From the Heartland News Desk: Reassessing LTBI – Who We Missed and Where Are They Now?

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Webcast

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

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

Reassessing LTBI – Who We Missed and Where Are They Now?

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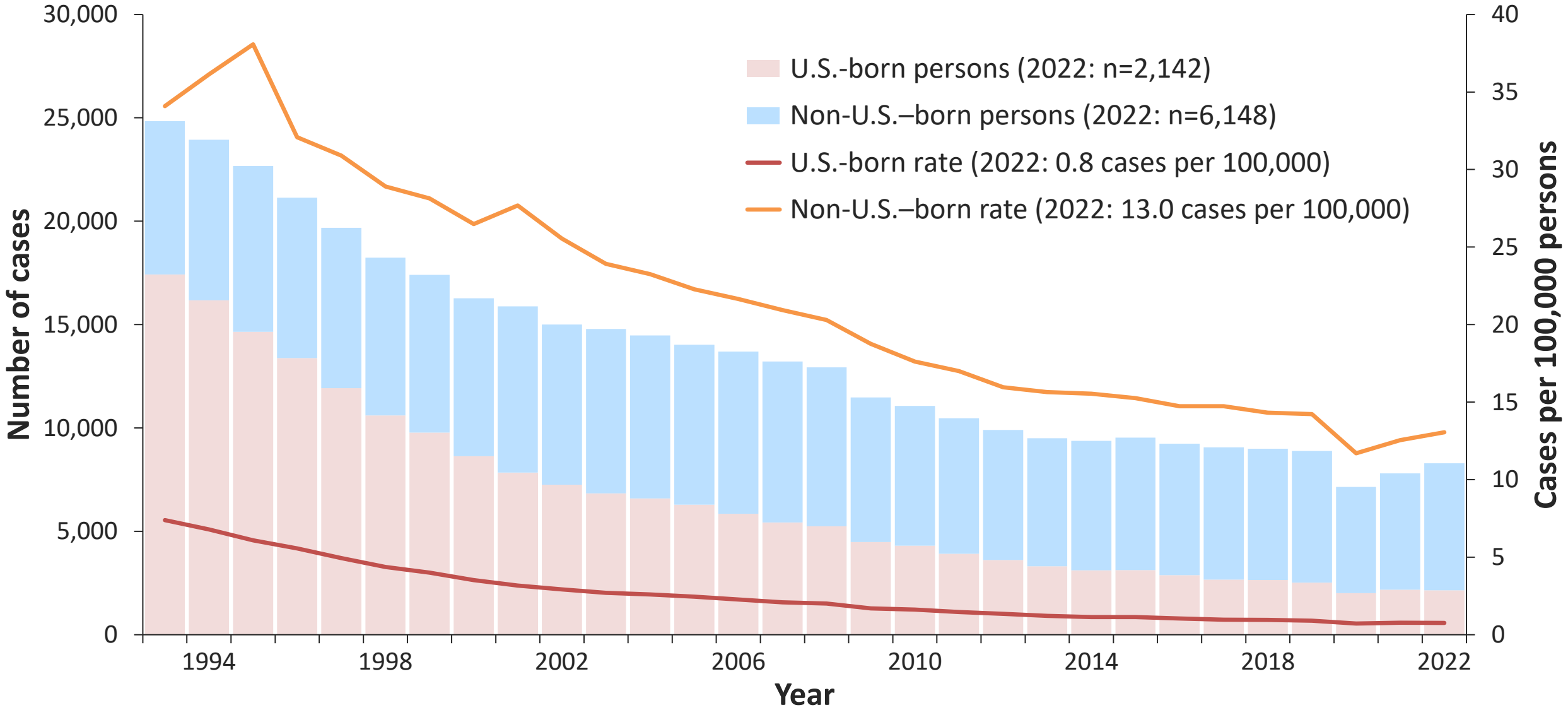
World TB Day 2024
San Antonio, Texas
March 20, 2024

Some San Antonio numbers

- 22 confirmed active TB cases for 2024
  - 2019-2022 only 14-15 cases by WTBD
- Ages 10 months to 88 years
- 15 (68.2%) are foreign born, another 2 lived outside the US
  - 9 patients arrived in the US < 5 years ago
  - 6 patients arrived between 14-83 years ago

TB Cases and Incidence Rates by Origin of Birth,* United States, 1993–2022



*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.

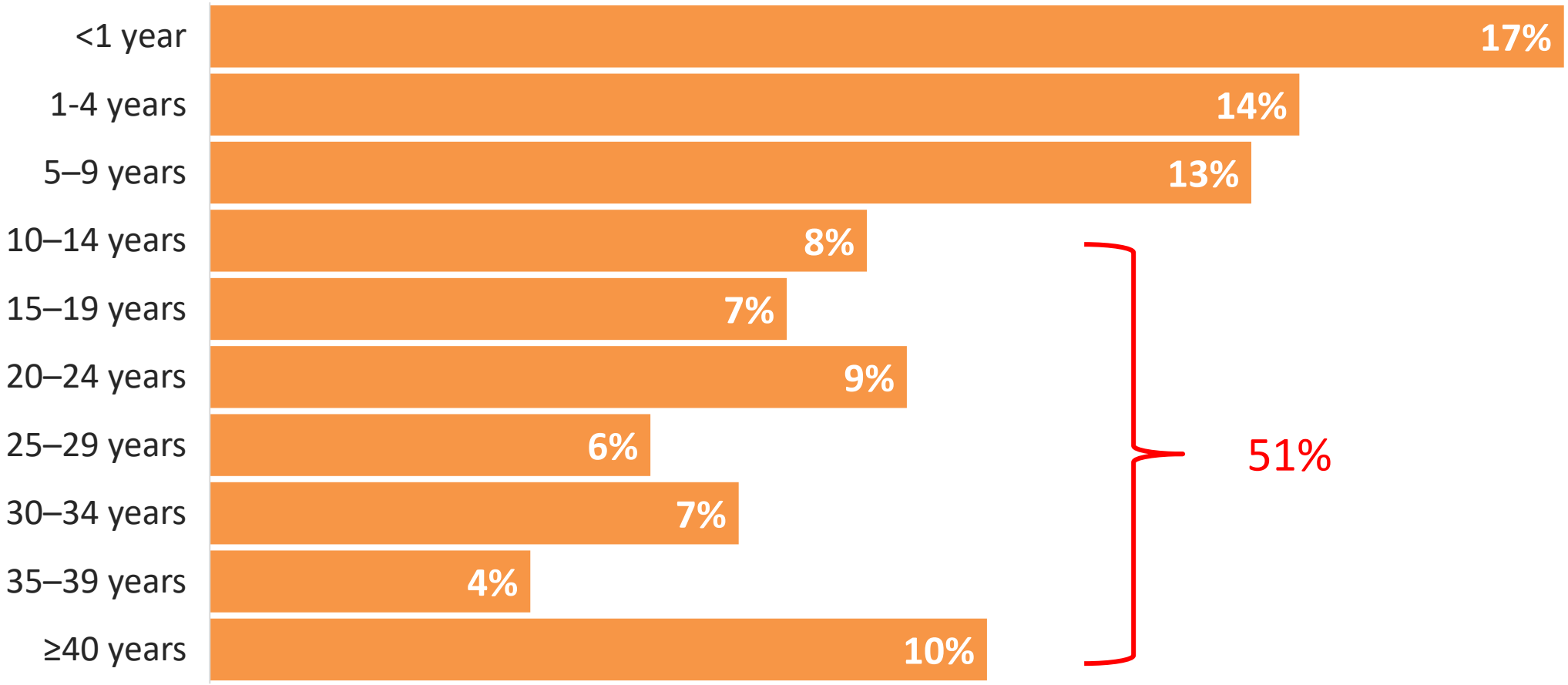
Been a Long Time…..

50-year-old man from Honduras, immigrated to the US 20 years ago. He recently changed jobs and they require an IGRA for employment. He tests positive.

He had a positive TST in the past that he attributed to being BCG vaccinated. He is currently without symptoms and has a negative CXR.

What is your messaging to this man regarding LTBI treatment?

Percentage of TB Cases Among Non-U.S.–Born* Persons by Years Since Initial Arrival in the United States at Diagnosis,† 2022 (N=6,148)



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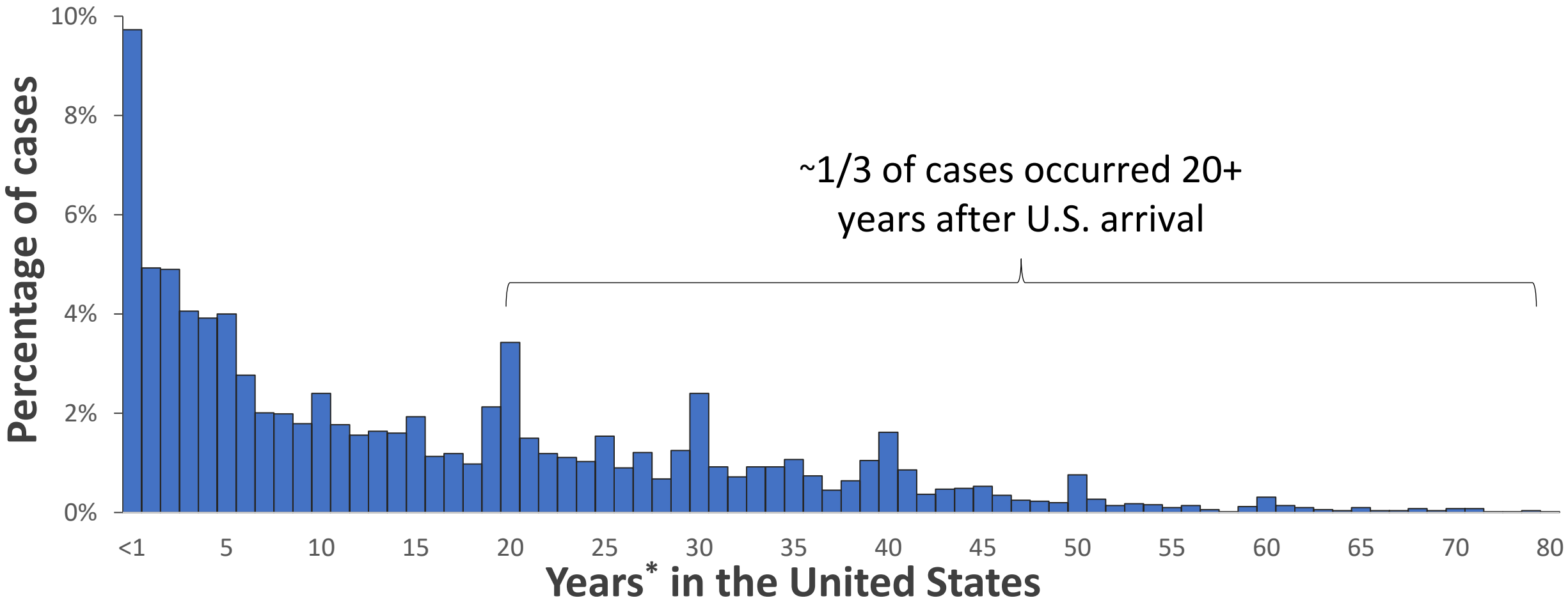
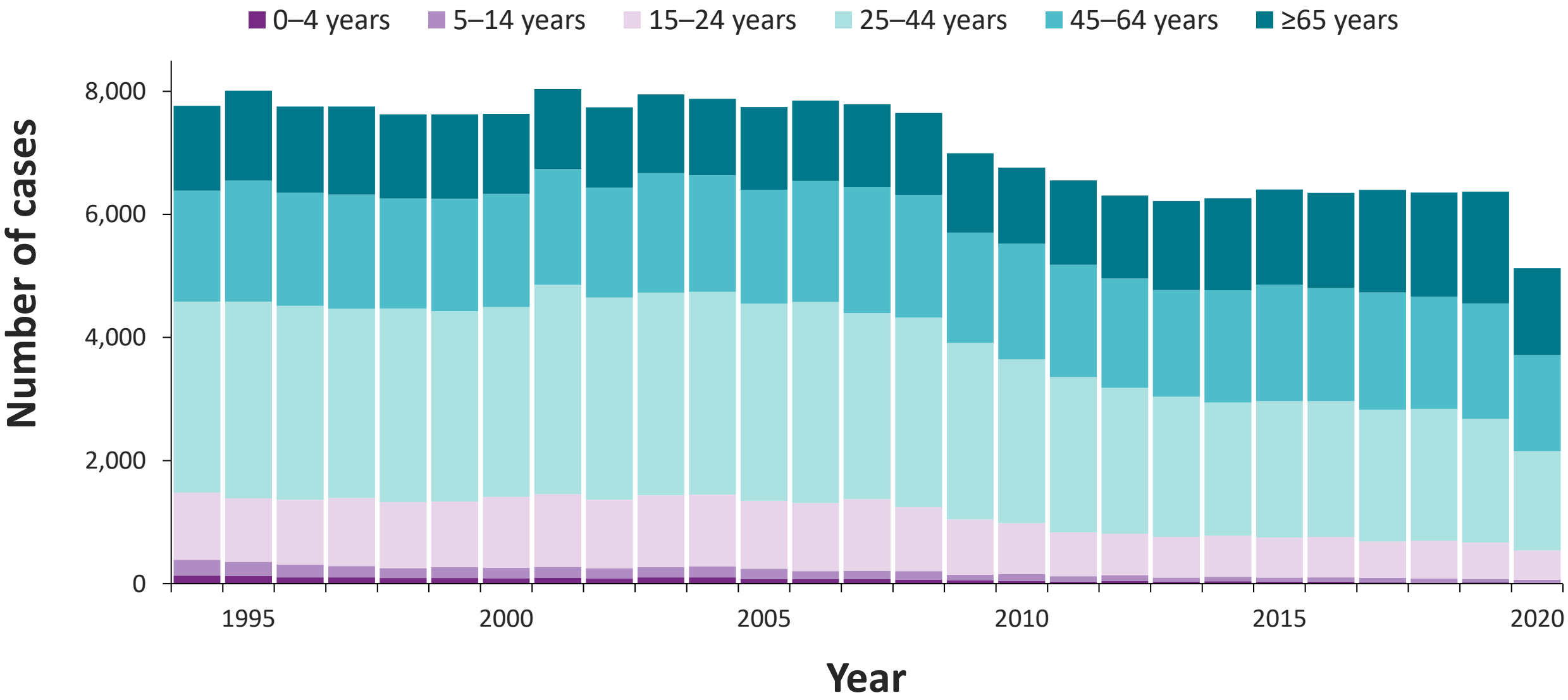
†The number of years since initial arrival in the United States at diagnosis was unknown or missing for 7% of non-U.S.–born persons. These persons were included in the denominator when percentages were calculated.

Percentage of TB Cases Among Non-U.S.–born Persons by Year Since Initial Arrival in the United States at Diagnosis, 2020 (N=5,127)



* Years since arrival was missing/unknown for 585 cases (11.4%).

TB Cases Among Non-U.S.–born Persons by Age Group, United States, 1994–2020



So….How to Treat?

You discuss risk with the patient and he agrees to treatment.

What do you treat with?

TB Infection Treatment Options

CDC Recommended Treatment regimens:

- INH/Rifapentine x 3 months (3HP)
  - Once weekly DOT x 12 weeks
  - Average of 10 pills at once

- Rifampin x 4 months
  - Daily (10 mg/kg: 600 mg max)

- INH +rifampin x 3 months
  - INH daily (5 mg/kg: 300 mg max) + rifampin daily (10 mg/kg: 600 mg max)

- INH x 6-9 months
  - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)

ATS/IDSA/NTCA. November 2018.

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults.

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

Treatment completion:

Rifampin	79%
INH	63% ($p < 0.001$)

Clinically significant (drug stopped) hepatotoxic events:

Rifampin	0.3%,
INH	1.7% ($p < 0.001$)

4 months of rifampin was not inferior to 9 months INH for preventing development of active TB but with significantly higher completion rates and greater safety than INH.

Rifampin (rifamycin) Toxicity

Cutaneous Reactions: 6%, generally self- limited

Orange discoloration of body fluids

Gastrointestinal symptoms: nausea, anorexia, abdominal pain

Flulike symptoms: < 1% of patients on intermittent therapy.

Severe immunologic reactions: thrombocytopenia, hemolytic anemia, acute renal failure and thrombotic thrombocytopenic purpura (each < 0.1% of patients)

Severe Hepatotoxicity: nearly 0% as monotherapy, may appear cholestatic

Common Rifampin (Rifamycin) Drug Interactions

HMG-CoA reductase inhibitors
Oral anticoagulants
Oral contraceptives
Cyclosporine/Tacrolimus
Digoxin
Glucocorticoids
Itraconazole/ketoconazole
Methadone
Phenytoin
Theophylline
Verapamil/diltiazem
Amiodarone
Midazolam
Thyroid hormone

Consider rifabutin!

INH LTBI Therapy

- The standard treatment regimen for LTBI has been nine months of daily INH.
- New guidelines suggest 6 months to be adequate
- The regimen is very effective and is the preferred regimen for HIV infected people taking antiretroviral therapy with drug-drug interactions that do not allow a rifamycin
- Is the option when drug-drug interactions with the rifamycins are significant and must be avoided

But less than 60% complete

Primarily due to long duration of treatment but also increased adverse effects

INH Hepatotoxicity

Asymptomatic elevation of aminotransferases: 20% of patients

Clinical hepatitis: 0.6% of patients

Fulminant hepatitis (hepatic failure)

- Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

10 patients with CDC on-site investigation

All patients had:

- indications for LTBI treatment,
- were prescribed INH within recommended dosage range,
- took the medication as prescribed

Prescribers followed guidelines for monthly clinical monitoring

Symptoms 1-7 months after INH started

2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

"Medical providers should emphasize to patients that *INH treatment should be stopped immediately upon the earliest onset of symptoms* (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

INH Side Effects

Hepatotoxicity

Migraine Headaches

Gastrointestinal

- Nausea, Diarrhea, Constipation

Rash

Peripheral Neuropathy

- Pyridoxine 50mg daily can help prevent this

Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis of 8 new and 53 previously included studies.

Zenner D et al. AIM;167:248-255

Table 2. ORs and Treatment Rankings for Hepatotoxicity, Derived From the Network Meta-analysis

Regimen	OR vs. Placebo (95% CrI)	OR vs. No Treatment (95% CrI)	Rank (95% CrI)
No treatment	0.24 (0.06-0.75)	1.00 (reference)	4 (2-7)
Placebo	1.00 (reference)	4.12 (1.33-15.88)	9 (7-10)
INH 6 mo	0.27 (0.10-0.60)	1.10 (0.40-3.17)	5 (3-7)
INH 9 mo	0.41 (0.08-1.62)	1.70 (0.35-8.05)	6 (3-10)
INH 12-72 mo	0.66 (0.26-1.32)	2.72 (0.96-7.44)	8 (6-10)
RPT-INH	0.13 (0.03-0.42)	0.52 (0.13-2.15)	2 (1-5)
RMP	0.03 (<0.02-0.16)	0.14 (0.02-0.81)	1 (1-2)
RMP-INH 3-4 mo	0.17 (0.05-0.46)	0.72 (0.21-2.37)	3 (2-6)
RMP-INH-PZA	0.58 (0.07-3.72)	2.41 (0.25-20.02)	7 (2-10)
RMP-PZA	0.80 (0.25-2.17)	3.32 (0.99-11.23)	9 (6-10)

CrI = credible interval; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RMP = rifampicin; RPT = rifapentine.

USPSTF recommendations for LTBI

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults who are at increased risk for tuberculosis	The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.	B

Return to Table of Contents

USPSTF Recommendation Grades	
Grade	**Definition**
A	Recommended.
B	Recommended.
C	Recommendation depends on the patient's situation.
D	Not recommended.
I statement	There is not enough evidence to make a recommendation.

Questions?

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