PEDIATRIC TB & LTBI

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NO DISCLOSURES

LEARNING OBJECTIVES

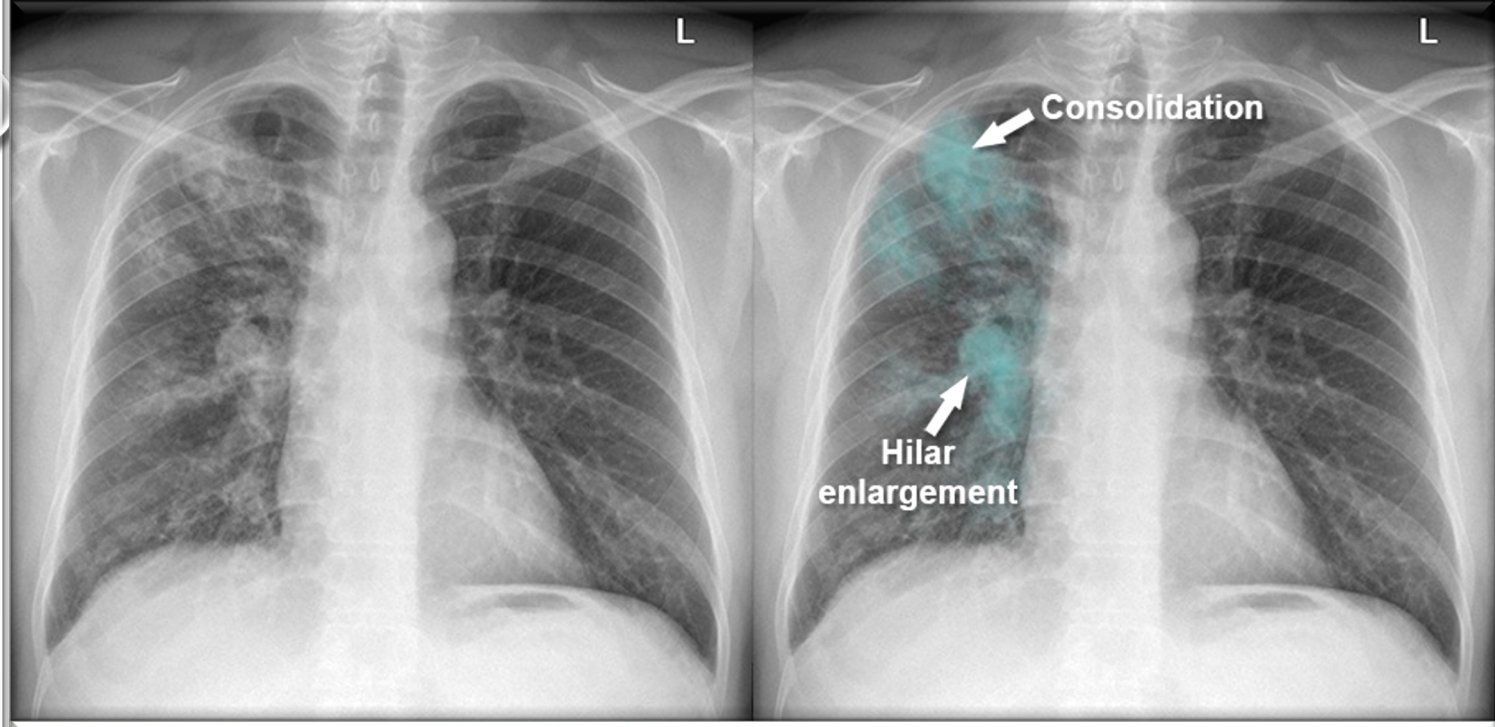
- UNDERSTAND EPIDEMIOLOGY OF ACTIVE PEDIATRIC TB

- IDENTIFY AND ASSESS YOUNG CHILDREN AT RISK OF TB EXPOSURE OR PROGRESSION
  - IMMUNOSUPPRESSED
  - BIRTH/TRAVEL IN ENDEMIC AREA
  - KNOWN TB EXPOSURE

- UNDERSTAND HOW TO RULE OUT TB DISEASE BEFORE DIAGNOSING LTBI

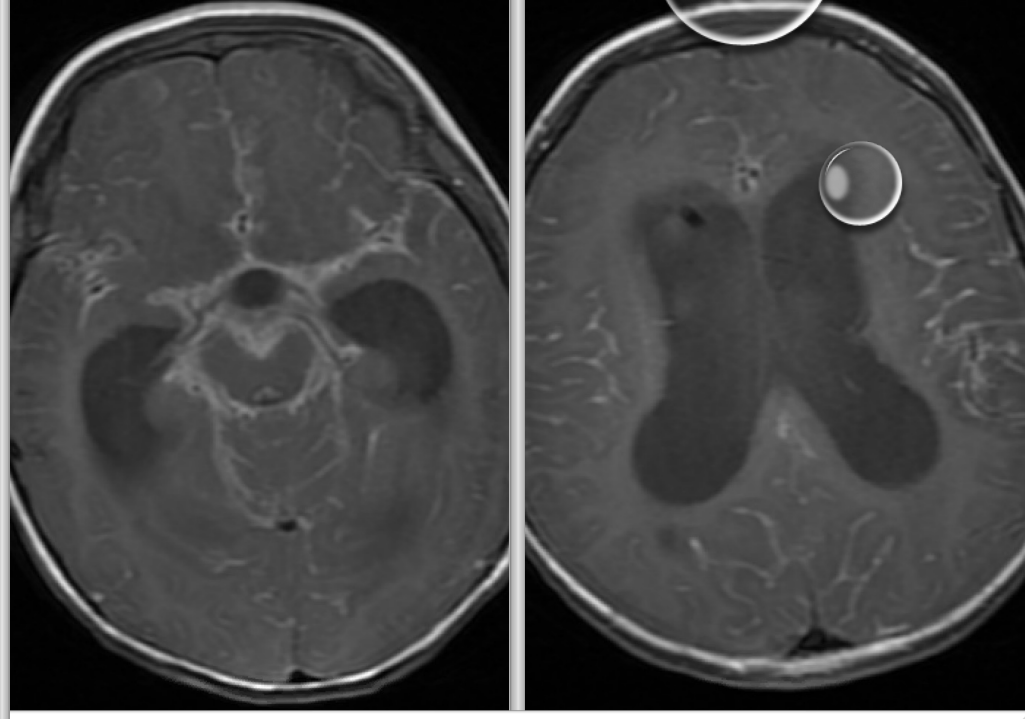
- TREATING LTBI AND TB DISEASE

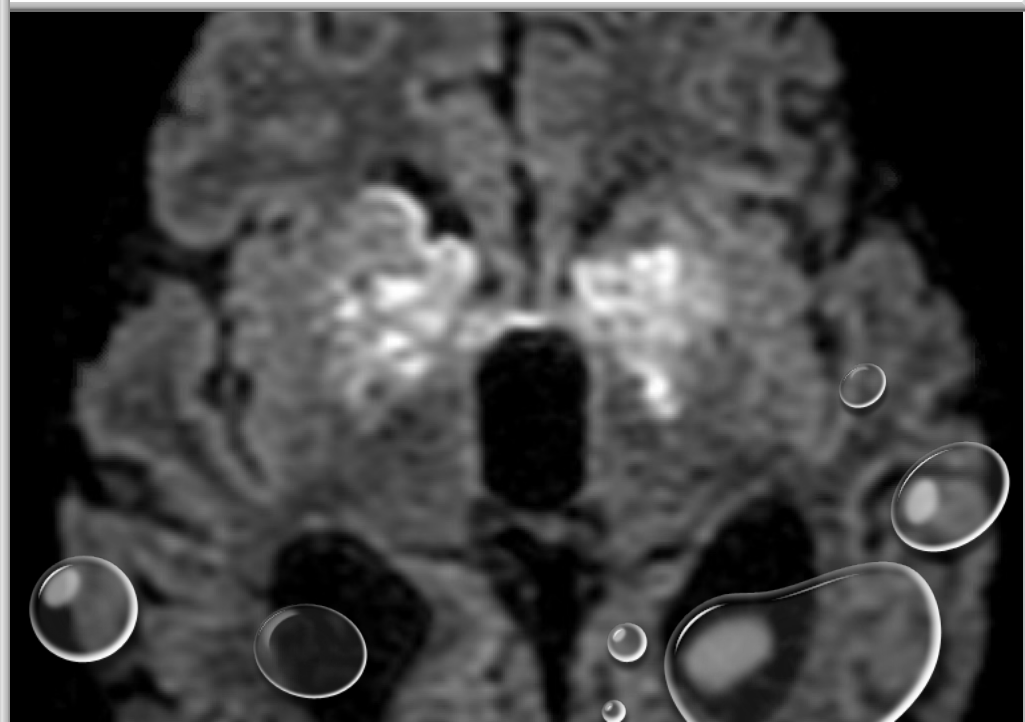
WHY DO WE CARE ABOUT TB?



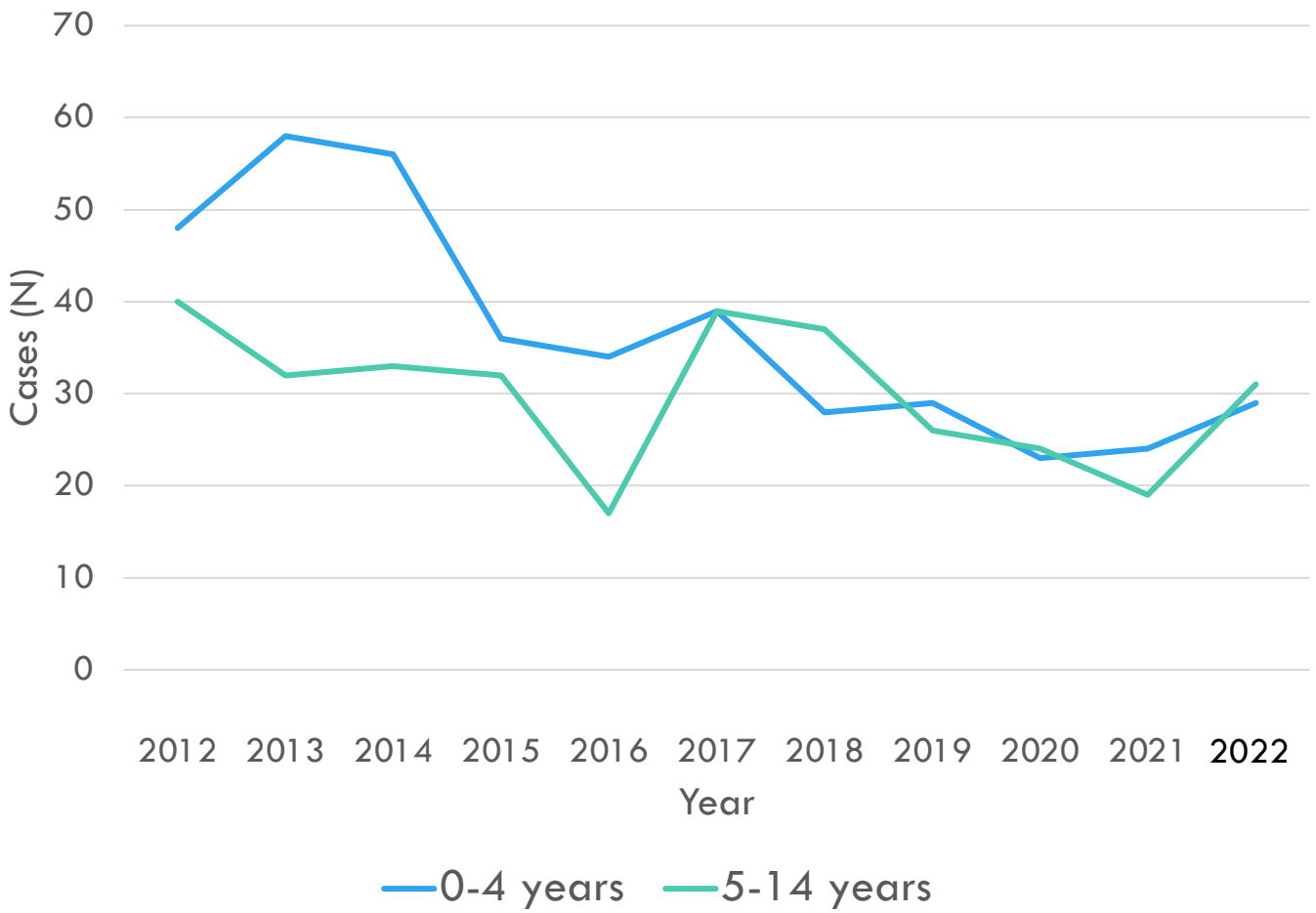
LIFELONG CONSEQUENCES, BUT PREVENTABLE!

- 1YO MO US-BORN MALE WITH TRAVEL TO MEXICO
- RECURRENT ER VISITS FOR FEVERS, URI SX
- FINAL PRESENTATION WITH STROKE



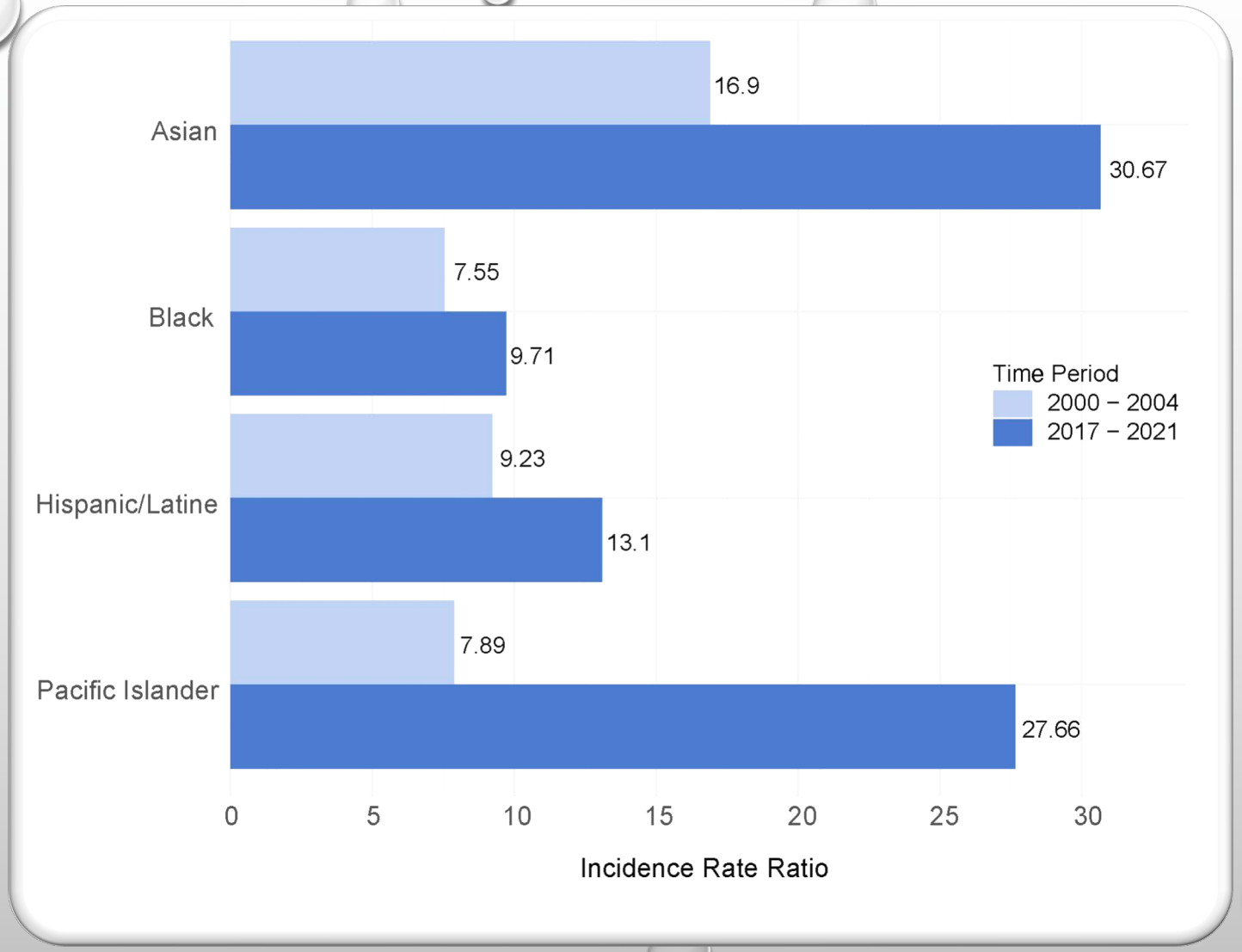


PEDIATRIC TB CASES <15 YEARS OLD, CALIFORNIA



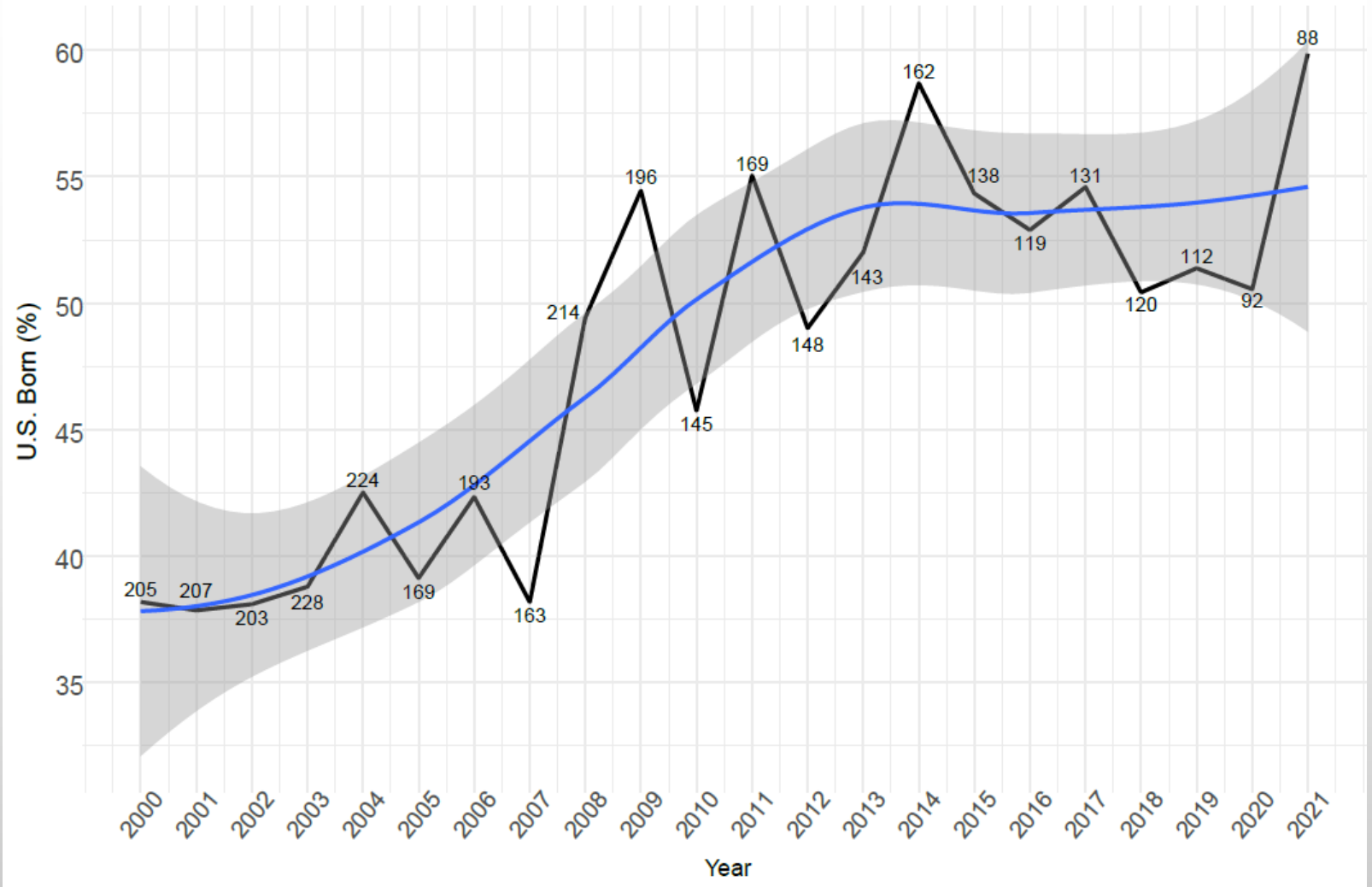
DEMOGRAPHIC CHARACTERISTICS 2000-2021

	Age 0-4 (N=1566)	Age 5-17 (N=1986)	Age 18-24 (N=4279)	Total: All < 25 (N=7831)
Sex				
Male	807 (51.5%)	975 (49.1%)	2427 (56.7%)	4209 (53.7%)
Female	759 (48.5%)	1010 (50.9%)	1852 (43.3%)	3621 (46.2%)
Race/Ethnicity				
White	73 (4.7%)	85 (4.3%)	185 (4.3%)	343 (4.4%)
Black	92 (5.9%)	127 (6.4%)	295 (6.9%)	514 (6.6%)
Hispanic/Latine	1084 (69.2%)	1240 (62.4%)	2242 (52.4%)	4566 (58.3%)
Asian	295 (18.8%)	504 (25.4%)	1529 (35.7%)	2328 (29.7%)
American Indian or Alaskan Native	2 (0.1%)	1 (0.1%)	3 (0.1%)	6 (0.1%)
Native Hawaiian or Pacific Islander	12 (0.8%)	18 (0.9%)	16 (0.4%)	46 (0.6%)
Multiple Races	3 (0.2%)	5 (0.3%)	4 (0.1%)	12 (0.2%)
Origin				
U.S. Born	1317 (84.1%)	1061 (53.4%)	1191 (27.8%)	3569 (45.6%)
Non-U.S. Born	248 (15.8%)	921 (46.4%)	3083 (72.0%)	4252 (54.3%)

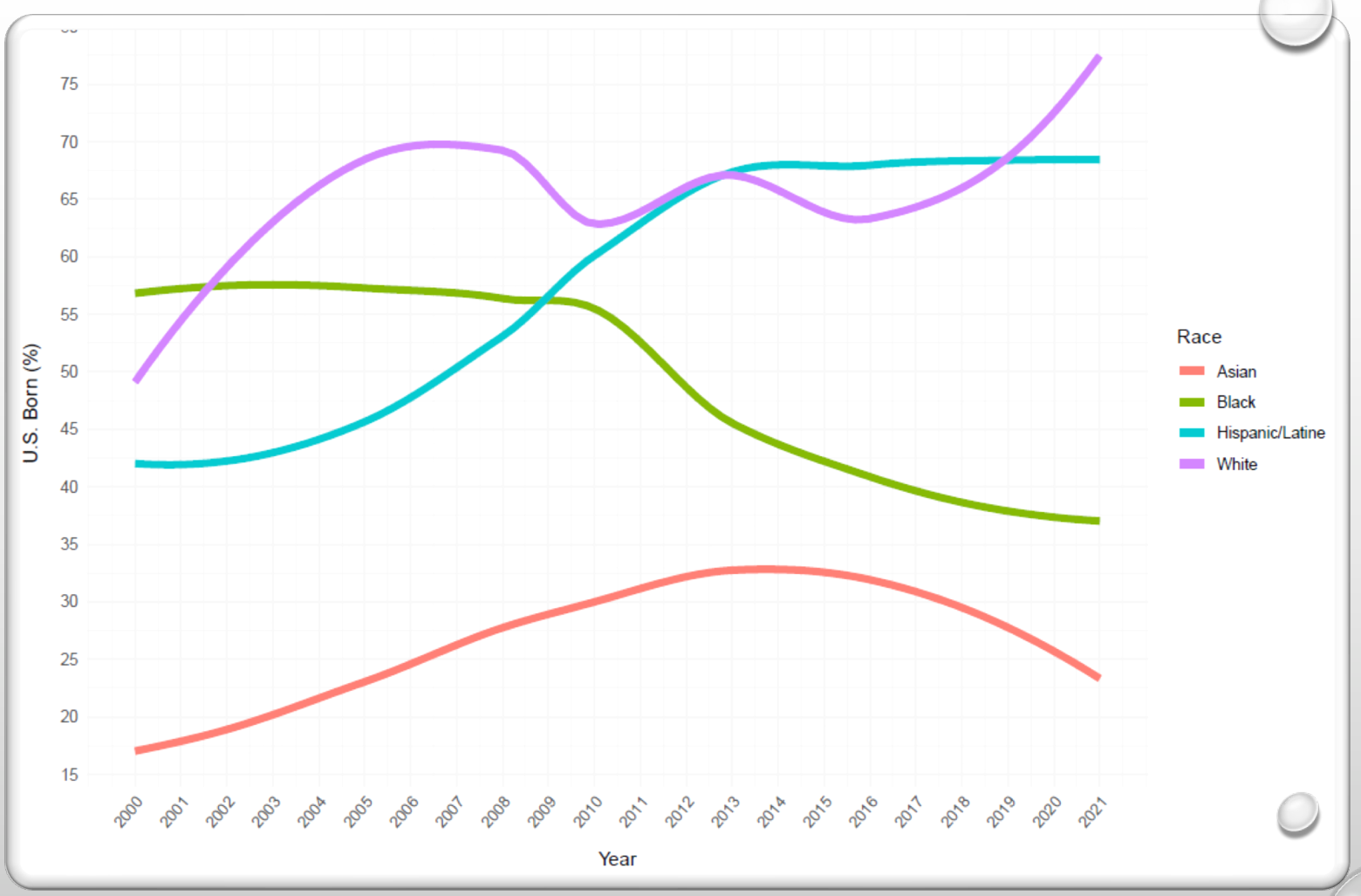


DISPARITIES AMONG TB CASES IN CHILDREN IN CA ARE WIDE AND INCREASING

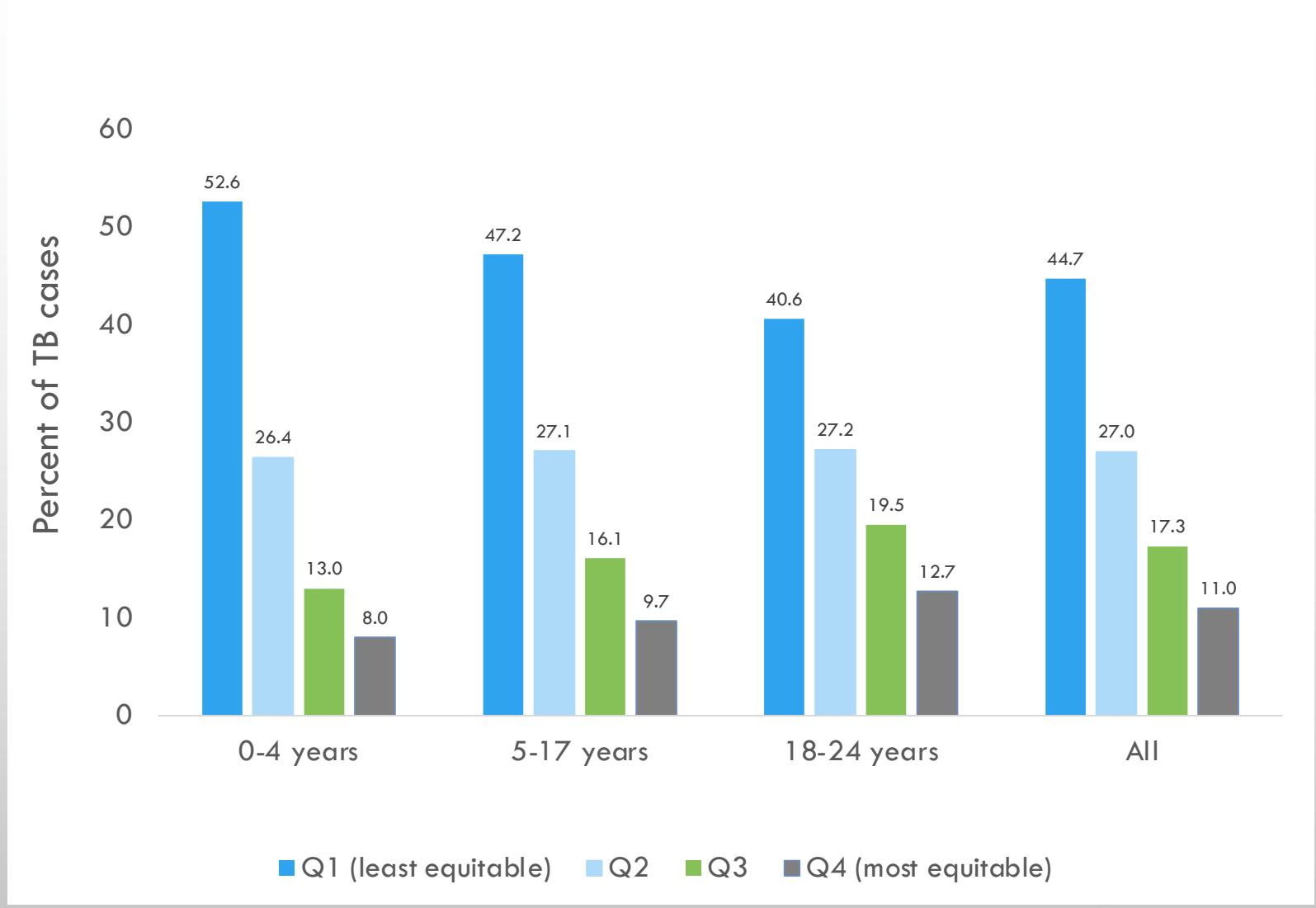
INCREASING PROPORTION OF TB CASES AMONG YOUTH <25 YEARS THAT ARE BORN IN US



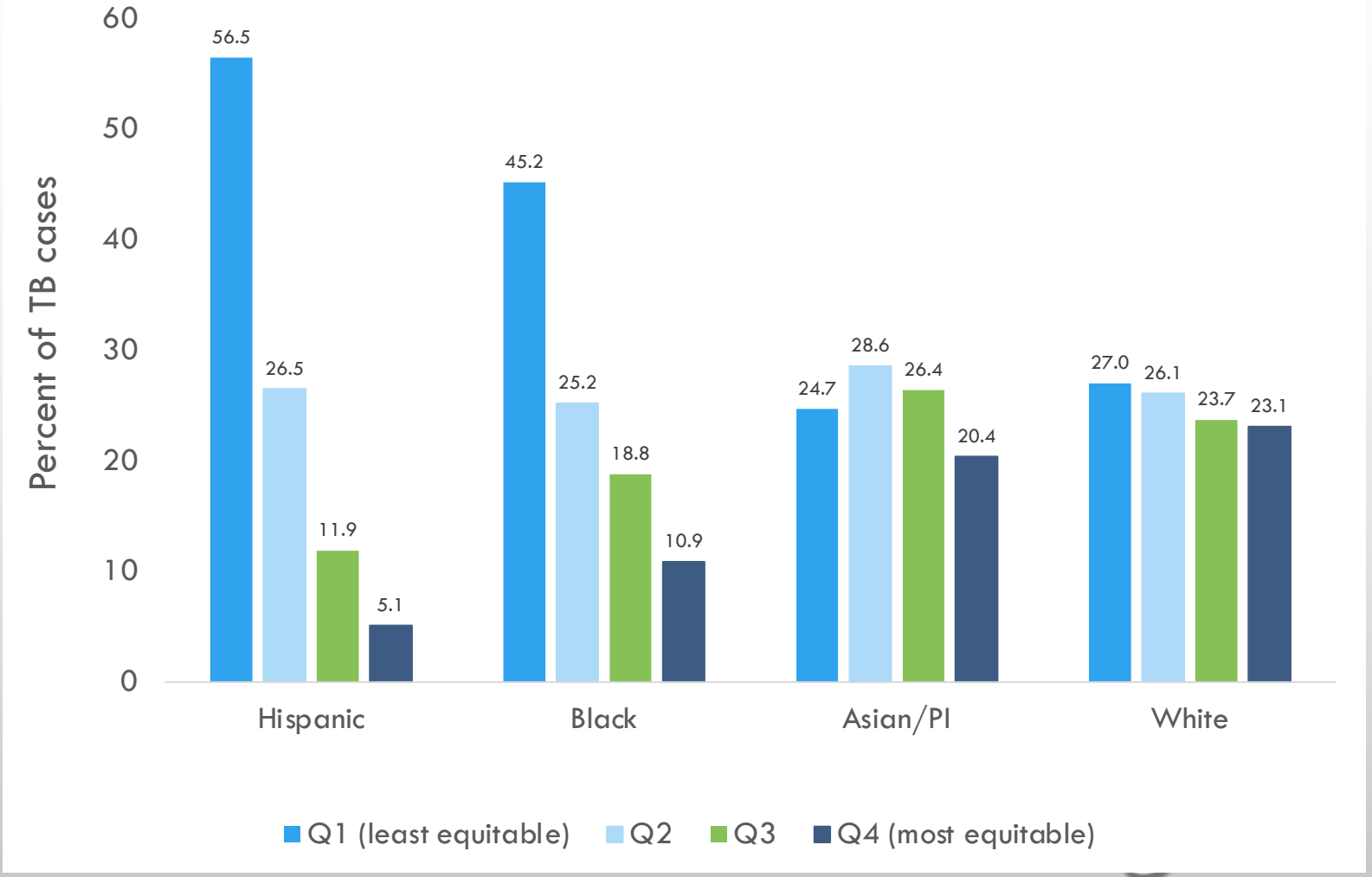
BIRTH PLACE OUTSIDE OF US BY RACIAL/ETHNIC GROUP



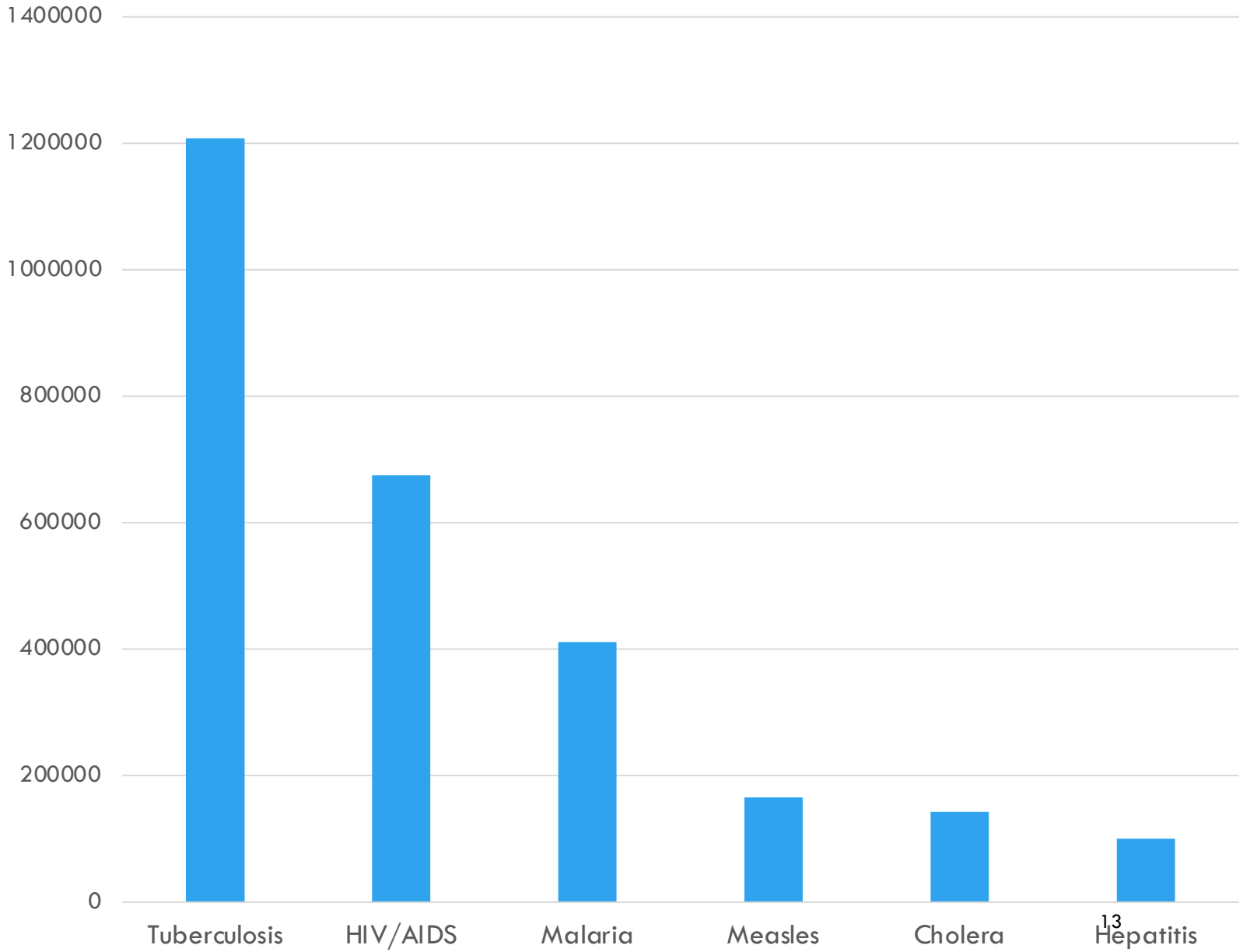
HEALTHY PLACES INDEX BY AGE GROUP



HEALTHY PLACES INDEX BY RACIAL/ETHNIC GROUP



GLOBAL DEATHS FROM COMMUNICABLE DISEASE, 2019

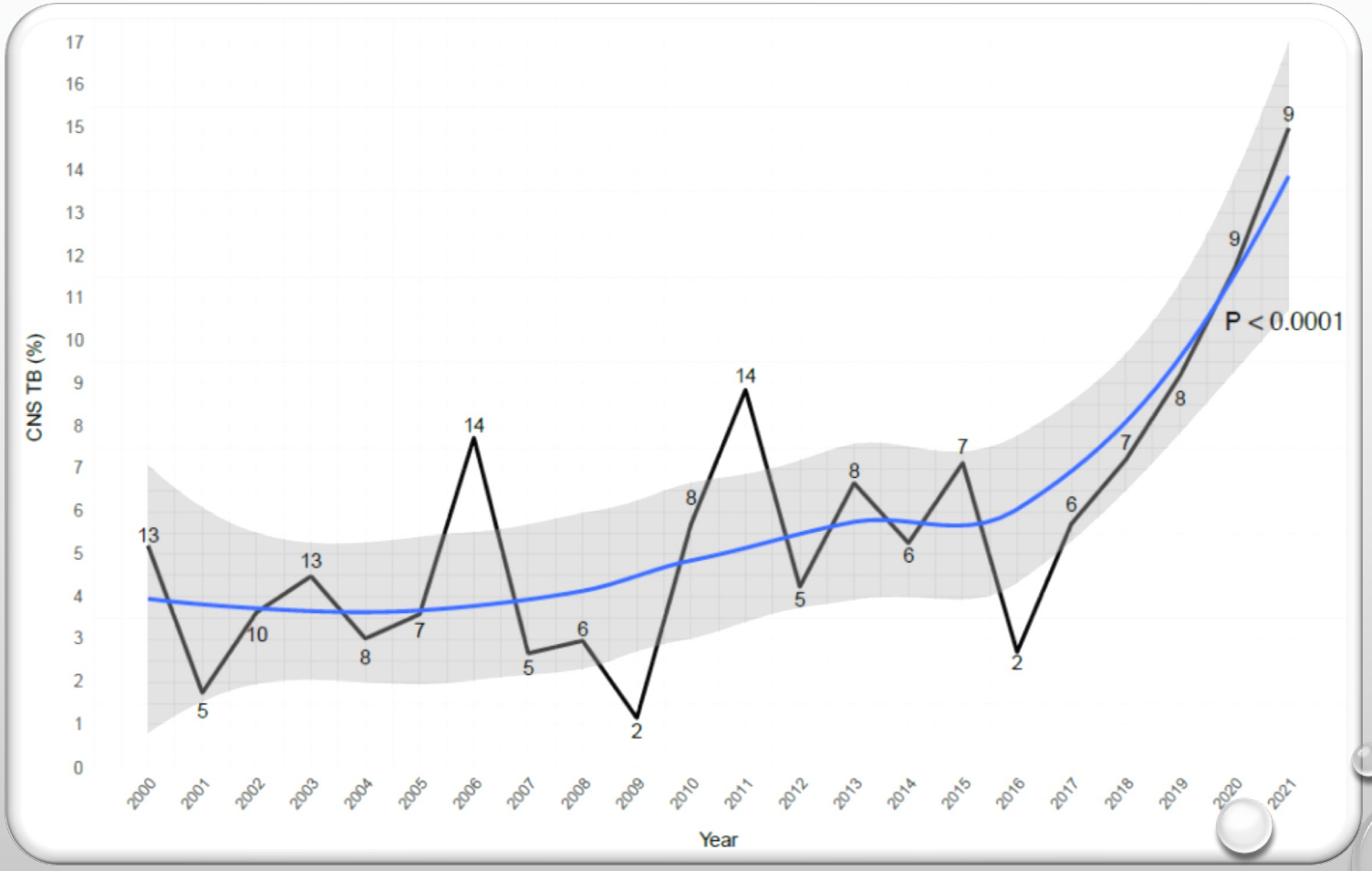


Statisa, published 2022

TB IS DEADLY IN CALIFORNIA

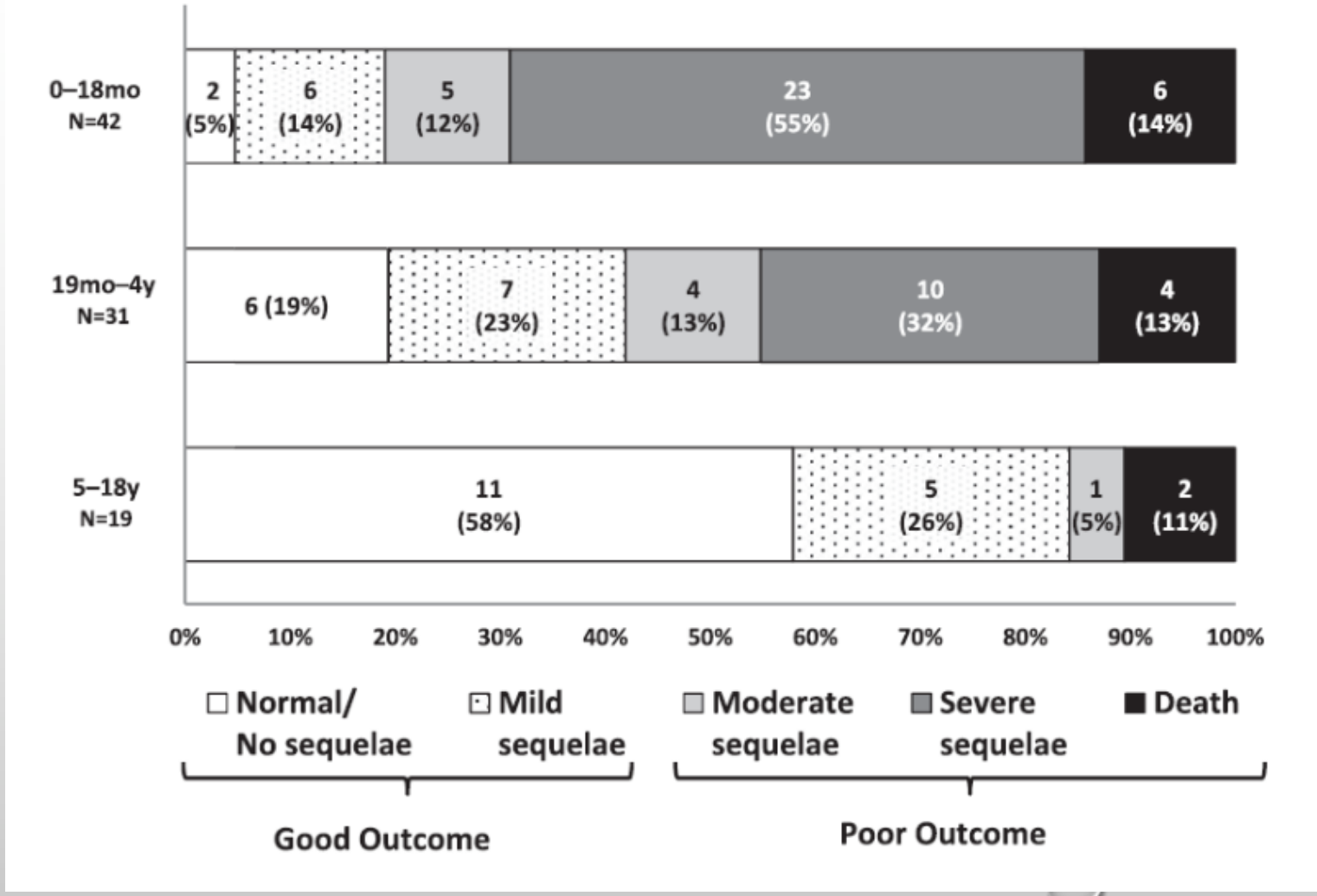
- IN 2020, 226 (**13% OF ALL TB CASES**) PEOPLE WITH TB DIED; THE HIGHEST PROPORTION SINCE 1993

- ~1/4 DIED BEFORE RECEIVING ANY TB TREATMENT



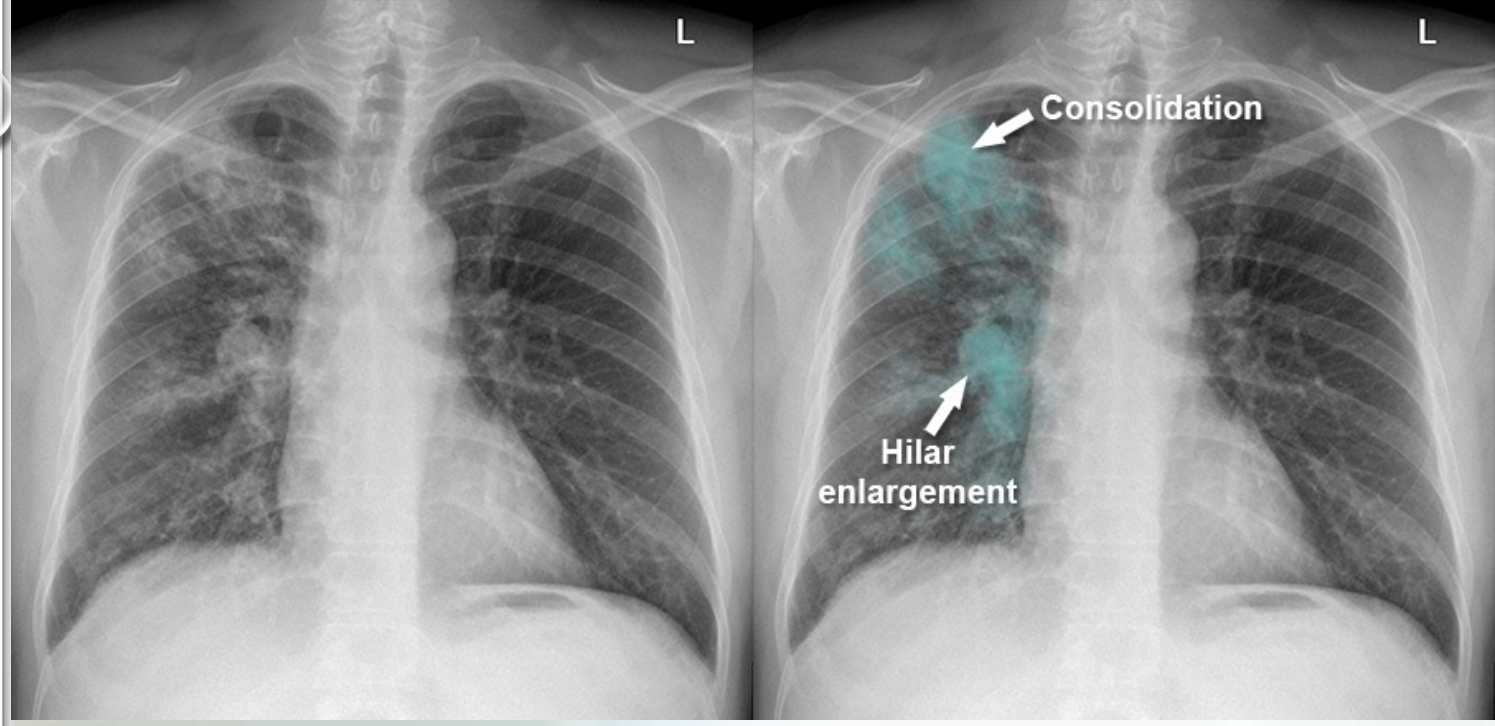
% OF TB PATIENTS CENTRAL NERVOUS SYSTEM TB AMONG YOUTH <18

CNS TB OUTCOMES BY AGE (CA 1993-2011)

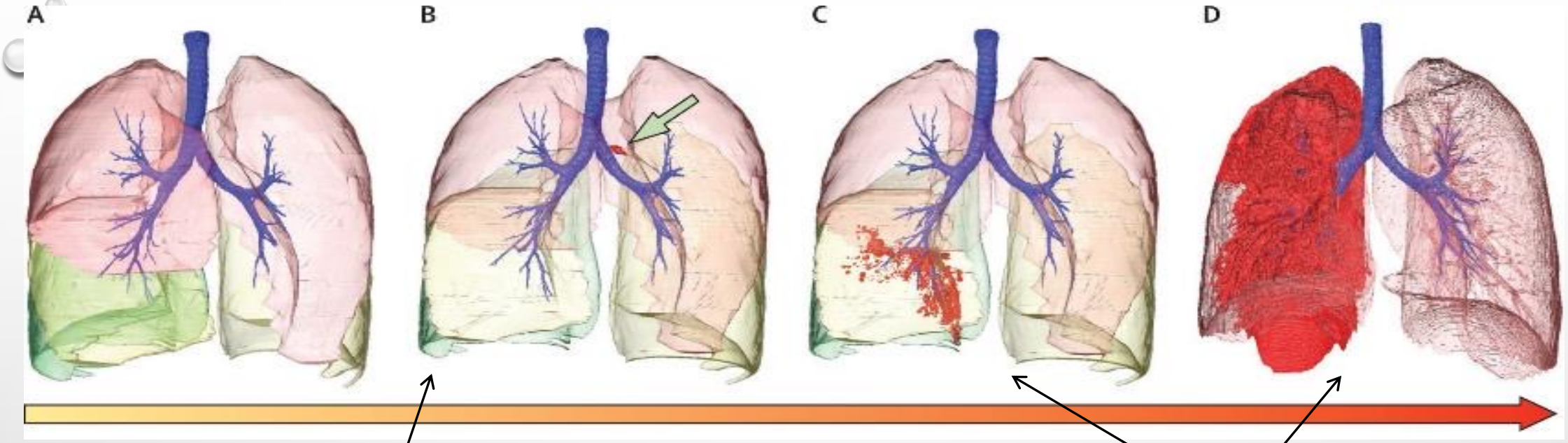


TB 101

TB VS LTBI IN KIDS



Goal Prevent Infectious TB



Latent TB Infection

- ***Absence of TB symptoms***
- Positive TST[1] or IGRA[2] result
- Chest radiograph normal
- Not infectious

Active TB Disease

- ***Symptoms such as cough, fever***
- TST or IGRA is usually positive
- Chest radiograph is usually abnormal
- Respiratory specimens usually culture positive (smear positive in about 50% of patients)

Image: Dheda K. Lancet, 2016

YOUNG CHILDREN WITH LTBI HAVE HIGHER RISK FOR PROGRESSION TO SEVERE TB

Age at primary infection	Any TB disease	Pulmonary disease	TB meningitis or miliary disease
<1 year	**50%**	30-40%	**10-20%**
1-2 years	**20-30%**	10-20%	**2-5%**
2-5 years	**5%**	5%	**0.5%**
5-10 years	2%	2%	<0.5%
>10	10-20%	10-20%	<0.5%

ADAPTED FROM MARAIS BJ ET AL. THE NATURAL HISTORY OF CHILDHOOD INTRA-THORACIC TUBERCULOSIS – A CRITICAL REVIEW OF THE PRE-CHEMOTHERAPY LITERATURE. INT J TUBERC LUNG DIS. 2004;8:392-402.

PREVALENCE OF ACTIVE TB AMONG CONTACTS IN HIGH-INCOME COUNTRIES*

	Included studies	Contacts with active TB	Contacts Screened	Proportion (%)	95% CI
All ages	*Fox GJ et al. *Eur Respir J* 2013; 41: 140-156				
All	87	5058	308048	1.4	1.1-1.8
Index smear +	27	1704	72936	3.3	2.2-4.8
Index XDR/MDR	2	0	554	0.0	
Household contact	29	2047	56221	3.0	2.0-4.4
All close contacts	45	3053	127699	1.9	1.3-2.7
Casual contacts	9	73	15607	0.4	0.2-0.6
HIV+ contacts	2	15	133	11.4	7.0-18.0
≤ 5 years	**10**	**212**	**4057**	**4.7**	**3.4-6.4**
5-14 years	9	253	5665	2.9	1.7-5.1
15 years +	9	507	17867	2.3	1.1-4.8

INTERFERON GAMMA RELEASE ASSAYS (IGRAS) VS. TUBERCULIN SKIN TEST (TST)

IGRA

- BLOOD DRAW
- **SPECIFIC SINGLE ANTIGENS**
- NO BOOSTING
- **NOT AFFECTED BY BCG**
- ONE PATIENT VISIT
- **MINIMAL INTER-READER VARIABILITY**

TST

- SKIN PRICK
- MULTIPLE ANTIGENS
- BOOSTING
- CAN BE AFFECTED BY BCG
- TWO PATIENT VISITS (F/U 48-72HRS)
- SIGNIFICANT INTER-READER VARIABILITY, SO TEST CAN BE INTERPRETED INCORRECTLY

IGRAS ARE BETTER SCREENING TESTS FOR ALL AGES

SUMMARY OF TST AND IGRA TEST CHARACTERISTICS FOR TB INFECTION IN YOUNG CHILDREN

Reference	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Bakir 2008 [18]				
TST	80 (52–96)	27 (25–31)	1.6 (0.8–3.0)	98.4 (96.0–99.6)
ELISPOT (T-SPOT like test)	73 (45–92)	59 (55–62)	2.9 (1.5–5.1)	99.2 (98.1–99.8)
Diel 2011 [13]				
TST	100 (29–100)	67 (45–84)	37.5 (9–76)	100 (79–100)
QFT-GIT	100 (29–100)	71 (49–87)	43 (10–82)	100 (80–100)
Stout 2018 [10]				
TST	69.1 (58.5–79.7)	73.9 (69.6–77.9)	10.0 (4.8–16.5)	98.3 (96.7–99.3)
QFT-GIT	71.2 (55.3–86.5)	98.9 (97.4–99.9)	73.1 (41.3–95.3)	98.8 (97.4–99.6)
T-SPOT	58.9 (42.7–76.2)	99.4 (98.4–99.9)	79.2 (52.0–96.3)	98.3 (96.5–99.4)
Ahmed 2020 [15]				
TST	50.0 (15.0–85.0)	73.4 (71.9–74.8)	0.2 (0.1–0.8)	99.9 (99.7–100)
QFT-GIT	75.0 (30.1–95.4)	90.1 (89.1–91.1)	0.9 (0.3–2.5)	100.0 (99.8–100)
T-SPOT	50.0 (15.0–85.0)	92.9 (92.0–93.7)	0.8 (0.2–2.9)	99.9 (99.8–100)

Abbreviations: CI, confidence interval; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

SAME

IGRA BETTER

IGRA BETTER

SAME

Turner et al, Journal of the Pediatric Infectious Diseases Society, 2023

CHILDREN <2 YEARS OLD WITH NEGATIVE QFT UNLIKELY TO PROGRESS TO TB DISEASE

Aggregate of 4 studies with data for children <2 years old:

- 0 cases of TB among 575 untreated children who were QFT negative
- 0 cases of TB among 70 who were QFT neg but TST pos

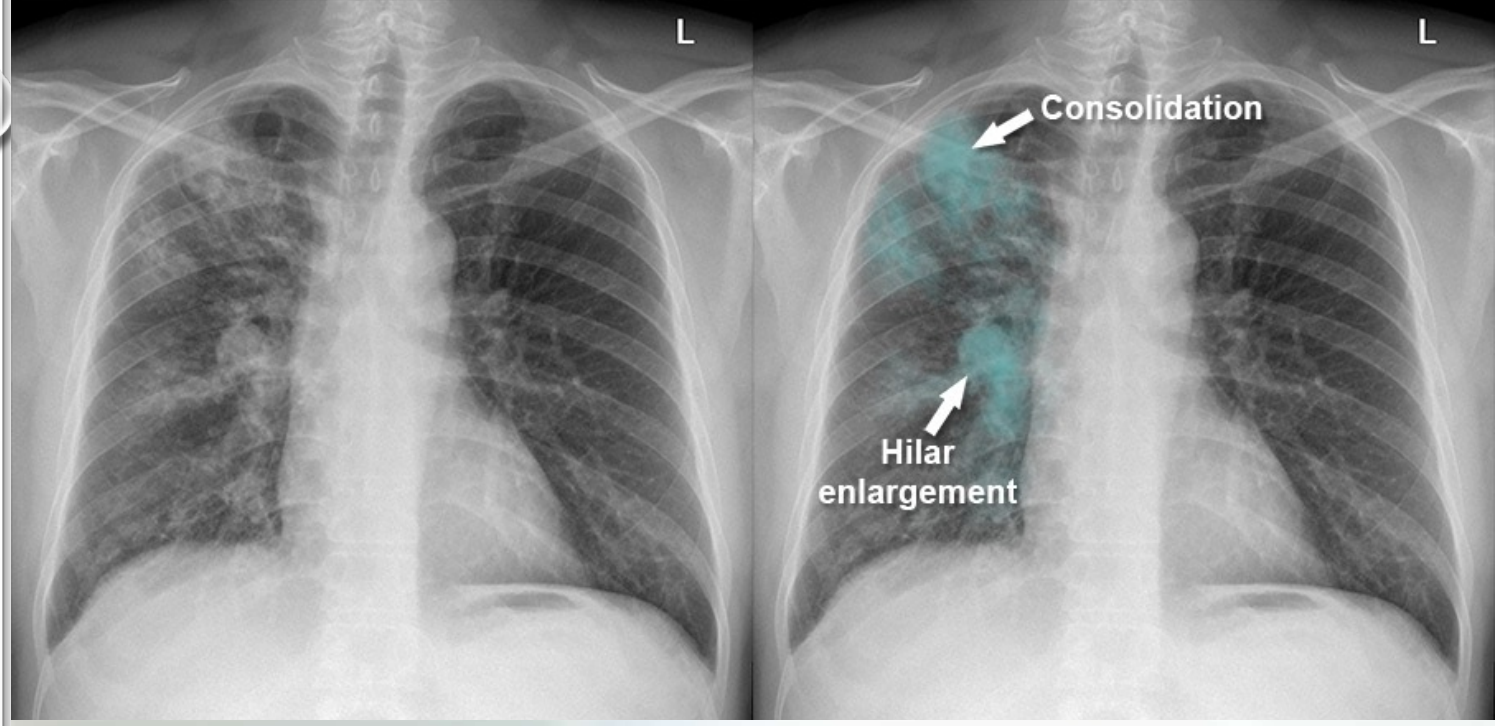
Turner et al, Journal of the Pediatric Infectious Diseases Society, 2023

Complete Results Expressly Stratified for Children Aged 0–2 Years

Reference	Setting	Population	Outcome
Grinsdale 2016	United States	Children <15 years old presenting for tuberculosis screening	Tuberculosis disease
			Median follow-up duration: 5.7 years 0 of 46 untreated children under age 2
		78% foreign born, 12% exposed to persons with active tuberculosis disease	who were QFT– or indeterminate progressed to tuberculosis disease
			0 of 1 untreated children under age 2 who were QFT–/TST+ progressed to tuberculosis disease
Gaensbauer 2020	United States	Children <2 years old tested with QFT	Tuberculosis disease
		30% foreign born, 22% exposed to persons with active tuberculosis disease	Median follow-up duration: 3.0 years
			0 of 104 untreated children under age 2 who were QFT– progressed to tuberculosis disease
			0 of 6 untreated children under age 2 who were QFT–/TST+ progressed to tuberculosis disease
Ahmed 2020	United States	Children <15 years old at high risk for tuberculosis infection	Tuberculosis disease
			Median follow-up duration: 4.3 years
		92% foreign born, 11% exposed to persons with active tuberculosis disease	0 of 54 untreated children under age 2 who were QFT–/TST+ progressed to tuberculosis disease
Wendorf 2020	United States	Refugees <5 years old	Tuberculosis disease
			Median follow-up duration: 3.0 years 0 out of 425 untreated children <2
			years old who were QFT– progressed to tuberculosis disease
			0 out of 9 untreated children who were QFT–/TST+ progressed to tuberculosis disease

Abbreviations: IGRA, interferon-gamma release assay; QFT, QuantiFERON; TST, tuberculin skin test.

SCREENING FOR TB IN KIDS



WHICH CHILDREN ARE AT RISK FOR TB IN CA?

LTBI testing is recommended if any of the 3 boxes below are checked.

☐ **Birth, travel, or residence** in a country with an elevated TB rate for at least 1 month

- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe

☐ **Immunosuppression,** current or planned

HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥2 weeks) or other immunosuppressive medication

☐ **Close contact** to someone with infectious TB disease during lifetime

Treat for LTBI if LTBI test result is positive and active TB disease is ruled out.

(1) CHILD WITH INCREASED RISK OF TB PROGRESSION

- 10 YO WITH NEW DIAGNOSIS OF CHRON'S PLANNING TO START INFLIXIMAB
- US-BORN WITH NO BIRTH/TRAVEL TO ENDEMIC AREA FOR TB

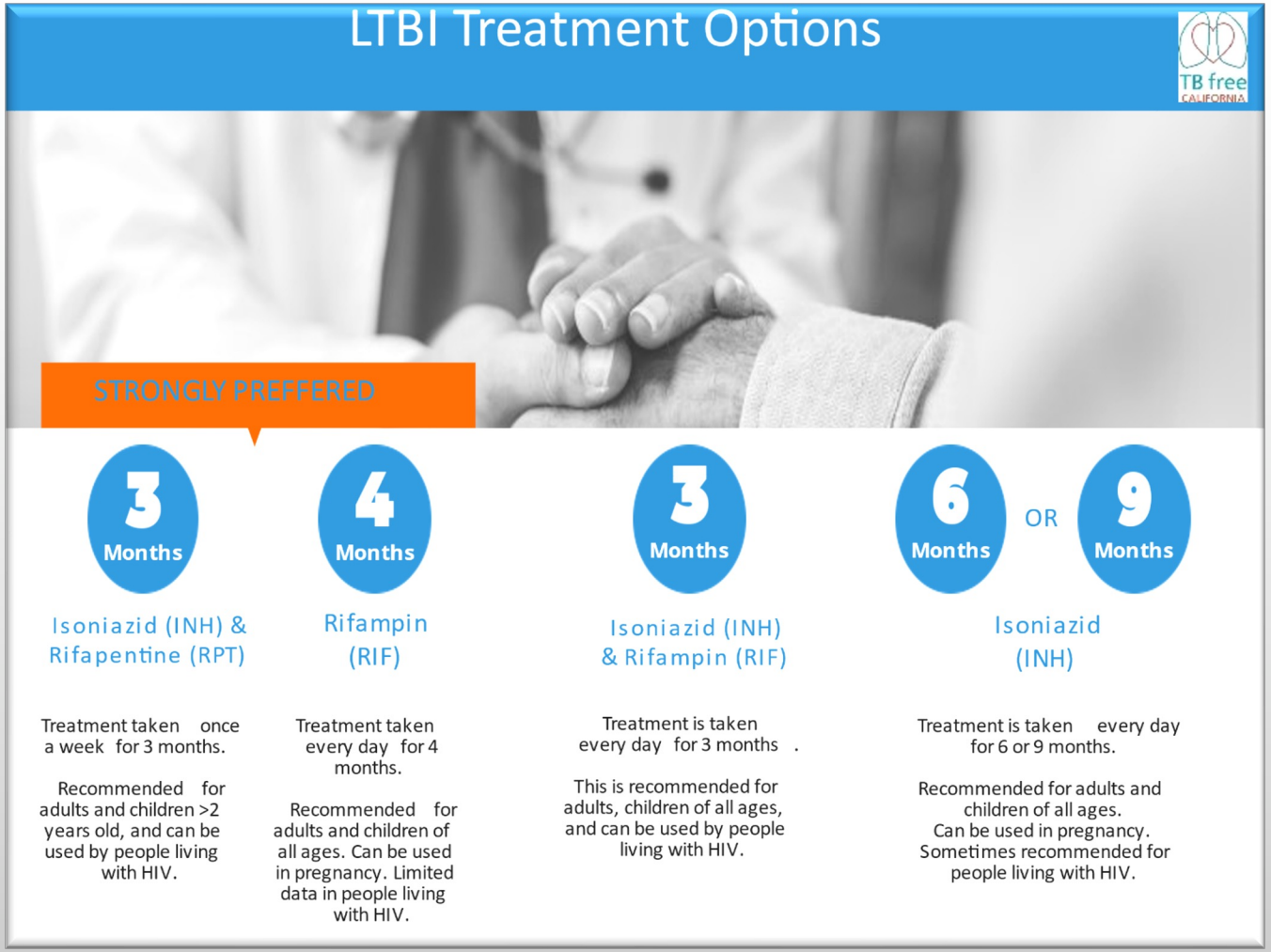
- WHAT EVALUATION DO YOU DO?
  A. NOTHING
  B. TB TEST
  C. MEDICAL/SYMPTOM REVIEW
  D. PHYSICAL EXAM
  E. CXR
  F. B, C, AND D
  G. ALL OF THE ABOVE

(1) CHILD WITH CHRONS DISEASE

- **ALWAYS EXAMINE, REVIEW MEDICAL HISTORY/DO PHYSICAL EXAM, TB TEST**
- TB TEST IS NEGATIVE
  - CONTINUE WITH INFLIXIMAB
  - ANNUAL TB TESTING WHILE ON ANTI-TNF
- IF CHILD IS ALREADY IMMUNE-SUPPRESSED, TB TESTING CAN BE FALSELY NEGATIVE

(2) CHILD WITH BIRTH/TRAVEL IN ENDEMIC AREA

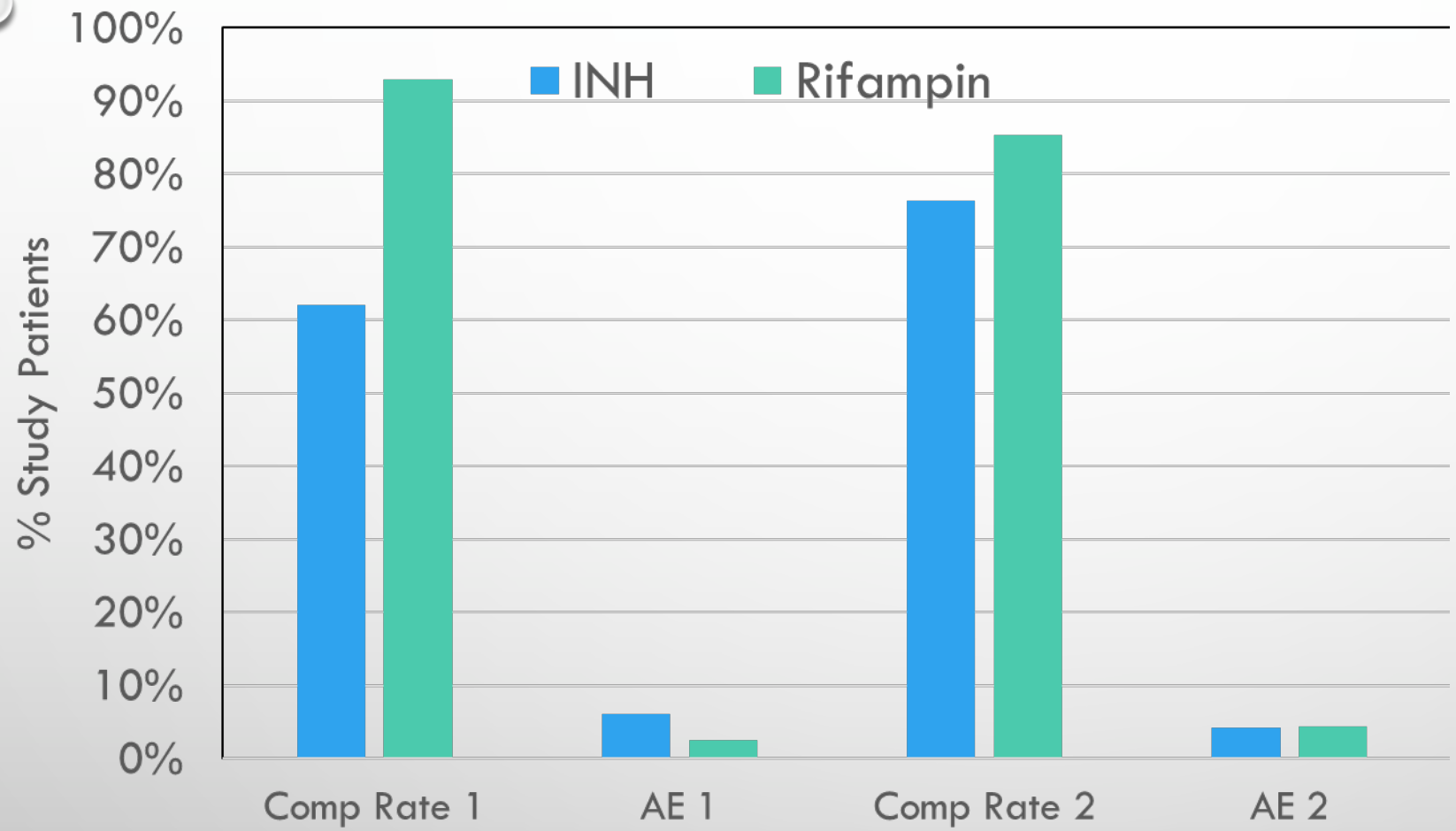
- 8 YO HEALTHY CHILD SEEN FOR SCHOOL PHYSICAL
- BORN IN MEXICO, NO RECENT TRAVEL, NO KNOWN TB EXPOSURES
- WHAT TO DO?
  - **MEDICAL/SYMPTOM REVIEW**
  - **PHYSICAL EXAM**
  - **TB TEST -> IGRA**
- HIS EXAM IS NORMAL AND HE DENIES TB SYMPTOMS, HE IS AT THE 50%ILE FOR HEIGHT AND WEIGHT, BUT HIS IGRA IS POSITIVE
- WHAT DO YOU DO NEXT?
  A. TREAT FOR TB DISEASE
  B. TREAT FOR LTBI
  C. OBTAIN A CXR
  D. HAVE CHILD RETURN FOR EVALUATION IN 6 MONTHS



(2) CHILD WITH BIRTH/TRAVEL IN ENDEMIC AREA

- CXR IS NORMAL
- TREAT FOR LTBI

RIFAMPIN (4MO) VS ISONIAZID (9MO)

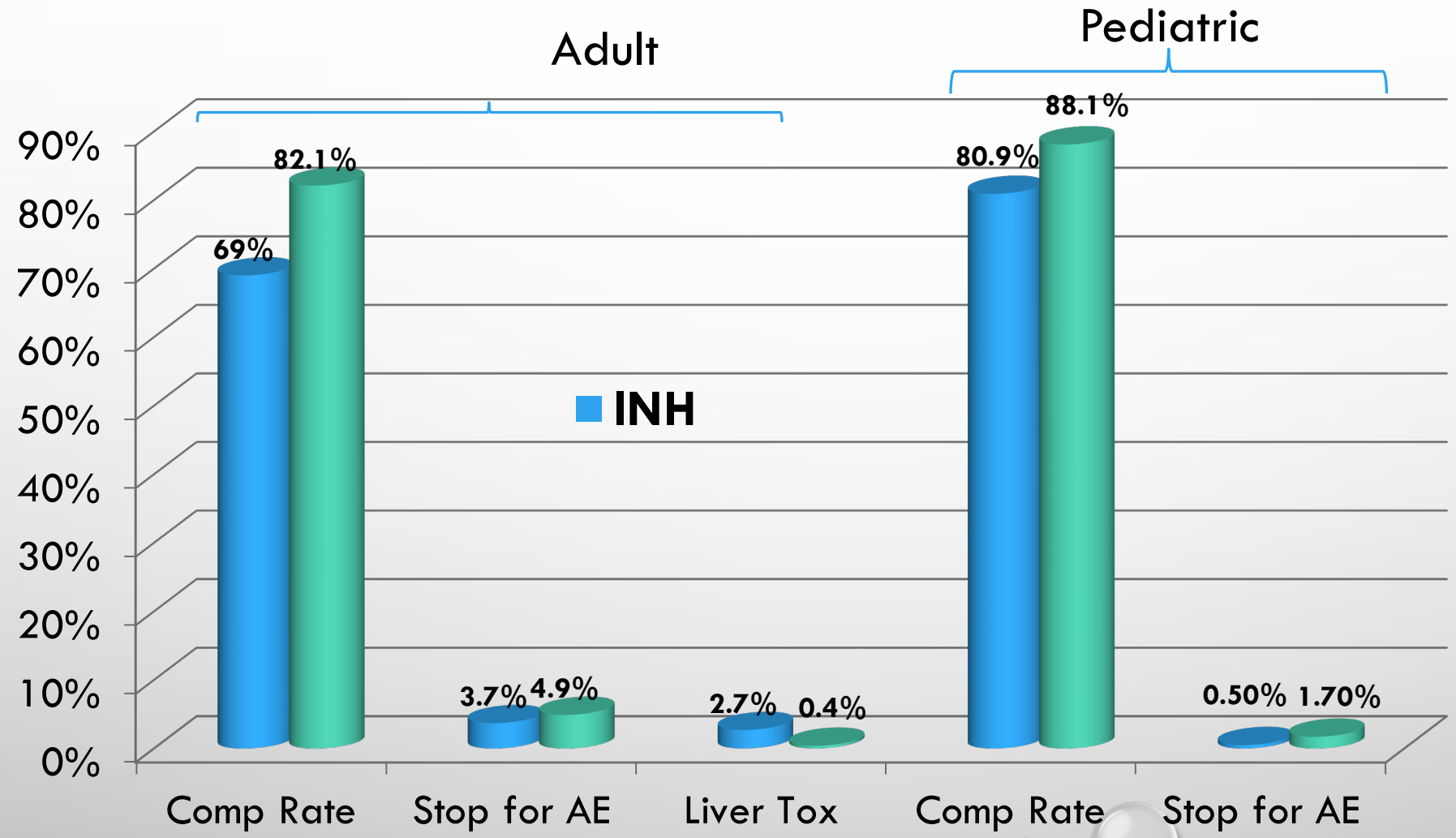


0 cases of TB during 562 person-years of follow-up with RIF

2 cases of TB during 542 person-years of follow-up with INH

Cruz AT, Starke JR. *Int J Tuberc Lung Dis* 2014;18:1057-61
Diallo T, Menzies. *N Engl J Med* 2018;379:454-63
Page, KR et al. *Arch Intern Med* 2006;166:1863-70.

3HP WEEKLY (12 WEEKS) VS INH (9MO)



RCT found 3HP non-inferior to INH for 2-17 yr olds

Sterling TR et al. NEJM 2011;365:2155-66.
Villarino ME et al. *JAMA Ped* 2015;169:247-55.

ISONIAZID + RIFAPENTINE

What are the doses?

Drug	Dosage	Maximum dose
INH	15 mg/kg rounded to nearest 50/100 mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years	
Rifapentine	10.0 – 14.0 kg = 300 mg	900 mg
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg	
Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills		

LTBI MONITORING

- BASELINE MONITORING
  - USUALLY NONE UNLESS ON OTHER HEPATOTOXIC MEDS, LIVER PROBLEMS, OR USING DRUGS/ETOH

- MONTHLY MONITORING
  - WEIGHT
  - COMPLIANCE
  - SIGNS/SYMPTOMS OF TB OR MEDICATION TOXICITY
- ENSURE THERAPY COMPLETION
  - 3HP = 11 DOSES WITHIN 16 WEEKS
  - RIFAMPIN = 120 DOSES WITHIN 6 MONTHS
  - ISONIAZID = 270 DOSES WITHIN 12 MONTHS
- PROVIDE DOCUMENTATION OF LTBI TREATMENT COMPLETION

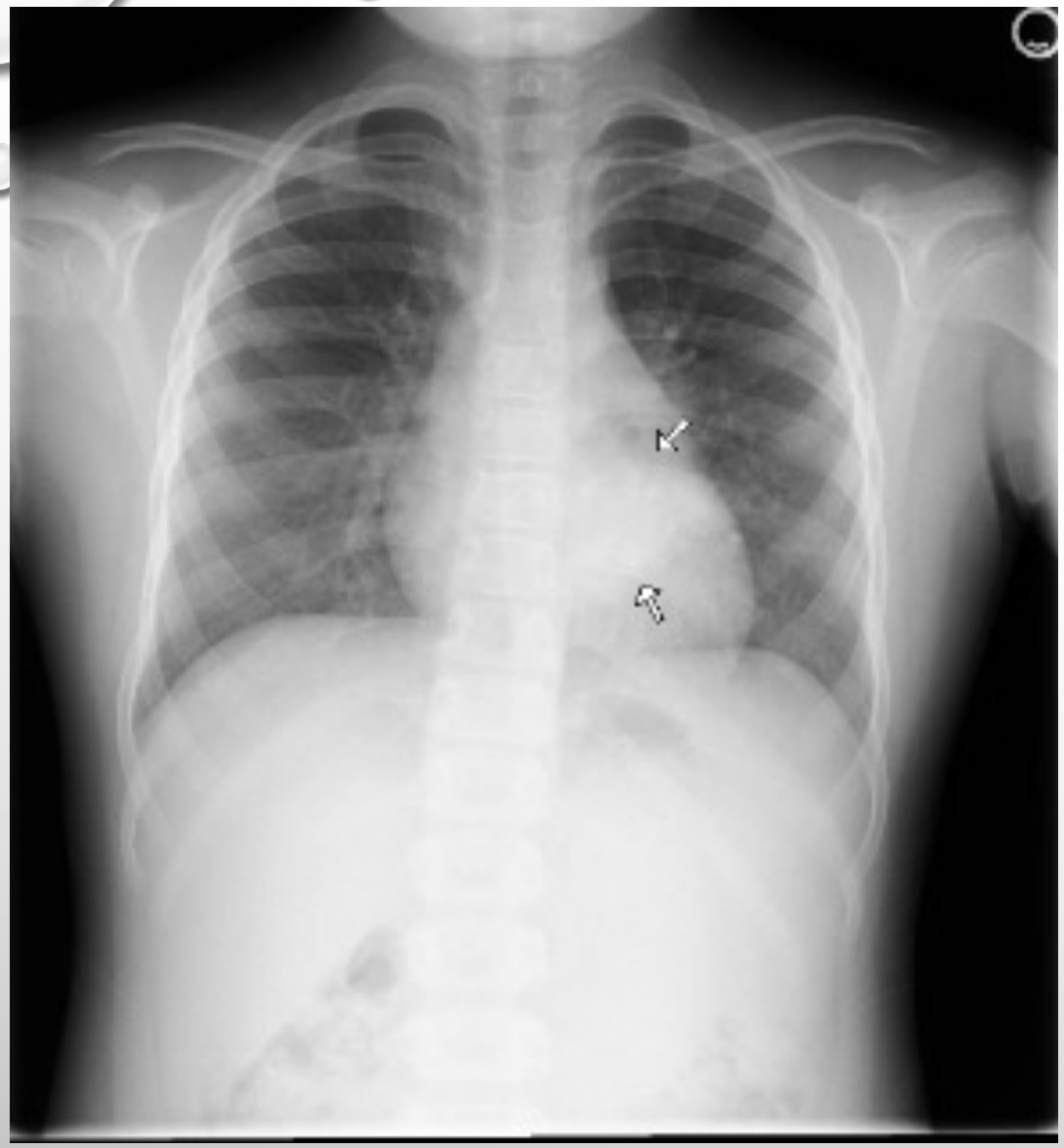
(3) PEDIATRIC CONTACT: THE NANNY

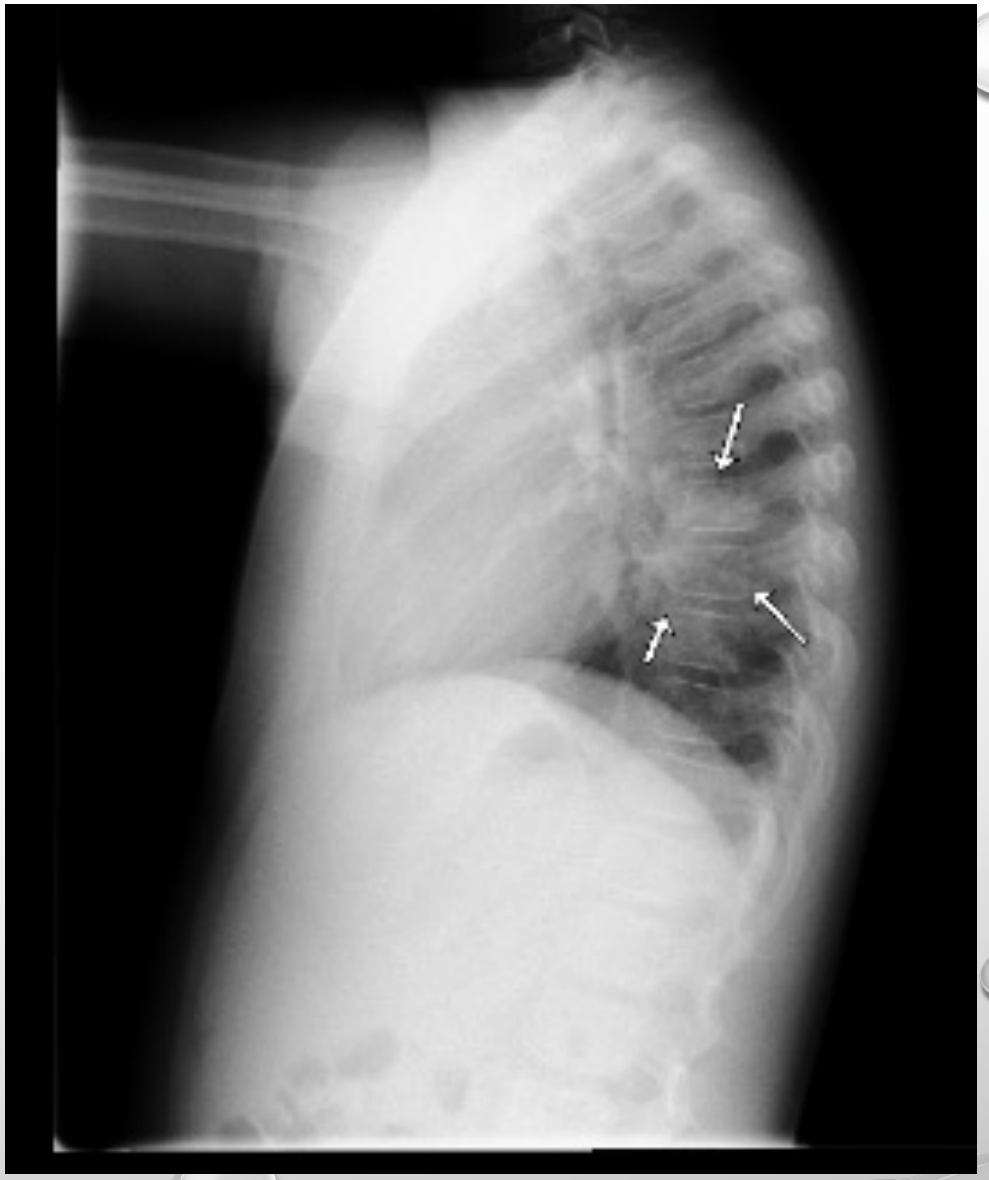
- 5 YO US-BORN CHILD REFERRED BY PUBLIC HEALTH
- TB EXPOSURE HISTORY
  - NANNY RECENTLY DIAGNOSED WITH PULMONARY TB
  - NANNY HAS CAVITARY, 4+ TB DISEASE
  - XPERT SHOWS NO RIF RESISTANCE
- WHAT DO YOU DO?
  - **MEDICAL/SYMPTOM REVIEW**
  - **PHYSICAL EXAM (GROWTH CHART!!)**
  - **TB TEST**

6 YO EVALUATION

- NO PMH
- NO SYMPTOMS
- NORMAL PE
  - CHILD TRACKING ON GROWTH CURVE (25%ILE)
- TST 15MM

- **WHAT DO WE DO NEXT?**
  a. TREAT LTBI
  b. COLLECT SPUTUM
  c. CXR
  d. TREAT FOR TB DISEASE
  e. FOLLOW-UP IN 6 MONTHS
  f. GET AN IGRA





PULMONARY TUBERCULOSIS

- NEW INFILTRATE (DESPITE NO SYMPTOMS) AND POSITIVE TB TEST

- COLLECT SPECIMENS
  - INDUCED SPUTUM IF COOPERATIVE (EVEN AS YOUNG AS 2 YRS!)
    - OFTEN EFFORT DEPENDENT
    - BRONCHODILATORS + HYPERTONIC SALINE
  - GASTRIC ASPIRATES VERY USEFUL IN YOUNG CHILDREN
    - CURRY CENTER VIDEO BY DR. ANN LOEFFLER
    - XPERT IS HELPFUL

- TREAT FOR ACTIVE TB
  - GASTRIC ASPIRATE SMEAR NEGATIVE, CULTURE POSITIVE FOR MTB
  - TREATED FOR 6 MONTHS

PEDIATRIC TB TREATMENT

FOR ALL CHILDREN:

- INTENSIVE PHASE (2 MONTHS)
  - RIFAMPIN
  - ISONIAZID
  - ETHAMBUTOL (UNTIL INH-S KNOWN)
  - PYRAZINAMIDE
- CONSOLIDATION PHASE (**4 MONTHS**)
  - RIFAMPIN
  - ISONIAZID

FOR CHILDREN WITH LIMITED TB DISEASE*

- INTENSIVE PHASE (2 MONTHS)
  - RIFAMPIN
  - ISONIAZID
  - ETHAMBUTOL (UNTIL INH-S KNOWN)
  - PYRAZINAMIDE
- CONSOLIDATION PHASE (**2 MONTHS**)
  - RIFAMPIN
  - ISONIAZID

* SHINE trial. NEJM 2022

(3) PEDIATRIC CONTACT: THE GRANDPA

- 2 YO US-BORN CHILD REFERRED BY PUBLIC HEALTH
- TB EXPOSURE HISTORY
  - GF RECENTLY DIAGNOSED WITH PULMONARY TB, DIED WITHIN A FEW DAYS OF DIAGNOSIS
  - CHILD SPEND MOST WEEKDAY/DAYTIME WITH GRANDPA
  - XPERT SHOWS NO RIF RESISTANCE

- WHAT DO YOU DO?
  - **MEDICAL/SYMPTOM REVIEW**
  - **PHYSICAL EXAM (GROWTH CHART)**
  - **TB TEST**

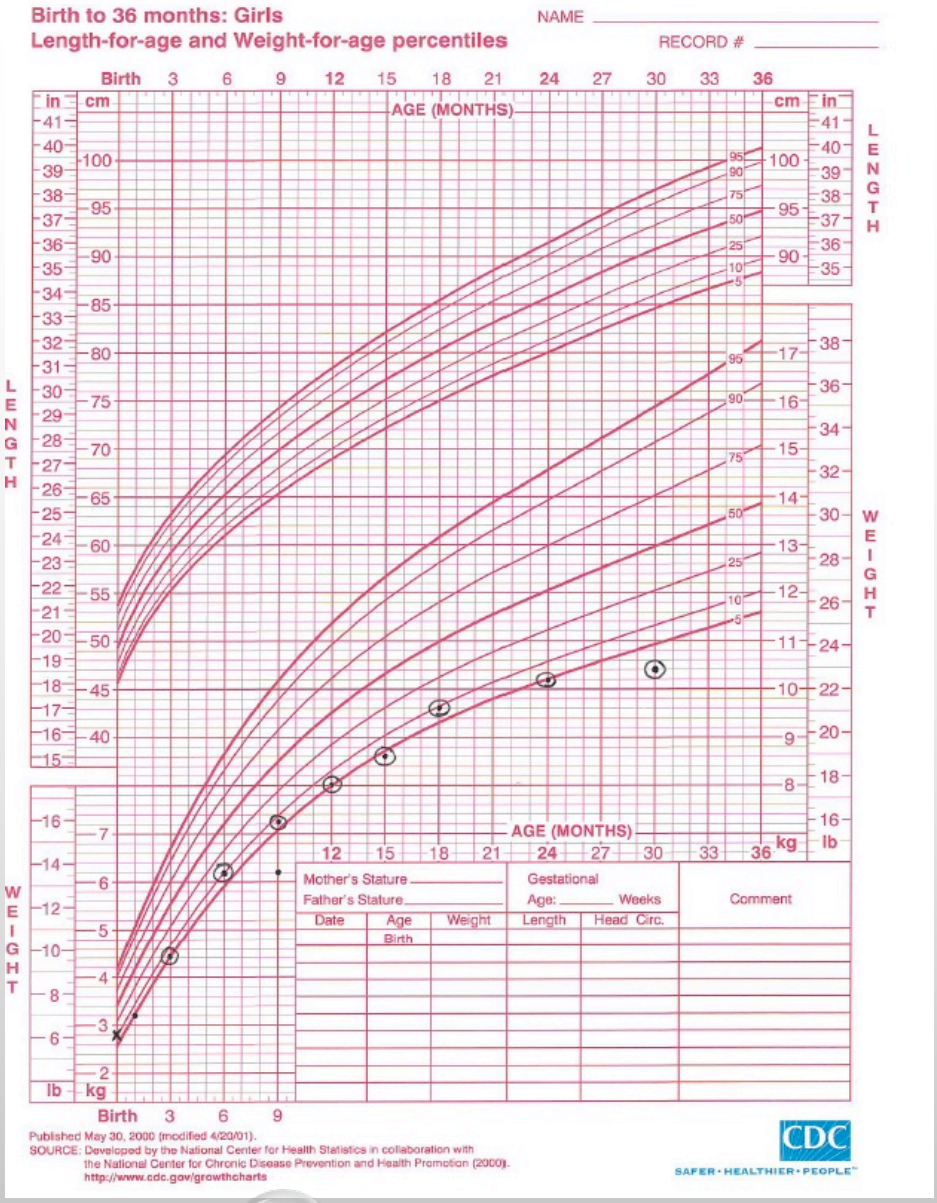
- NO PMH
    - CHILD TRACKING ON GROWTH CURVE (50%ILE)
- NO SYMPTOMS
- ENLARGED LYMPH NODE
- **QFT POSITIVE**
- NORMAL CXR
- **WHAT IS THIS?**

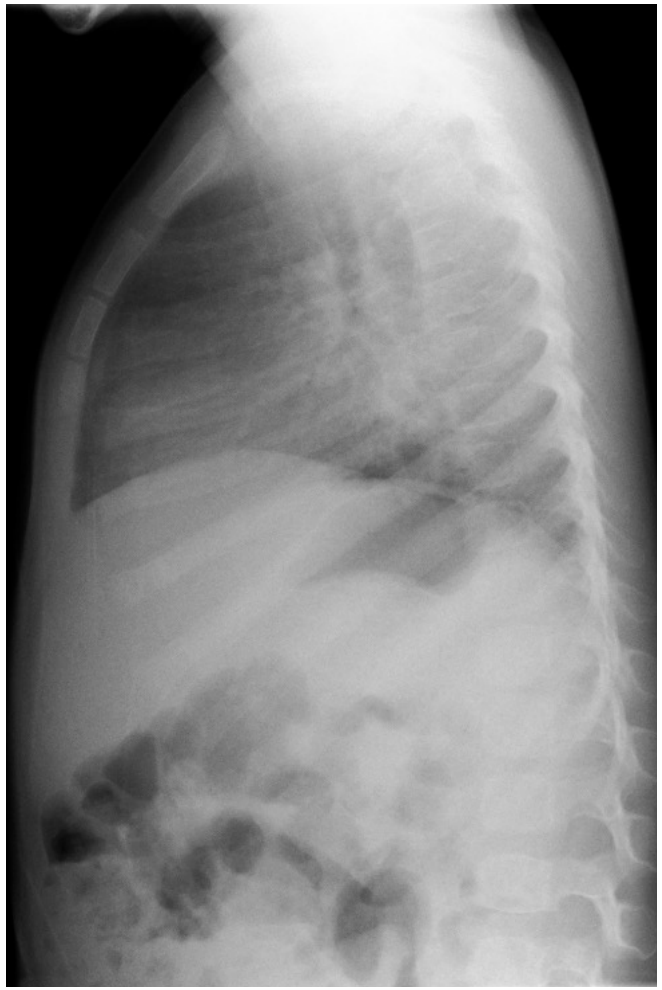
CHILDCOMPLETED 6 MONTHS OF ACTIVE TB TREATMENT FOR SCROFULA

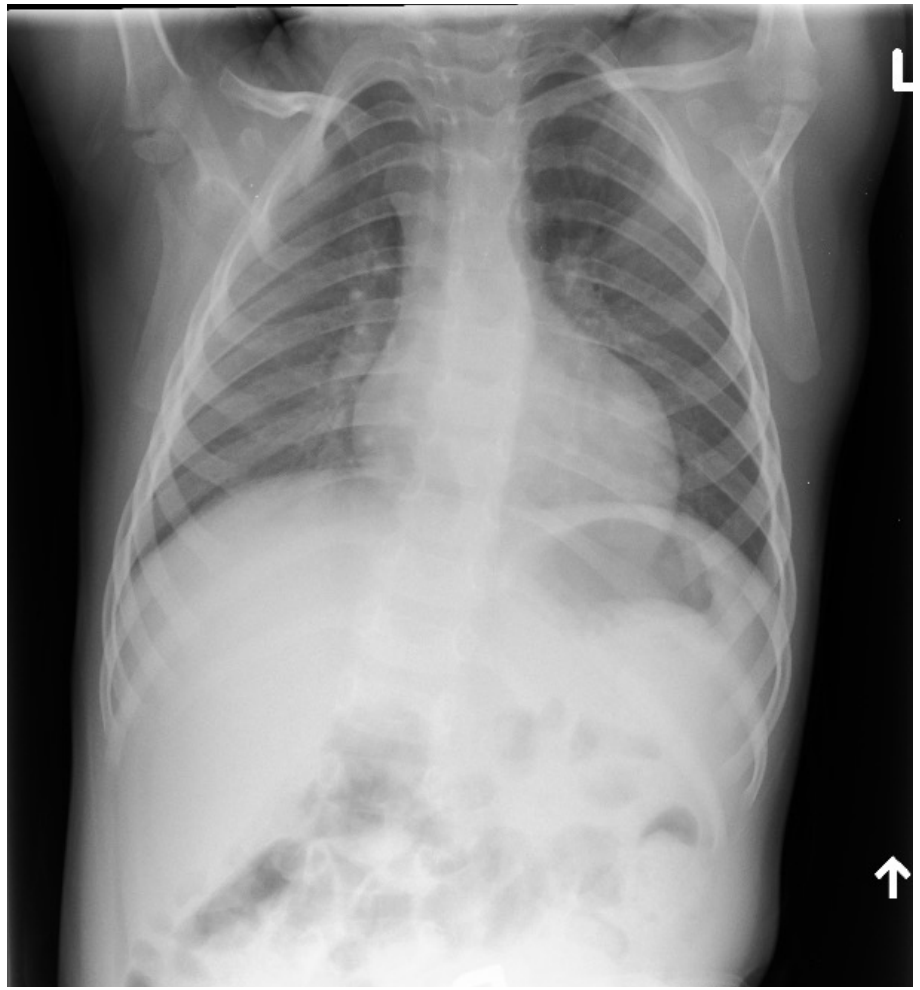
(3) PEDIATRIC CONTACT EVALUATION – THE COUSIN

- US-BORN 2.5 YO EXPOSED TO COUSIN WHO STAYS IN THE HOME ON WEEKENDS
  - PULMONARY TB
  - INH-RESISTANT

- 2.5 YO EVALUATION
  - MEDICAL/SYMPTOM EVAL NEG
  - NORMAL PE, BUT ->>>>
  - TST **25 MM** (US-BORN)







PEDIATRIC TB CAN BE VERY SUBTLE!

- MOST COMMON FORM OF TB IS INTRATHORACIC
- OFTEN ONLY ENLARGED NODES ON CXR, POSITIVE TB TEST
- CHILDREN TYPICALLY ASYMPTOMATIC
- ONLY ~30% CULTURE POSITIVE
- TREAT THESE KIDS – CONSIDER THE 4 MONTH TREATMENT OPTION

CONCLUSION

- TB IS DEVASTATING BUT PREVENTABLE IF WE IDENTIFY AND TREAT LTBI AND TB EARLY

- SCREEN ALL KIDS AND TEST AT RISK FOR TB EXPOSURE AND PROGRESSION
  - IMMUNE COMPROMISED
  - BIRTH/TRAVEL IN ENDEMIC AREA
  - KNOWN EXPOSURE

- ALWAYS EVALUATE FOR ACTIVE TB DISEASE BEFORE TREATING FOR LTBI
  - TB DISEASE IS OFTEN SUBTLE AND A CLINICAL DIAGNOSIS!

- TREAT LTBI
  - 12 DOSES OF INH/RIFAPENTINE (3HP)
  - 4 MONTHS OF DAILY RIFAMPIN

- TREAT TB DISEASE, LIMITED DISEASE MIGHT ONLY REQUIRE 4 MONTHS OF TREATMENT

THANK YOU!

QUESTIONS?

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