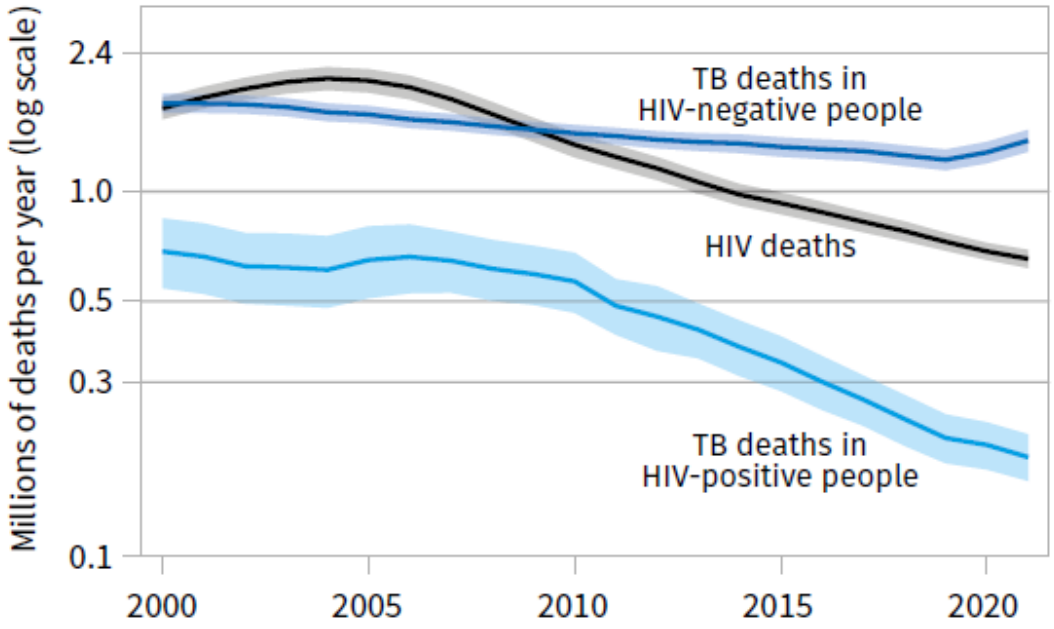


FIG. 7

Global trends in the estimated number of deaths caused by TB and HIV, 2000–2021[a,b]

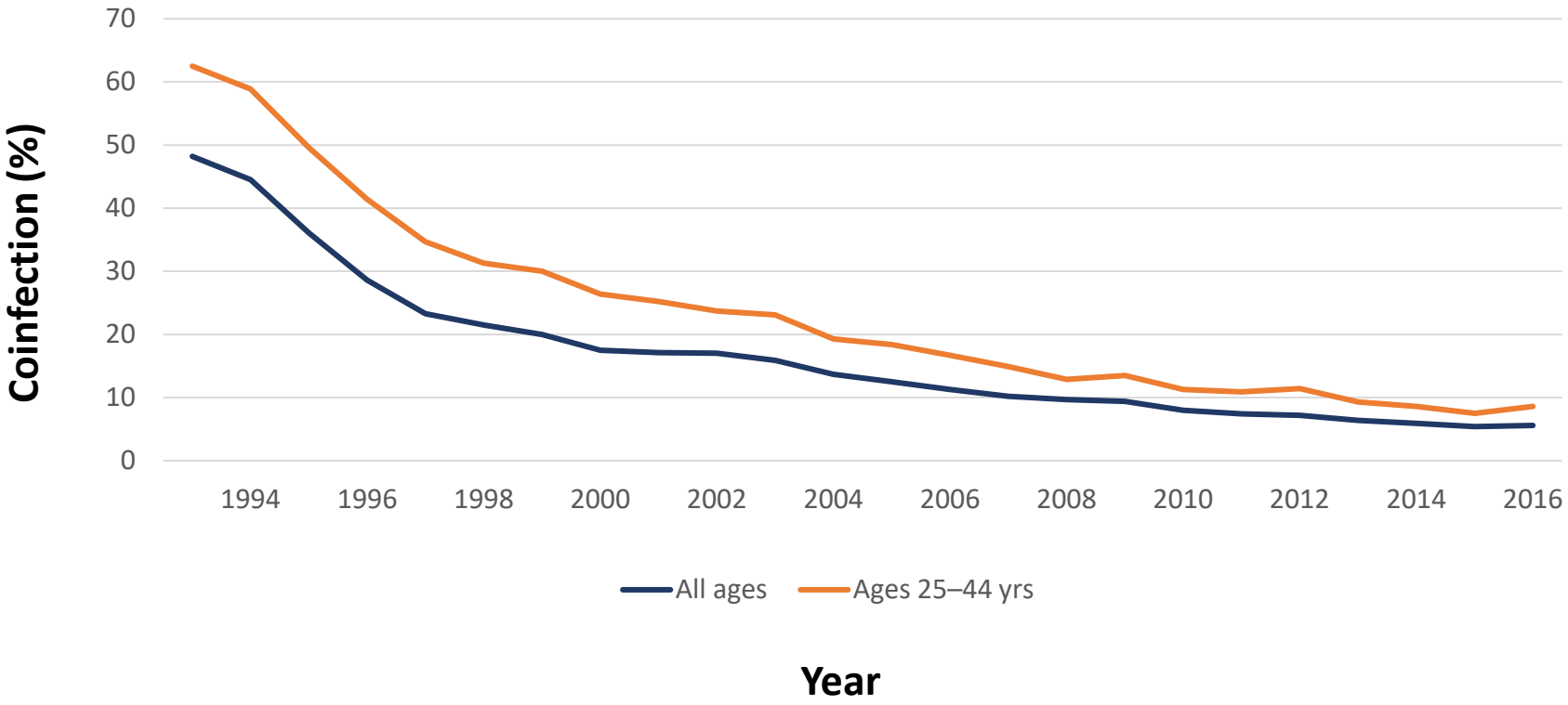
Shaded areas represent 95% uncertainty intervals.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2021 that have been published by UNAIDS are available at http://www.unaids.org/en/ (accessed 15 August 2022). For TB, the estimates for 2021 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

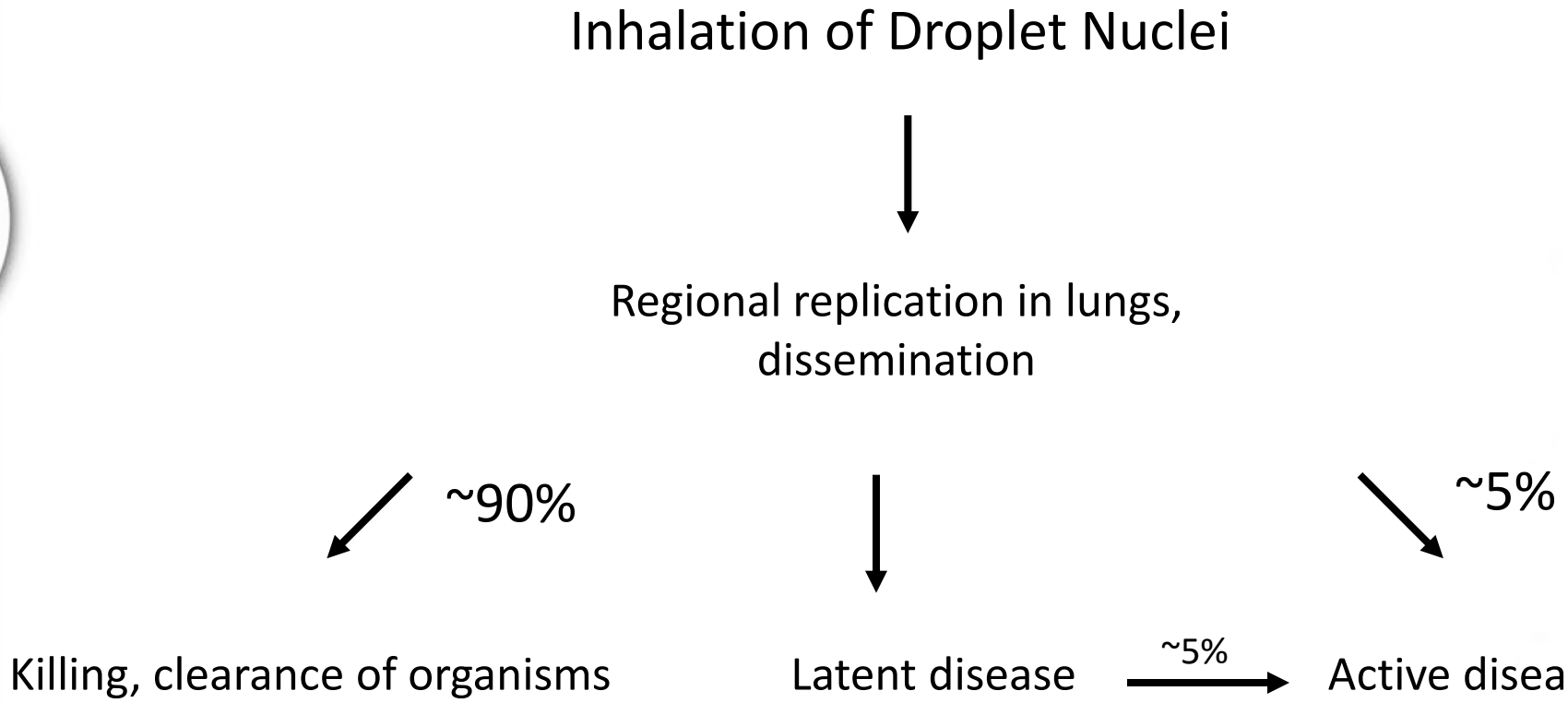
Estimated HIV Coinfection Among Persons Reported with TB, United States, 1993–2016*



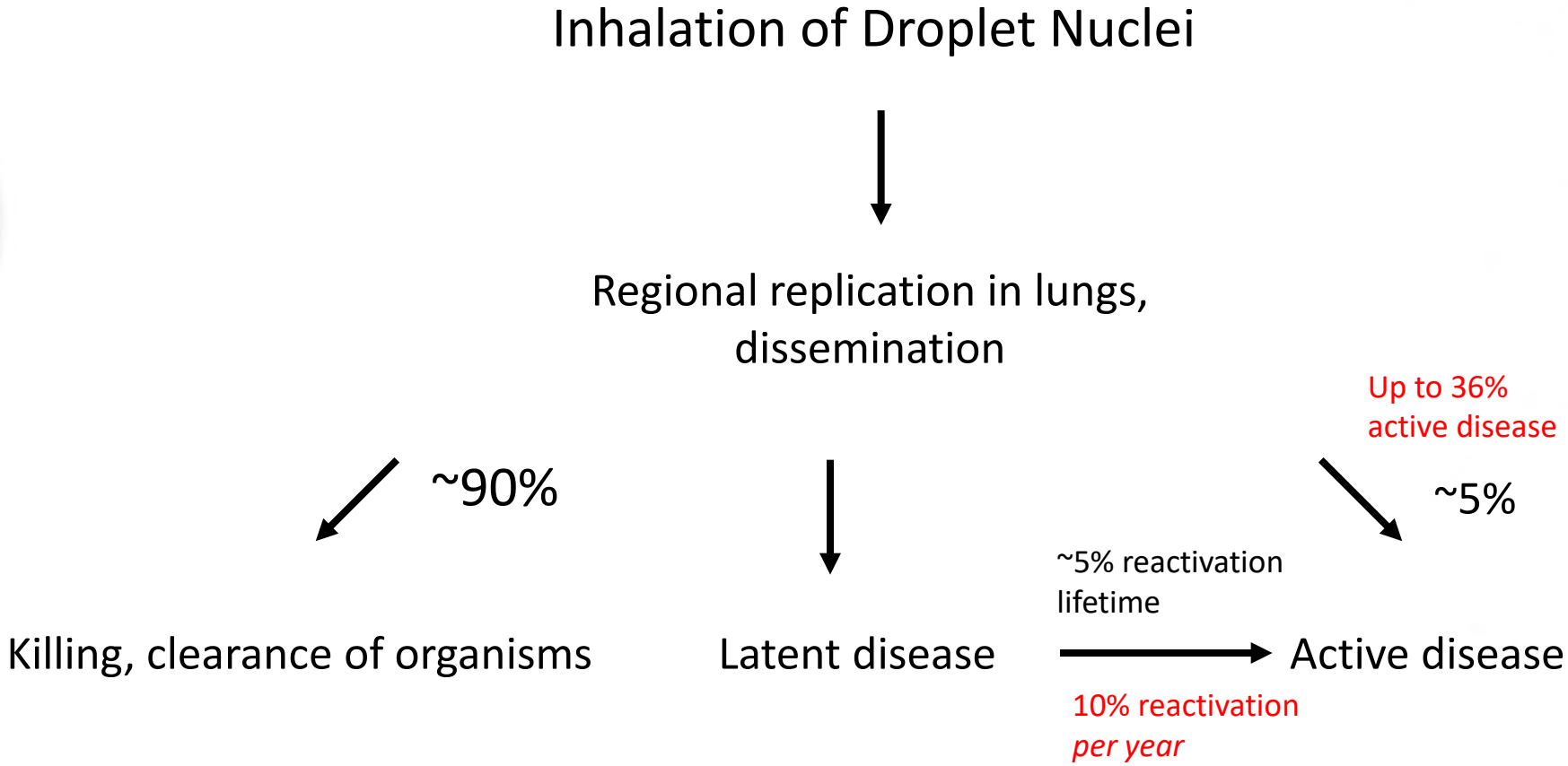
* As of June 21, 2017.

Note: Minimum estimates are based on reported HIV-positive status among all TB patients in the age group.

Outcomes of Exposure to *M. tuberculosis*



Outcomes of Exposure to *M. tuberculosis* in HIV-negative and HIV-positive patients



Diagnosis of Tuberculosis in Persons Living with HIV

TB screening in PLWH

- All persons with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII).**

- Persons with advanced HIV infection (CD4 count <200 cells/mm^3) and negative diagnostic tests for LTBI should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3

- Annual testing for LTBI using TST or IGRA is recommended only for people with HIV who have a history of a negative test for infection and are at high risk for repeated or ongoing exposure to persons with active TB disease (targeted testing)

Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

TST Limitations

- Technical problems in administration and reading
- >1 visit needed
- False-negative responses
  - Anergy (compromised immunity)
  - TST reversion at old age
- Repeated TSTs boost the immune response
  - Need 2-step approach in serial testing
- False positives
  - Nontuberculous mycobacteria (NTM)
  - Bacille Calmette-Guerin vaccination (BCG)

Diagnosis

Table 1. Bacteriological and histological results observed during HIV-associated TB as a function of immune status

	CD4 < 200/mm^3	CD4 > 200/mm^3	References
Positive tuberculin skin test reaction (> 5 mm without BCG)	30% *	50% *	[23]
Acid-fast bacilli on smear	56–60%	50–58%	[22,23,25]
Acid-fast bacilli on biopsy	60–65%	50–56%	[22]
Granuloma in biopsy	60–75%	67–100%	[23,31,32]
Mycobacteraemia	20–49%	0–7%	[22,30]

Clinical Microbiology and Infection, Volume 10 Number 5, May 2004

Infection (2022) 50:597–606
https://doi.org/10.1007/s15010-022-01789-9

REVIEW

Diagnostic accuracy of the interferon-gamma release assay in acquired immunodeficiency syndrome patients with suspected tuberculosis infection: a meta-analysis

Hao Chen[1] · Atsushi Nakagawa[2] · Mikio Takamori[3] · Seitarou Abe[4] · Daisuke Ueno[5] · Nobuyuki Horita[6] · Seiya Kato[7] · Nobuhiko Seki[1,8]

Received: 2 January 2022 / Accepted: 22 February 2022 / Published online: 6 March 2022

- 45 articles, 6,525 PLWHIV (2661 with active disease, 806 with LTBI)
- QFT sensitivity/specificity 0.663/0.867
- Tspot sensitivity/specificity 0.604/0.862
- Sensitivity of IGRAs in diagnosing LTBI was 0.64

Signs & Symptoms - Pulmonary TB

Pulmonary Symptoms:

- Productive, prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

Systemic Symptoms:

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

Testing for TB Infection

- Clients who have a + TST result, a positive IGRA result or symptoms suggestive of TB (regardless of TST/IGRA results) *should be evaluated with a chest x-ray*

- Patients with HIV who may not react to testing by TST or IGRA should have a chest x-ray if TB is suspected or if exposed to an active TB case

- If abnormalities are noted, or the client has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted

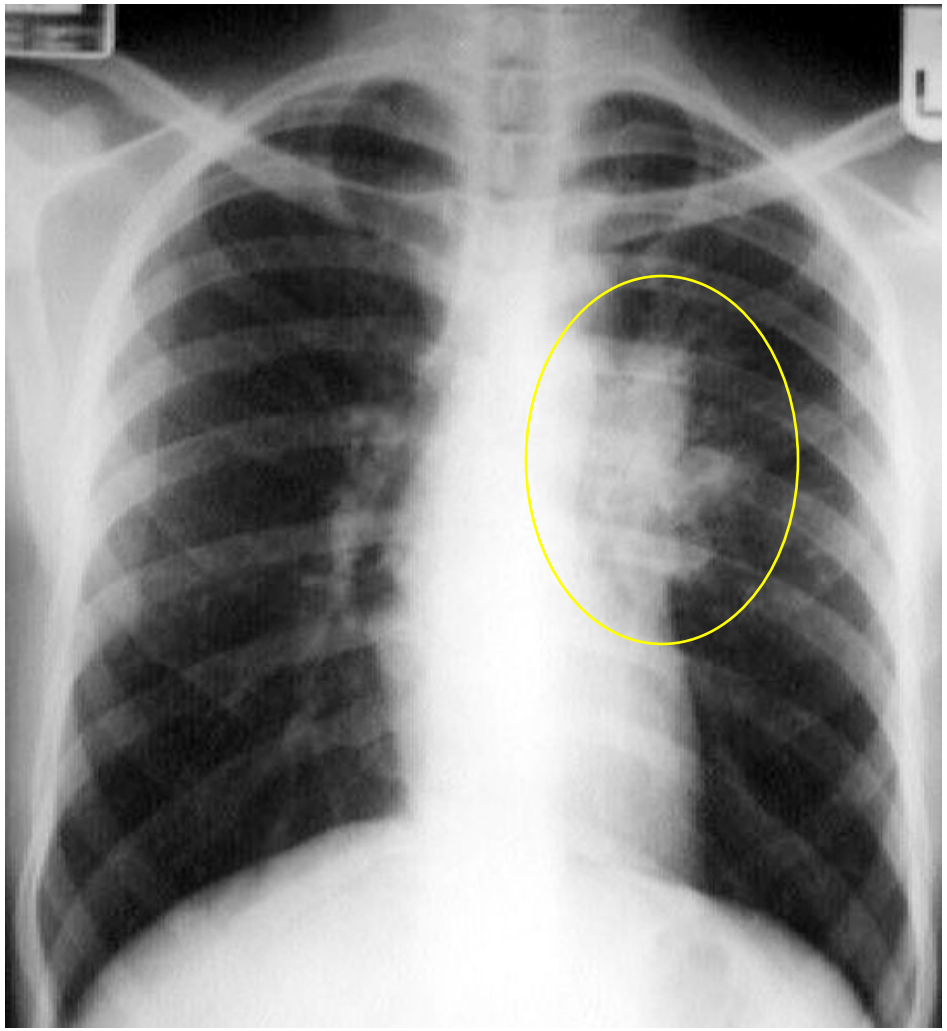
CXR – HIV infected persons

In HIV-infected persons almost any abnormality on CXR may indicate TB

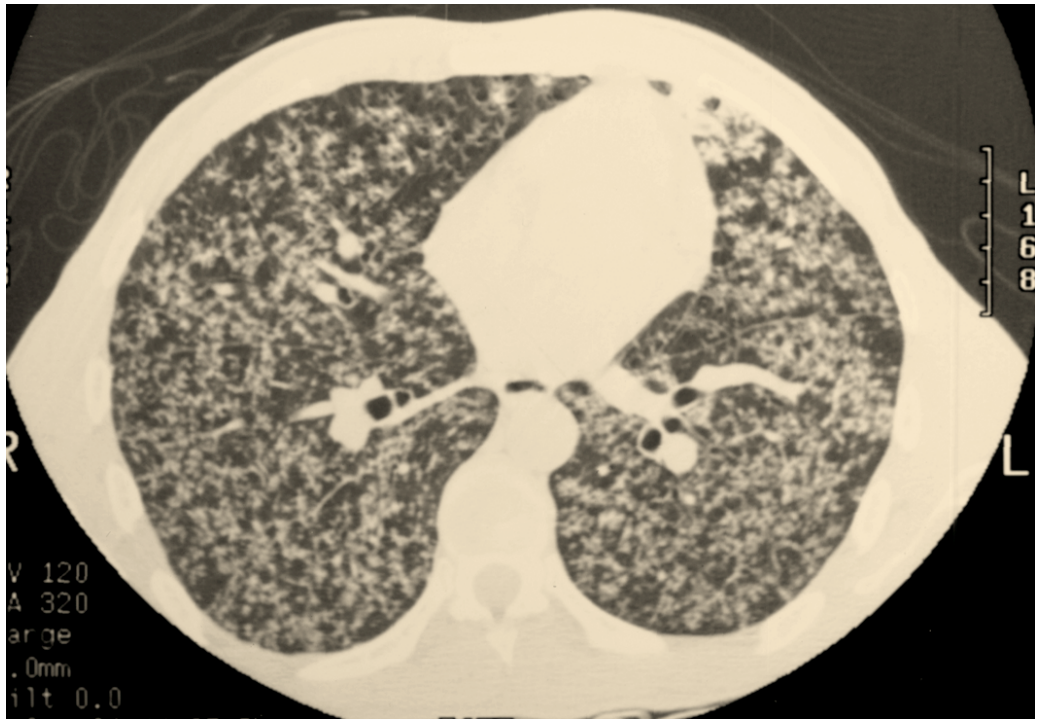
- May cause infiltrates without cavities in any lung zone
- May cause mediastinal or hilar lymphadenopathy

  with or without infiltrates or cavities

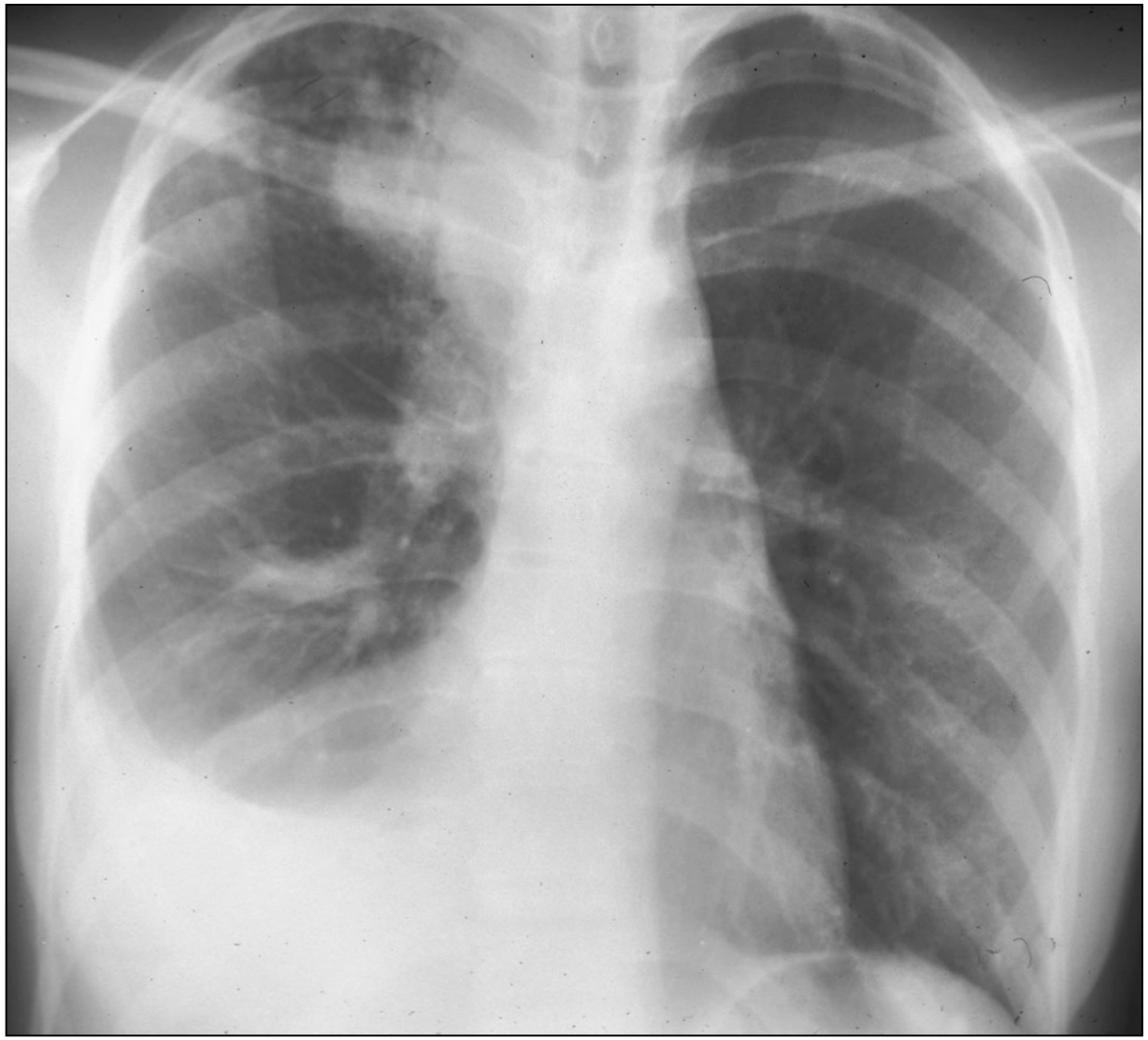
Primary Tuberculosis



Miliary tuberculosis



Tuberculosis and HIV



Screening for pulmonary tuberculosis in HIV-infected individuals: ACTG Protocol A5253

IJTLD 17(4): 532-9, 2013

- Comparison of evaluation tools for diagnosis of TB in HIV patients
  - SOC screening algorithm: cough, fever, weight loss, night sweats in previous 30 days, sputum smear, CXR (if not pregnant)
  - Enhanced screening tool added other symptoms to screening (GI, GU, neuro, derm) and fluorescent microscopy
- 801 patients, average 33 y/o, median CD4 275
- Results:
  - 51% with TB had a normal CXR
  - SOC sensitivity 54%, specificity 76%, PPV 24%, NPV 92%
  - Cough was the most sensitive symptom (especially when combined with abnl CXR, LN, or CD4 count < 200)
  - Only 6 of 54 (11.1%) with positive TB culture had positive smear

An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV

N Engl J Med 2010;362:707-16.

Appendix Table 1. Smear and culture results of patients with TB (N=267), stratified by symptoms and chest radiograph result.

Category		Enrolled patients, n	TB diagnosed, n (% of enrolled patients)	Positive acid-fast smear, n (% of TB diagnosed)	Number of positive cultures, n (% of TB diagnosed)	
Symptoms*	Chest radiograph				1	>1
Absent	Normal	493	7 (1)	0	5 (71)	2 (29)
Present	Normal	865	87 (10)	26 (30)	40 (46)	47 (54)
Absent	Abnormal	56	11 (20)	3 (27)	2 (18)	9 (82)
Present	Abnormal	334	162 (49)	92 (57)	21 (13)	140 (87)

*Any one of: any cough in the past 4 weeks, any fever in the past 4 weeks, or night sweats for ≥3 weeks.

Evaluation of the Xpert MTB/RIF Assay at a Tertiary Care Referral Hospital in a Setting Where Tuberculosis and HIV Infection Are Highly Endemic

linical Infectious Diseases 2012;55(9):1171–8

Justin O'Grady,[1,2,a] Matthew Bates,[1,2,a] Lophina Chilukutu,[2] Judith Mzyece,[2] Busiku Cheelo,[2] Moses Chilufya,[2] Lukundo Mukonda,[2] Maxwell Mumba,[2] John Tembo,[2] Mumba Chomba,[2] Nathan Kapata,[2,3] Markus Maeurer,[4] Andrea Rachow,[5] Petra Clowes,[5] Michael Hoelscher,[5,6] Peter Mwaba,[2,7] and Alimuddin Zumla[1,2]

[1]Department of Infection, University College London Medical School, Royal Free Hospital, United Kingdom; [2]University of Zambia and University College London Medical School Research and Training Programme, University Teaching Hospital, [3]National Tuberculosis Control Programme, Lusaka, Zambia; [4]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden; [5]Mbeya Medical Research Programme, Tanzania; [6]Department for Infectious Diseases and Tropical Medicine, Klinikum of the University of Munich, Germany; and [7]Ministry of Health, Lusaka, Zambia

- All patients who could produce a sputum screened
- 881 patients enrolled, 70.9% HIV positive
- Culture confirmed TB in 201
- Persons with HIV (with culture proven TB):
  - 88.2% sensitivity overall
  - 74.7% sensitive in smear negative, culture + specimens

Bacteriologic or histologic exam

- Sputum
  - Three (8-24 hours apart, at least one first thing in the morning)
- Tissue
  - Lymph node biopsy
  - Bone marrow biopsy
- Other specimens
  - Urine
  - CSF
  - Peritoneal fluid
  - Pleural fluid (pleural biopsy)

Diagnosis – Summary

- Requires a high index of suspicion and must utilize many pieces of information in making the diagnosis
- TB can present very differently in HIV-infected patients when compared to HIV-negative patients
- The most effective tool in diagnosing TB disease in PLWH is an astute physician.

Latent TB Infection (LTBI) in HIV

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

HIV-infected persons, regardless of age, should be treated for LTBI *if they have no evidence of active TB* and exhibit the following characteristics:

- 1) a positive diagnostic test for LTBI and no prior history of treatment for active or latent TB (AI);
- 2) a negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB (AII); and
- ~~3) a history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI (AII)~~

Mycobacterium tuberculosis Infection and Disease | NIH (hiv.gov)

Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection

TB Drug	ARV Drugs	Dose of TB Drug
Isoniazid (INH)	• All ARVs • **Note:** for information on coadministration of ARVs with rifampin or rifapentine, see entries below	Use INH with pyridoxine 25–50 mg PO daily (50 mg once weekly if used with 3HP) *For 3HP (weekly INH + rifapentine x 12 weeks)* • 15 mg/kg PO once weekly (900 mg maximum) *For 3HR (daily INH + rifampin x 3 months), or 1HP (daily INH + rifapentine x 4 weeks), or INH alone (daily INH x 6–9 months)* • 300 mg PO daily
Rifampin[a]	• NRTIs (TAF with caution[b]) • EFV 600 mg • DTG, RAL (twice daily), and MVC without a strong CYP3A4 inhibitor (**note:** doses of these ARV drugs need to be adjusted when used with rifampin) • IBA, T-20	*For 3HR (daily rifampin + INH x 3 months), or 4R (daily rifampin x 4 months)* • 600 mg PO daily
	• All other ARVs	**Not recommended**
Rifapentine[a] **3HP** *Weekly rifapentine + INH x 12 weeks*	• EFV 600 mg, RAL or once daily DTG • NRTIs (TAF with caution[b]) • IBA, T-20	• Weighing 32.1–49.9 kg: 750 mg PO weekly • Weighing ≥50.0 kg: 900 mg PO weekly
	• All other ARVs	**Not recommended**
Rifapentine[a] **1HP** *Daily rifapentine + INH x 4 weeks*	• NRTIs (TAF with caution[b]) • EFV 600 mg • IBA, T-20	• Weighing <35 kg: 300 mg PO daily • Weighing 35–45 kg: 450 mg PO daily • Weighing >45 kg: 600 mg PO daily
	• All other ARVs	**Not Recommended**

Treatment for Active TB

TB and HIV Co-infection: Treatment Principles

- The treatment of TB in patients with HIV infection should follow the same principles as for the treatment of persons without HIV infection

- Initiate TB treatment immediately
  - Directly observed therapy is strongly recommended

- Initiate or optimize ART
  - Concomitant therapy for both TB and HIV shown to reduce mortality
    - Low CD4 count is risk factor for mortality
    - IRIS more common if ART is initiated early in course of TB treatment, but not associated with mortality

ATS recommendations for treatment of tuberculosis

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance. *	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior. *	Lesser

When should HIV treatment be started?

- Considerations
  - Treatment of HIV improves outcomes in patients with TB
    - Decreased death or relapse
  - Multiple medications with multiple potential toxicities that are overlapping

Initiation of ART in patients with HIV/TB

- In patients with CD4 counts ***<50 cells/mm^3***, ART should be initiated within 2 weeks of starting TB treatment **(AI)**

- In patients with CD4 counts ***≥50 cells/mm^3*** with clinical disease of major severity ART should be initiated within 2 to 4 weeks of starting TB treatment.
  - CD4 count 50 to 200 cells/mm3 **(BI)**
  - CD4 count >200 cells/mm3 **(BIII)**

- In patients with CD4 counts ***≥50 cells/mm^3*** who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation.
  - CD4 count 50 to 500 cells/mm3 **(AI)**
  - CD4 count >500 cells/mm3 **(BIII)**

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Initiation of ART in patients with HIV/TB

- In patients with CD4 counts ***<50 cells/mm³***, ART should be initiated within 2 weeks of starting TB treatment **(AI)**

- In patients with CD4 counts ***≥50 cells/mm³*** with clinical disease of major severity ART should be initiated within 2 to 4 weeks of starting TB treatment.
  - CD4 count 50 to 200 cells/mm3 **(BI)**
  - CD4 count >200 cells/mm3 **(BIII)**

- In patients with CD4 counts ***≥50 cells/mm³*** who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation.
  - CD4 count 50 to 500 cells/mm3 **(AI)**
  - CD4 count >500 cells/mm3 **(BIII)**

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Initiation of ART in patients with HIV/TB

- In patients with CD4 counts <50 cells/mm^3: Initiate ART as soon as possible, but within 2 weeks of starting TB treatment (AI).
- In patients with CD4 counts ≥50 cells/mm^3: Initiate ART within 8 weeks of starting TB treatment (AIII).
- In all HIV-infected pregnant women: Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV (AIII).
- In patients with tuberculous meningitis: Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial (AI).

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB

TB Drug	ARV Drugs	Daily Dose of TB Drug
Isoniazid	• All ARVs	5 mg/kg (usual dose 300 mg) Use INH with pyridoxine 25–50 mg PO daily
Rifampin[a,b]	• NRTIs (use TAF with caution[c]) • EFV 600 mg • DTG, RAL (twice daily), MVC without a strong CYP3A4 inhibitor (**note**: doses of these ARVs need to be adjusted when used with rifampin) • IBA, T-20	10 mg/kg (usual dose 600 mg)
	• DOR, ETR, EFV 400 mg, NVP, RPV (PO) • BIC, EVG/c, RAL (daily) • CAB/RPV (IM/PO) • HIV PIs	**Not recommended**

TB Drug	ARV Drugs	Daily Dose of TB Drug
	• LEN (SC/PO), FTR, MVC with a strong CYP3A4 inhibitor	
Rifabutin[a]	• NRTIs (use TAF with caution[c]) • ETR without boosted PIs • DOR and RPV (PO) (**note**: doses need to be adjusted when used with rifabutin) • DTG, RAL • MVC without a strong CYP3A4 inhibitor • IBA, T-20, FTR	5 mg/kg (usual dose 300 mg)
	• PIs with RTV • MVC with a strong CYP3A4 inhibitor	150 mg daily[e]
	• EFV	450–600 mg
	• ETR with boosted PIs • BIC, EVG/c • CAB/RPV (IM/PO) • PIs with COBI • LEN (SC/PO)	**Not recommended**
Rifapentine	• EFV • NRTIs (use TAF with caution[c])	1,200 mg/day for people weighing ≥40 kg
	• All other ARVs	**Not recommended**

https://clinicalinfo. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacteriumhiv.gov/en/guidelines

PLWH with MDR - Bedaquiline

- Use with Protease Inhibitors……no
- Use with NNRTIs
  - Nevirapine, doravirine, rilpivirine, no change in dose of either medication.
  - Efavirenz/etravirine……no
- Use with INSTIs
  - BIC, CAB (PO and IM), DTG, RAL, no change in dosing of either medication
  - Elvitegravir…..no
- Use with CCR5 antagonists, temavir, lenacapavir ……no data

IRIS
(Immune Reconstitution Inflammatory Syndrome)

Restoration of pathogen-specific immune responses to opportunistic infections

- Unmasking IRIS
  - New presentation of a previously subclinical infection
- Paradoxical IRIS
  - Deterioration of a treated infection
  - Reported in 8-40% of patients starting ART after TB diagnosis
  - Most occur within 3 months of starting ART
  - Predictors:
    - CD4 count < 50
    - Higher on-ART CD4 count
    - High pre-ART and lower on-ART viral load
    - Severity of disease (high pathogen burden)
    - < 30 days between start of TB and HIV treatments

IRIS
(Immune Reconstitution Inflammatory Syndrome)

- Rule out other causes
  - Drug resistance (do you have susceptibilities?)
  - Other opportunistic infections
- Management
  - Mild cases use NSAIDS
  - More severe cases use steroids

Treatment - Summary

- TB testing for PLWH remains inadequate in many circumstances
- Every effort should be made to treat within the CDC guidelines to
  - increase the chances of treatment success,
  - decrease the chances of relapse and
  - minimize the length of time with toxicities.
- Rifamycins are the cornerstone of treatment for TB. Though drug interactions with ARVs are a concern, data continues to emerge regarding effective dosing options.
- HIV infection does not negatively impact patients with TB disease if diagnosed early and treated appropriately

TB in the Elderly

- Hepatotoxicity and as well as other medication toxicities are more common
- Elderly patients tend to be on more medications and drug drug interactions are a concern
- May want to weigh the risk/benefit of using PZA

Questions?