Pediatric MDR-TB

Lisa Y Armitige, MD, PhD

Professor, Medicine and Pediatrics

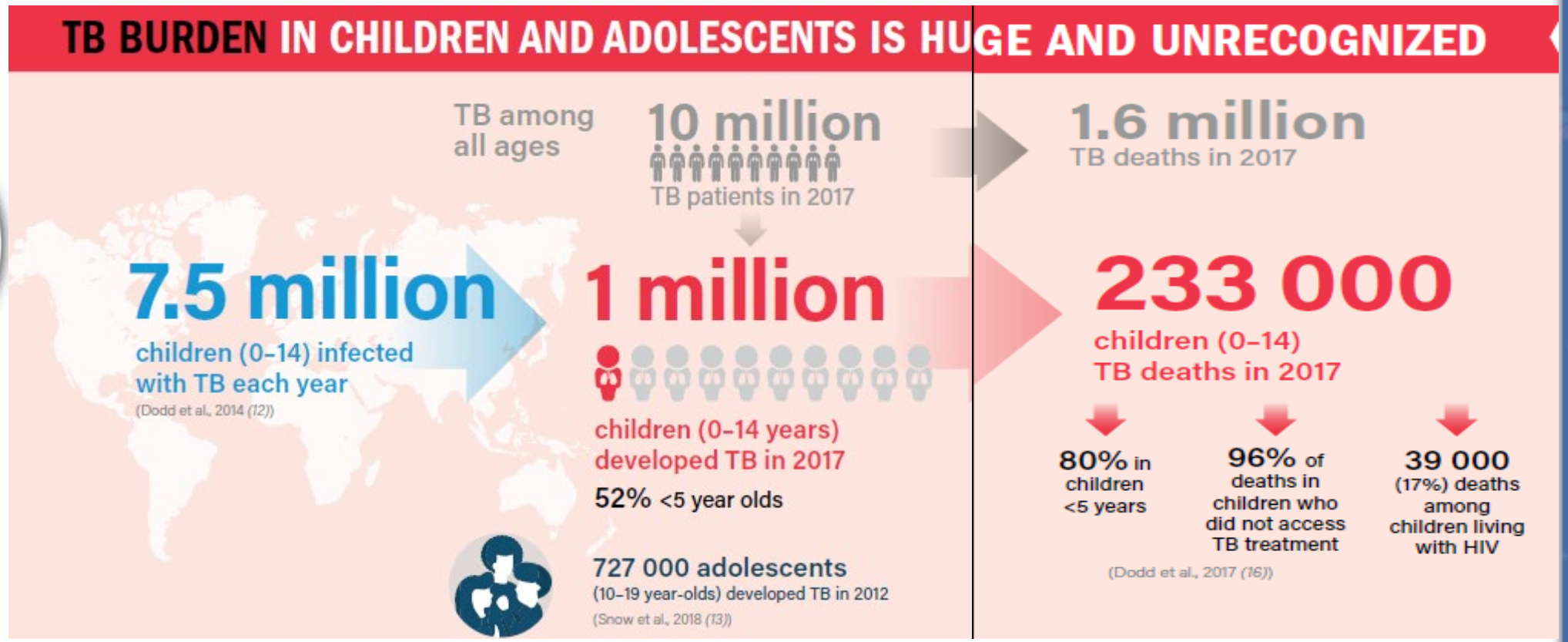
Division of Adult Infectious Diseases

Assistant Medical Director

Heartland National TB Center

Epidemiology of Pediatric TB

Global Pediatric TB

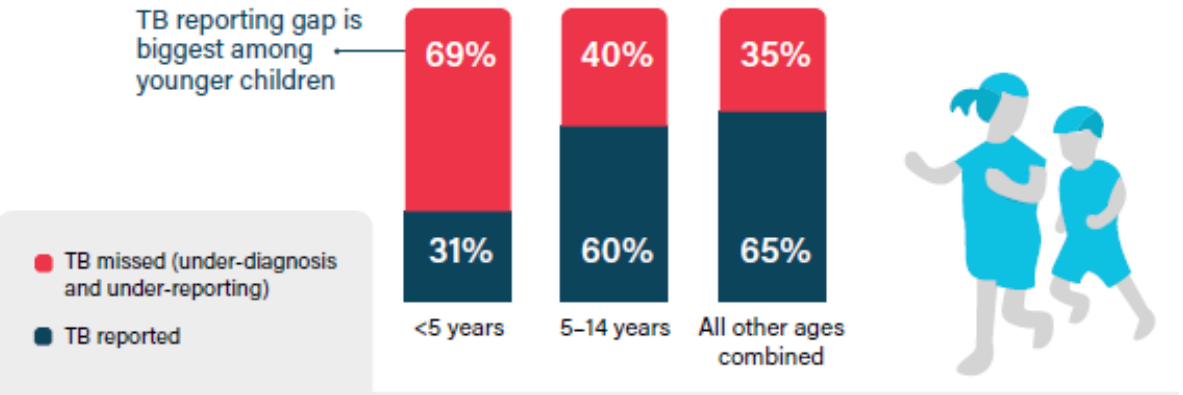


https://www.who.int/tb/cHILD2.jpg

Global Pediatric TB

CASE DETECTION GAP

% of TB patients that are missed in different age groups



Overall 55% of estimated children with TB (0–14 years) are **not reported** to national TB programmes

TB can be a cause or co-morbidity of common child illnesses, especially pneumonia and malnutrition. More specific tests are needed to improve diagnosis.

(Oliwa et al., 2015 *(14)*; Patel and Detjen, 2017 *(15)*)

PREVENTION GAP

Globally in 2017, over 75% (of 1.3 million eligible household contacts under 5 years of age) **did not access preventive therapy**

WHO recommends TB prevention including:

- Preventive therapy
- Infection control measures
- BCG vaccination

In the 158 countries for which data on BCG coverage are available, **120 reported coverage of at least 90% in 2017**

https://www.who.int/tb/cHILD1.jpg

Global Pediatric TB

TB/HIV

Link between HIV and TB in children and adolescents is well known but not acted upon

TB is the most common opportunistic infection in people living with HIV, including children and adolescents

Only around half of eligible children access antiretroviral therapy, which significantly reduces the risk of TB in children living with HIV.

(UNAIDS, 2018 *(17)*)

TB preventive therapy is not fully implemented as part of comprehensive HIV care for children and adolescents

(UNAIDS, 2018 *(17)*)

Children living with HIV who have severe immune suppression (low CD4 count) have a **5-fold higher** risk of TB compared to children with mild immune-suppression

(Dodd et al., 2017 *(18)*)

MDR-TB

An estimated 25 000 children <15 years fell ill with MDR-TB in 2014

Less than 10% of them were diagnosed and had access to treatment

(Dodd et al., 2016 *(19)*; Jenkins et al., 2014 *(20)*)

Drug-resistant TB is a major contributor to antimicrobial resistance

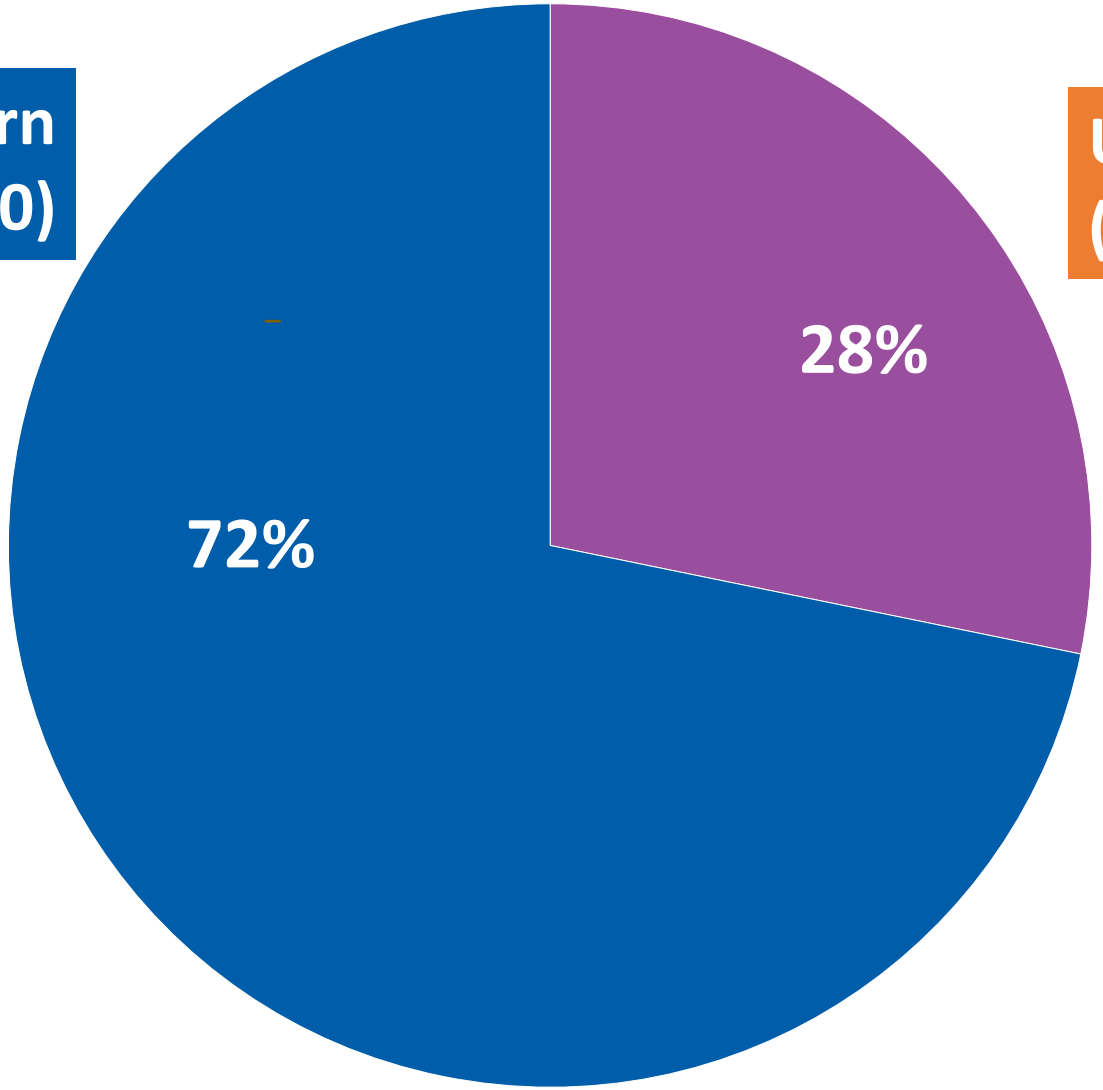
https://www.who.int/tb/cHILD3.jpg

Pediatric Drug Susceptible vs Drug Resistant TB

- Most cases of MDR TB in children are due to contact with an infectious person with MDR TB
- WHO estimates household contacts of patients with drug resistant TB are more likely to become infected than household contacts of persons with drug susceptible TB
- Principles of screening, evaluation and diagnosis are the same, regardless of the source susceptibility pattern, only treatment is different

TB Incidence Rates* and Percentages by Origin of Birth, United States, 2020 (N=7,145)

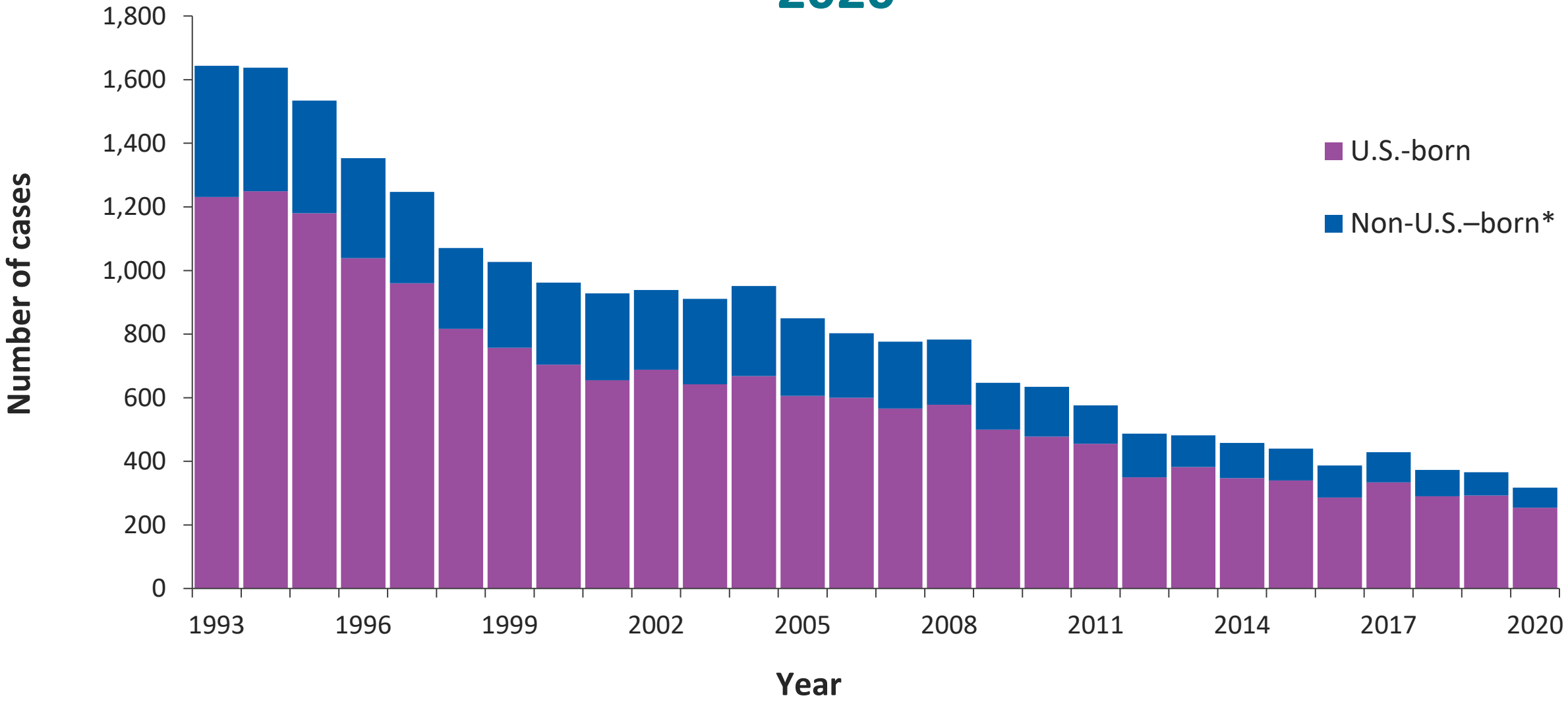
Non-U.S.–born (Rate: 11.7 per 100,000)



U.S.-born (Rate: 0.7 per 100,000)

*Cases per 100,000 persons

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

MDR Cases US-born vs Non-US born

Table 9. Tuberculosis Cases and Percentages, by Multidrug Resistance (MDR),[1] Origin of Birth, and Previous History of TB: United States, 1993–2020

See Surveillance Slide #56.

Year	All MDR[2]	Multidrug Resistant TB Cases																	
		Total MDR						U.S.-Born MDR[3]						Non-U.S.–Born[3,4] MDR					
		Previous TB			No previous TB			Previous TB			No previous TB			Previous TB			No previous TB		
		Eligible	No.	(%)	Eligible	No.	(%)	Eligible	No.	(%)	Eligible	No.	(%)	Eligible	No.	(%)	Eligible	No.	(%)
2018	104	289	18	(6.2)	6,550	85	(1.3)	57	1	(1.8)	1,866	12	(0.6)	232	17	(7.3)	4,683	73	(1.6)
2019	92	272	15	(5.5)	6,468	77	(1.2)	59	1	(1.7)	1,789	12	(0.7)	213	14	(6.6)	4,673	65	(1.4)
2020	56	213	9	(4.2)	5,216	47	(0.9)	41	0	(0.0)	1,411	3	(0.2)	172	9	(5.2)	3,788	44	(1.2)

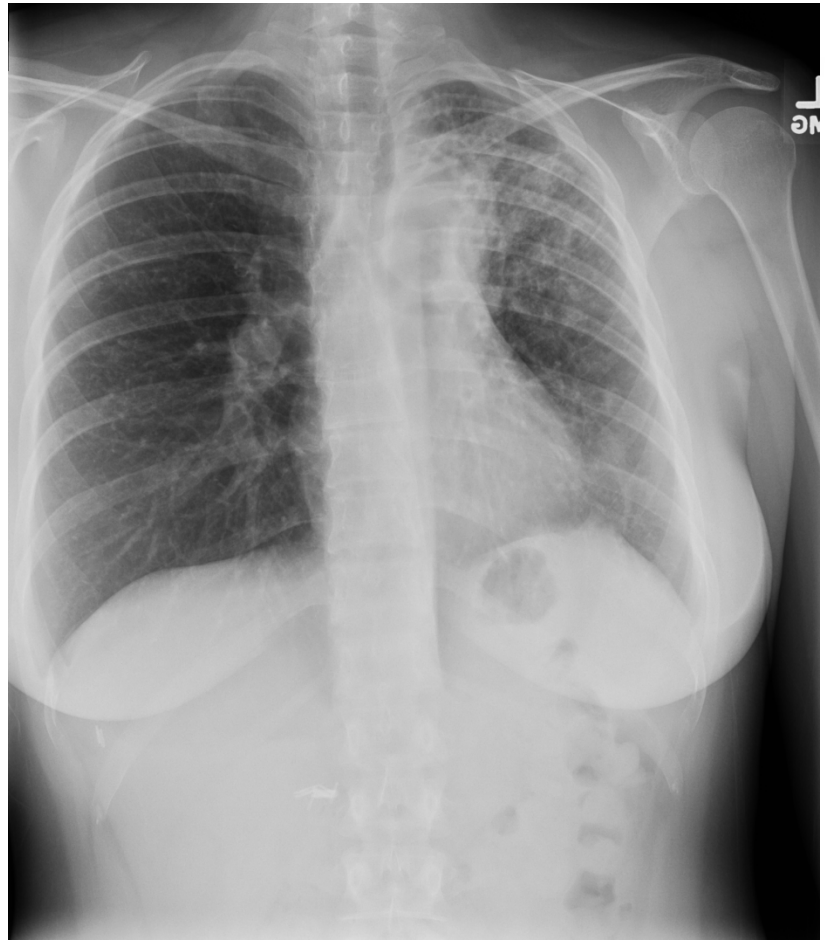
Pediatric Drug Susceptible vs Drug Resistant TB

- Most cases of MDR TB in children are due to contact with an infectious person with MDR TB
- WHO estimates household contacts of patients with drug resistant TB are more likely to become infected than household contacts of persons with drug susceptible TB
- Principles of screening, evaluation and diagnosis are the same, regardless of the source susceptibility pattern, only treatment is different

Reactivation Disease

Adults and older children

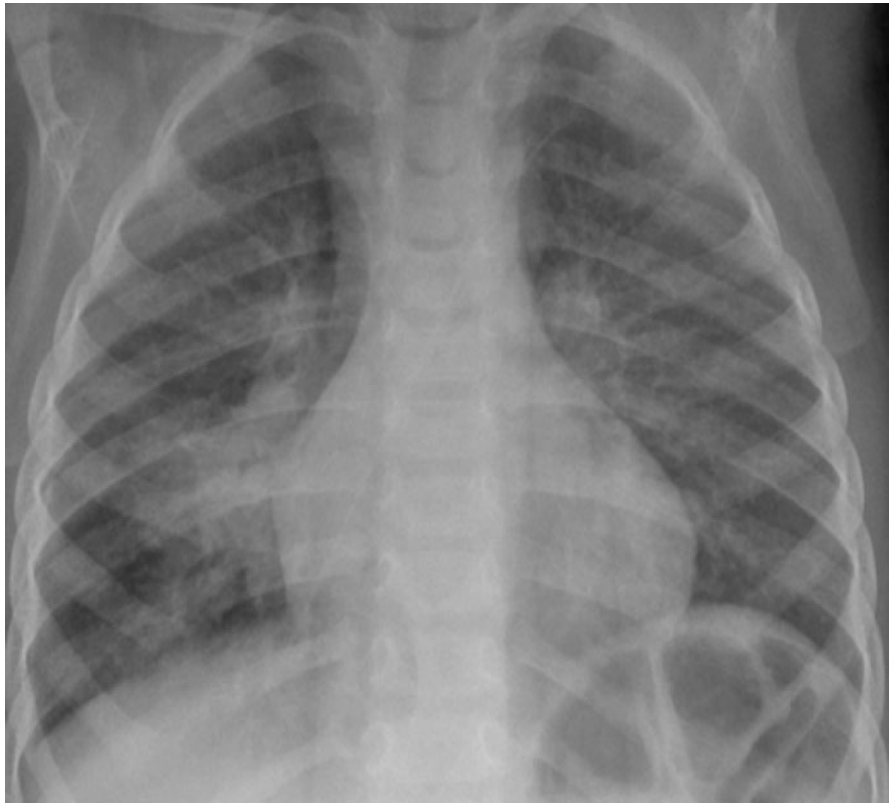
- Occurs years after infection
- Occasionally seen in teens
- May have cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious



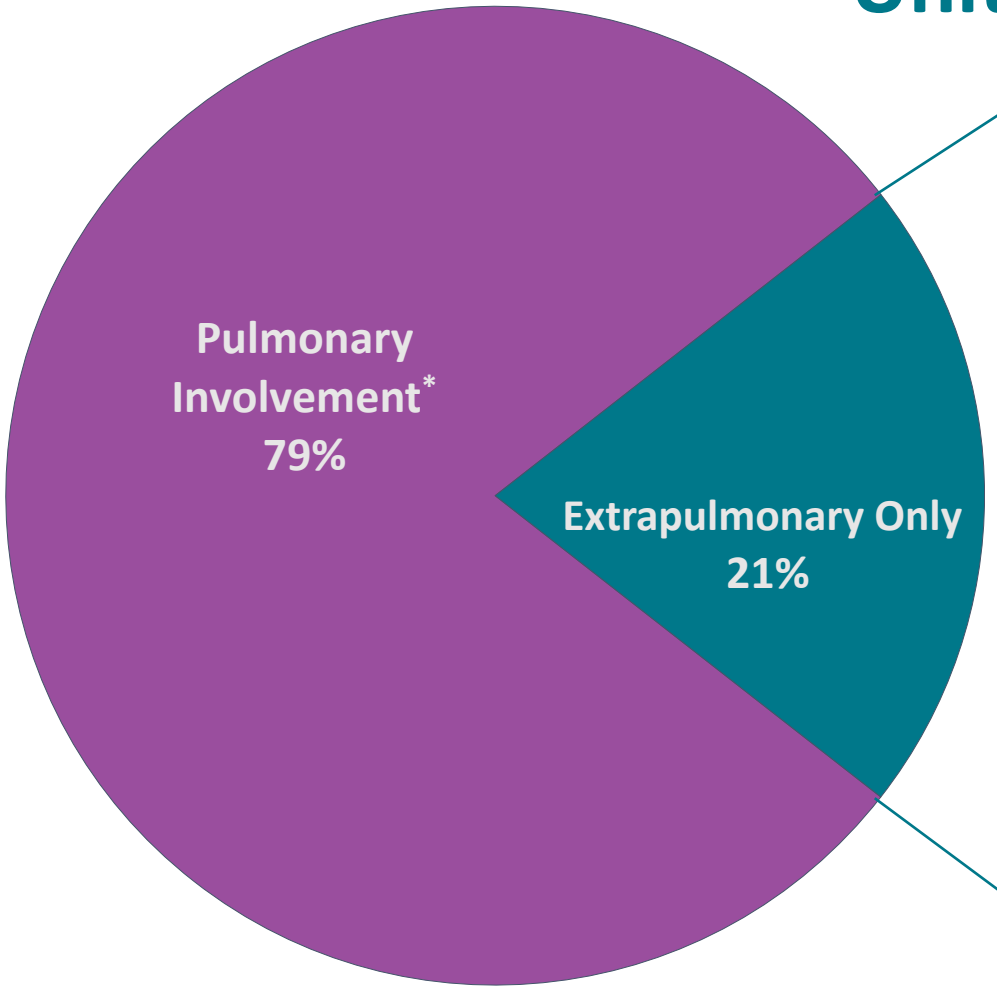
Primary Disease

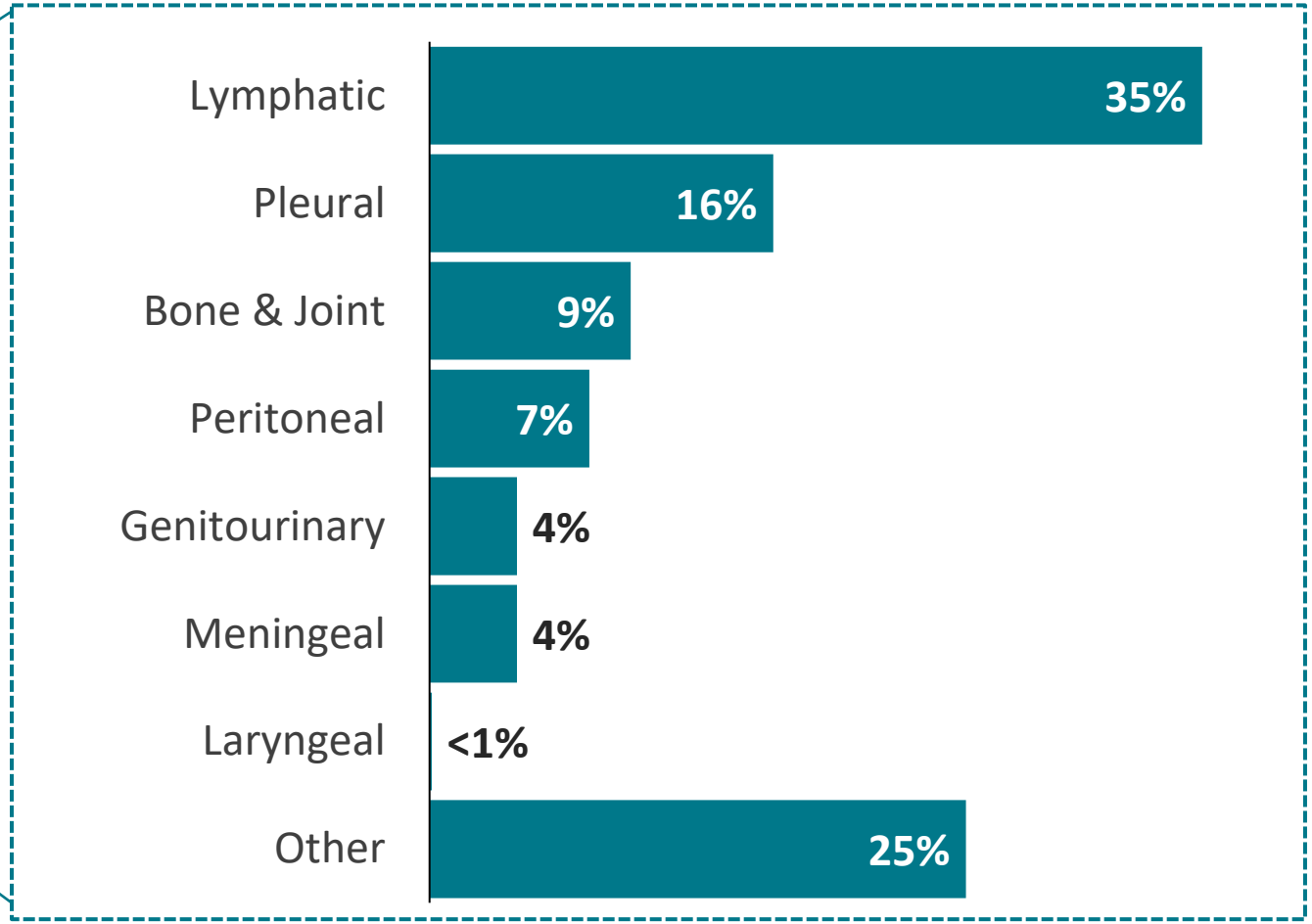
Small children and immunosuppressed

- 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%)



Percentage of TB Cases by Site of Disease, United States, 2020

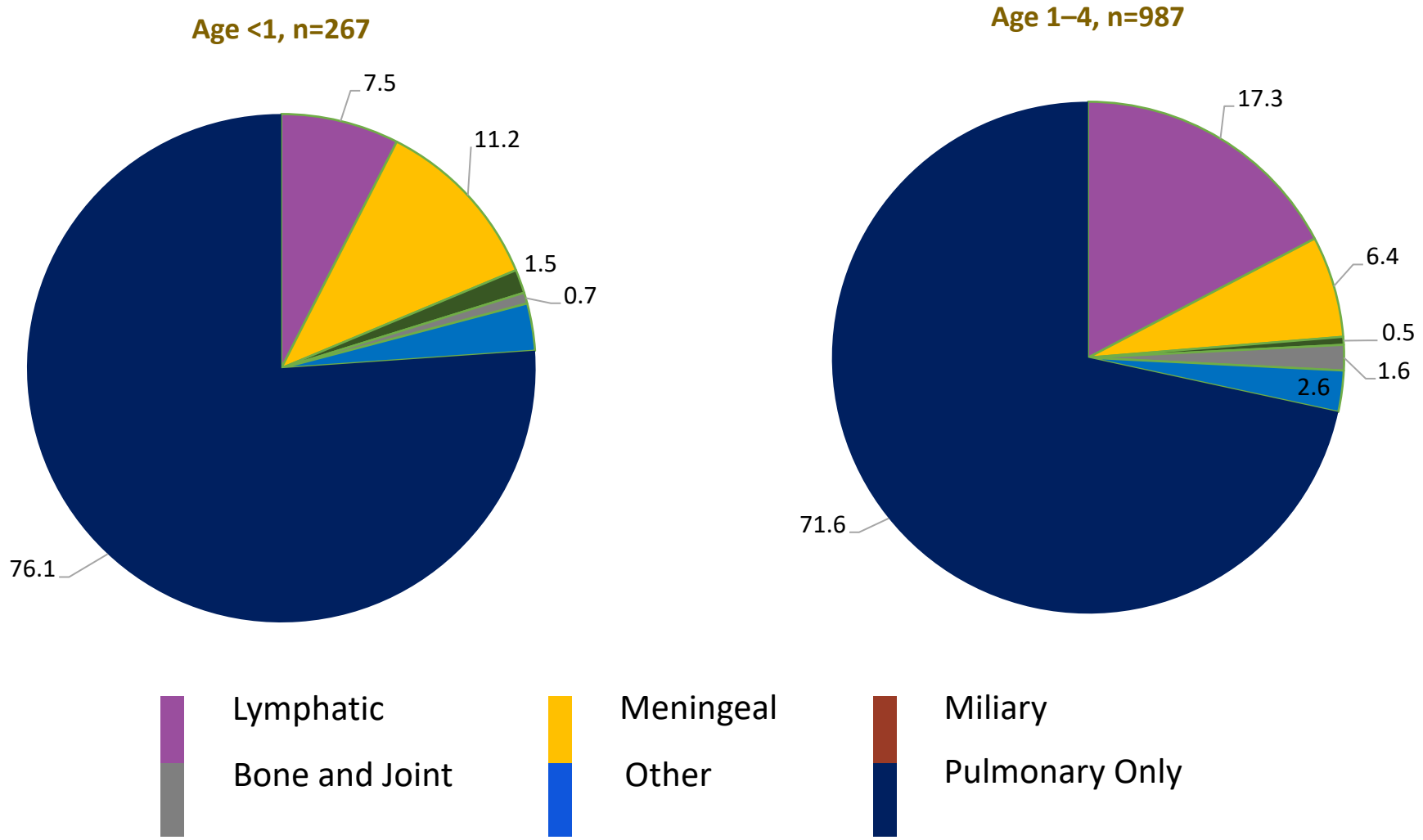




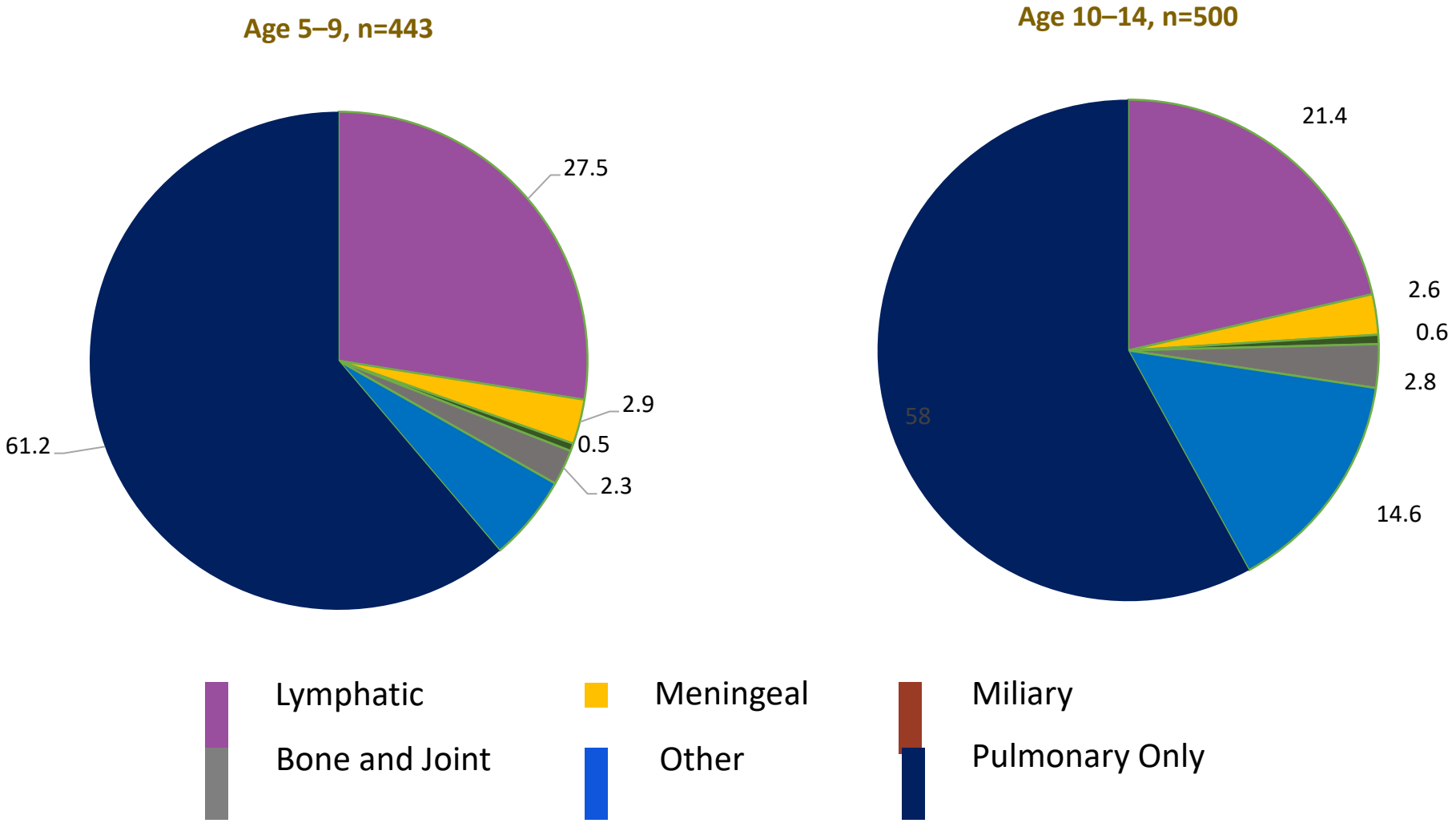
*Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

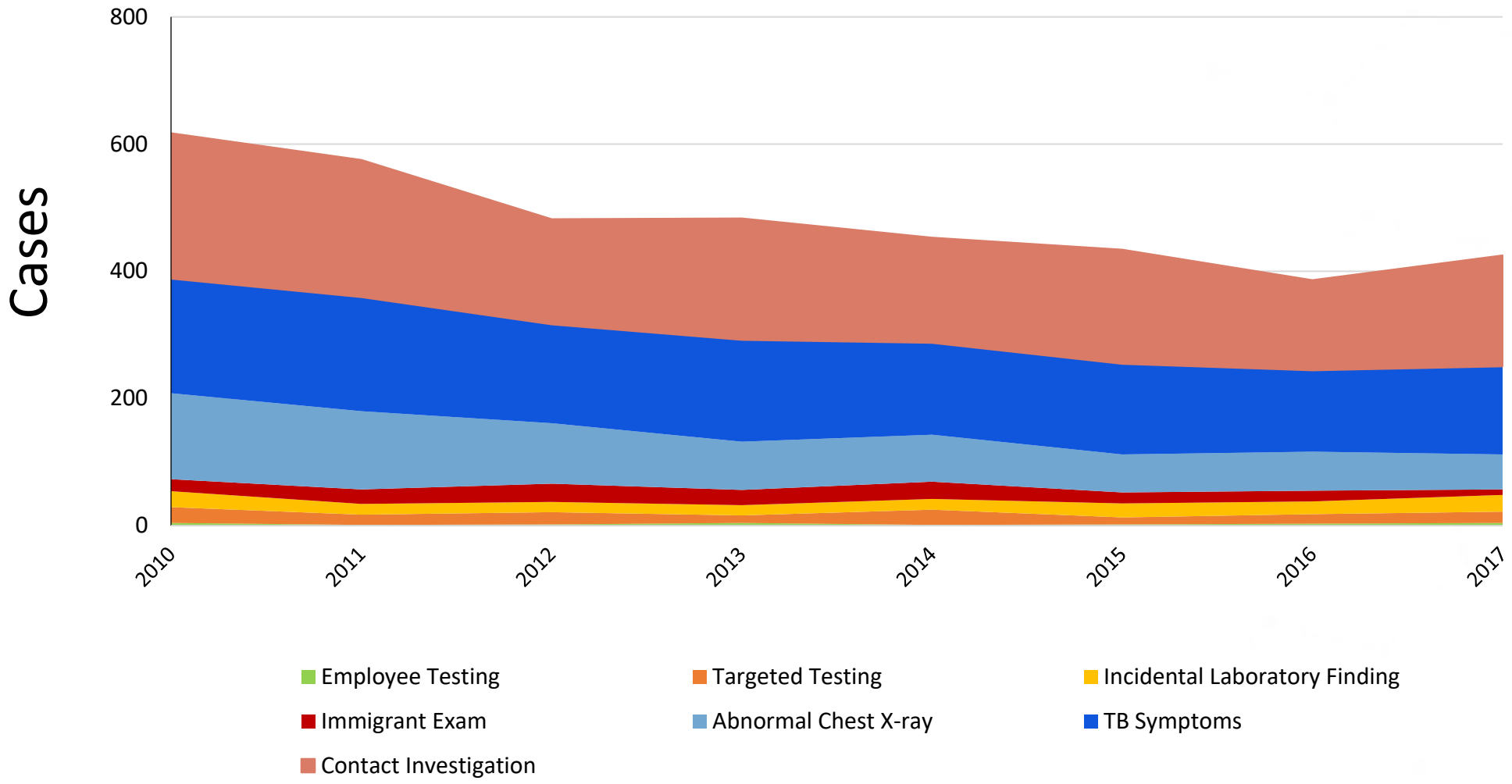
Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Age <5), Summed and Averaged Over 2013–2017



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



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



Treating MDR TB in Children

Window prophylaxis

- Sometimes treat…..sometimes not
- There is no data
- Decision to treat is based on
  - Likelihood of exposure
  - Risk if infected
  - Source case susceptibilities

Treatment for TB Infection – FQ susceptible

- Few studies
- Fluoroquinolones (moxifloxacin or levofloxacin)
- Studies looking at delamanid or bedaquiline
- Few child-friendly formulations

Treatment for TB Infection – FQ susceptible

Group	Medicine	Weight-based daily dose[b]	Formulations (mg/mL, as applicable)	Weight bands[a]								Usual upper daily dose[b]
				3 to <5 kg	5 to <7 kg	7 to <10 kg	10 to <16 kg	16 to <24 kg	24 to <30 kg	30 to <36 kg	36 to <46 kg	
A	Levofloxacin	15–20 mg/kg	100 mg dt	5 mL (0.5 dt)	1	1.5	2	3	-	-	-	1.5 g
			250 mg tab (250 mg in 10 mL = 25 mg/mL)	2 mL[c]	5 mL (0.5 tab)[c]	5 mL (0.5 tab)[c]	1	1.5	2	3	3	1.5 g
	Moxifloxacin	10–15 mg/kg (standard dose)[d]	100 mg dt (100 mg in 10 mL = 10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4	4	400 mg
			400 mg tab (400 mg in 10 mL = 40 mg/mL)	1 mL[c]	2 mL[c]	3 mL[c]	5 mL[c] (0.5 tab)	7.5 mL[c] (0.75 tab)	1	1	1	400 mg

Principles for MDR TB Treatment in Children

- TB cultures for children are frequently negative, source susceptibilities are crucial to appropriate treatment

- Children tend to have minimal disease which gives some flexibility to number of drugs and length of treatment

Drugs for Treatment of MDR in Children

Table 5.11. WHO drug groupings

Group	Drug	Abbreviation
A	Levofloxacin or moxifloxacin	Lfx or Mfx (or M)
	Bedaquiline	Bdq (or B)
	Linezolid	Lzd (or L)
B	Clofazimine	Cfz
	Cycloserine or terizidone	Cs or Trd
C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin in combination with clavulanic acid (amoxiclav)	Ipm-Cln
	Meropenem in combination with clavulanic acid (amoxiclav)	Mpm
	Amikacin or streptomycin [a]	Am or S
	Ethionamide or prothionamide	Eto or Pto
	P-aminosalicylic acid	PAS

[a] Amikacin and streptomycin are to be considered only in adolescents aged over 18 years and only if DST results confirm susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

Require IV administration

NOT recommended for children < 18 y/o

Weaker, more toxic options

Table 5.13. Cerebrospinal fluid penetration of TB medicines used for treatment of multidrug-resistant and rifampicin-resistant TB

Medicine	CSF penetration
Levofloxacin, moxifloxacin, linezolid, cycloserine, ethionamide, meropenem, pyrazinamide	Good penetration
Isoniazid in presence of isoniazid resistance, P-aminosalicylic acid, amikacin	Poor penetration, except in presence of meningeal inflammation
Ethambutol	Poor penetration
Bedaquiline, delamanid, clofazimine	Limited data available

WHO Recommendations

Table 5.12. Possible individualized multidrug-resistant and rifampicin-resistant TB treatment regimens for children of all ages and adolescents, by fluoroquinolone resistance and disease severity

Fluoroquinolone susceptibility	Regimen [a]	Additional medicines
Fluoroquinolone-susceptible	Bdq–Lfx–Lzd–Cfz-(Cs)	Cs, Dlm, PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant	Bdq–Lzd–Cfz–Cs–(Dlm) [e]	Dlm [e], PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant and bedaquiline (±clofazimine)-resistant	Lzd–Cs–Dlm [e]–E–Z [d]	Mpm/Clav, Eto [b,c], PAS [c]

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E:ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem–clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

[a] Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

[b] Use ethionamide only if the child or source case does not have a known or suspected *inhA* mutation.

[c] P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

[d] Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

[e] When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

BPaL…..BDaL?

- BPaL and BPaLM can be used in patients age ≥ 14 years of age
- Pretomanid (P) and Delamanid (D) are closely related, data suggests delamanid may be a little better
- Pretomanid can only be used in children 14 and older, delamanid can only be obtained by compassionate use

Table 5.14. Adverse effects of medicines used for multidrug-resistant and rifampicin-resistant TB by group

Group and name	Main adverse effects
WHO Group A	
Levofloxacin (Lfx)	Sleep disturbance Gastrointestinal disturbance Arthralgia/arthritis Headache Idiopathic raised intracranial pressure
Moxifloxacin (Mfx)	As for levofloxacin QT interval prolongation
Bedaquiline (Bdq)	Headache Nausea Liver dysfunction QT interval prolongation Arthralgia
Linezolid (Lzd)	Diarrhoea Headache Nausea Myelosuppression Peripheral neuritis Optic neuritis Lactic acidosis Pancreatitis

Additional Toxicities

WHO Group B	
Clofazimine (Cfz)	Skin discolouration Ichthyosis QT interval prolongation Abdominal pain
Cycloserine (Cs)/terizidone (Trd)	Neurological and psychological adverse effects Severe depression and suicidal ideation in adolescents

WHO Group C	
Ethambutol (E)	Optic neuritis
Delamanid (Dlm)	Nausea and vomiting Dizziness Paraesthesia Anxiety QTc prolongation Hallucinations and night terrors
Pyrazinamide (Z)	Arthralgia/arthritis (especially together with fluoroquinolone use) Hepatitis Skin rashes
Meropenem (Mpm)	Hypersensitivity reactions Seizures Nausea and vomiting Diarrhoea Hepatic and renal dysfunction
Amikacin[a] (Am) or streptomycin (S)	Ototoxicity (irreversible) Nephrotoxicity
Ethionamide (Eto)/ prothionamide (Pto)	Gastrointestinal intolerance Metallic taste Hypothyroidism
P-aminosalicylic acid (PAS)	Gastrointestinal intolerance Hypothyroidism Hepatitis
Other medicines	
Isoniazid (H) high-dose[b]	Hepatitis Peripheral neuropathy
Amoxicillin-clavulanate (amoxiclav)	Gastrointestinal intolerance Hypersensitivity reactions Seizures Hepatic and renal dysfunction
Pretomanid	Peripheral neuropathy Acne Anaemia Nausea and vomiting Headache Liver dysfunction Rash Pruritus Gastrointestinal intolerance

[a] Not recommended for use in children and adolescents aged under 18 years.

[b] If isoniazid is used, supplement with pyridoxine (vitamin B6) in infants and adolescents, in malnourished children, in children living with HIV, and when high-dose isoniazid is used to prevent peripheral neuropathy.

Source: adapted from Schaaf HS, Thee S, van der Laan L, et al. Adverse effects of oral second-line antituberculosis drugs in children. Expert Opin Drug Saf. 2016;15(10):1369–1381 *(124)*; and https://www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf.

Monitoring for Toxicity in Children

- Adolescents can likely give a good history if you engage them
- Older children, with work, can let you if something is wrong
- Infants and children: mostly dependent on the parents feedback
- Be mindful of the questions you ask……

Take Home Points

- Contact investigations around a source case to identify children is critical public health work
- There is little data for treatment of MDR TB in children (mostly modeled after adult disease) but good outcomes
- Toxicity associated with MDR TB treatment in children is not widely reported

Thank you for your attention

Questions?

Lisa.Armitige@dshs.texas.gov

1-800-TEX-LUNG

www.HeartlandNTBC.org