Who Should Be Treated & How Should We Treat Them?

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Screening & Treating Tuberculosis Infection
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- No conflict of interests
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Who Should Be Treated
&
How Should We Treat Them?

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Latent TB Infection

- Persons are infected with *Mycobacterium tuberculosis* but:
  - No Active TB Symptoms
  - Chest X-ray may be normal, or show granuloma, **stable** pleural or parenchymal scarring
  - Positive TST or IGRA

Latent TB Infection

- Persons with LTBI are NOT infectious
- 90+ % chance of never getting Active TB Disease
- TB Bacteria are metabolically active and dividing, but infection is controlled by the immune system.

- But the TB organism is in your body!

- "…a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB"

WHO Guidelines on the Management of Latent Tuberculosis Infection, 2015

Progression of LTBI to Active TB Disease Increased By

- HIV infection
- Chronic kidney disease
- Silicosis
- Recent exposure
- Diabetes
- Chest x-ray abnormality c/w previous inadequately treated TB
- Intravenous drug use
- Smoking – active and passive
- Underweight by >10% (*Maybe*)

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221

Progression of LTBI to Active TB Disease Increased By

- Immunosuppression
  - Pregnancy and first three months post partum
  - Hematologic cancers and head and neck cancers
  - Medications
    - TNFα inhibitors
    - Prednisone >15 mg, > 4 weeks
    - Chemotherapy
    - Other immunosuppressive drugs

Latent tuberculosis infection: the final frontier of tuberculosis elimination in the USA

LoBue PA[1], Mermin JH[2]. Lancet Infect Dis. Epub 2017

- After substantial progress during the past two decades, the rate of tuberculosis cases in the USA each year has now levelled off and remains well above the elimination threshold.

- Both epidemiological data and modelling underline the necessity of addressing ***latent tuberculosis infection*** if further progress is to be made in eliminating the disease.

- A major new effort is required and should consist of
  - a surveillance system or registry to monitor progress,
  - ***scale-up of targeted testing for latent tuberculosis infection in at-risk populations,***
  - ***scale-up of short-course treatment regimens***
  - increased public health staffing for implementation and oversight.

Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

The simplified version:

- Persons who are at increased risk for *M. tuberculosis* infection
- Persons at increased risk for progression to active disease if infected with *M. tuberculosis* (even if not at increased exposure risk)

And those who tend to be tested in addition:

- Persons tested for administrative reasons (e.g., mandatory employment testing)
- Persons with symptoms of active TB disease (fever, night sweats, cough, and weight loss)

Deciding When to Treat LTBI

Groups Who Should be Given High Priority for LTBI Treatment

People with a positive IGRA result or a TST reaction of ≥ 5 mm

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on CXR c/w old TB
- Organ transplant recipients
- Persons who are immunosuppressed for other reasons
  - taking the equivalent of >15 mg/day of prednisone for ≥ 1 month,
  - taking biologics

People with a positive IGRA result or a TST reaction of ≥ 10 mm

- Persons from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology lab personnel
- Children < 4 years of age,
- Children and adolescents exposed to adults in high-risk categories

Initiating Treatment for LTBI

Before initiating treatment for LTBI

- Rule out TB disease
  - i.e. wait for culture results if specimen obtained
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy

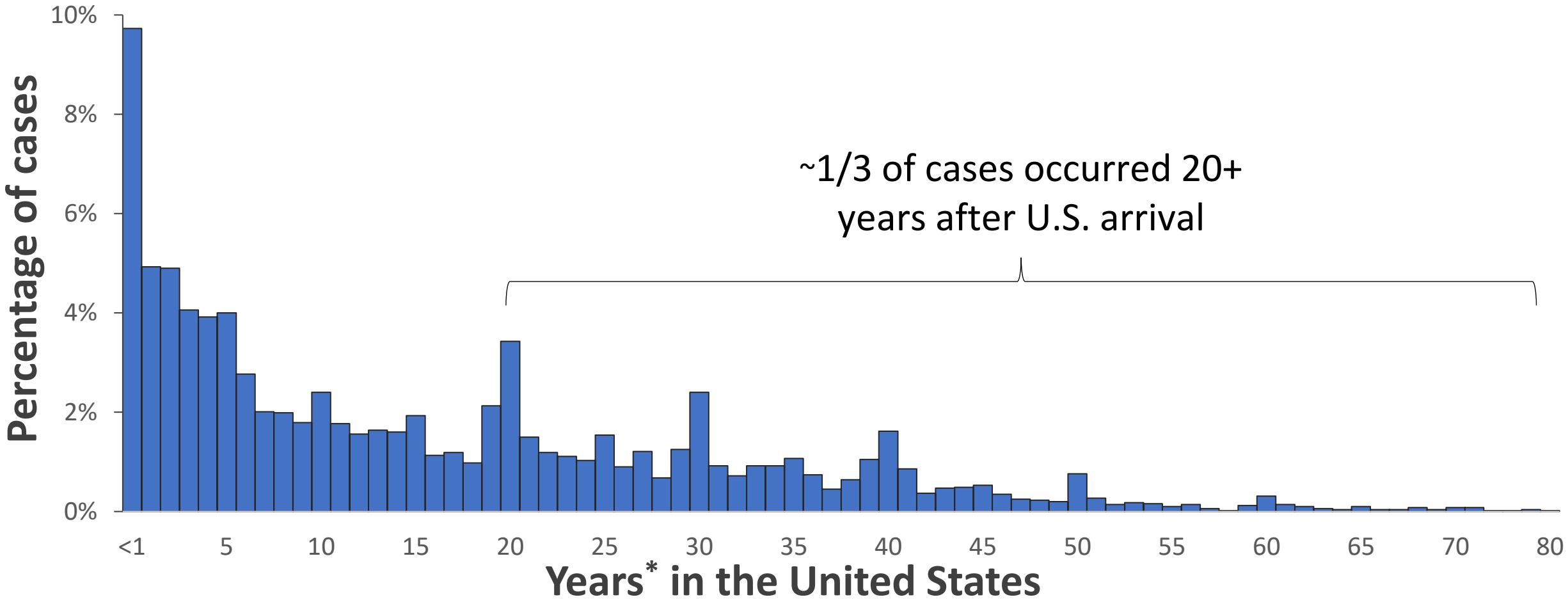
Contacts of Active TB Case

- Among close contacts approximately 30% have LTBI and 1-3% have active TB disease
- Without treatment, approximately 5% of contacts with newly acquired LTBI progress to TB disease within 2 years
- Examination of contacts is one of the most important activities for identifying persons with disease and with LTBI

Been a Long Time…..

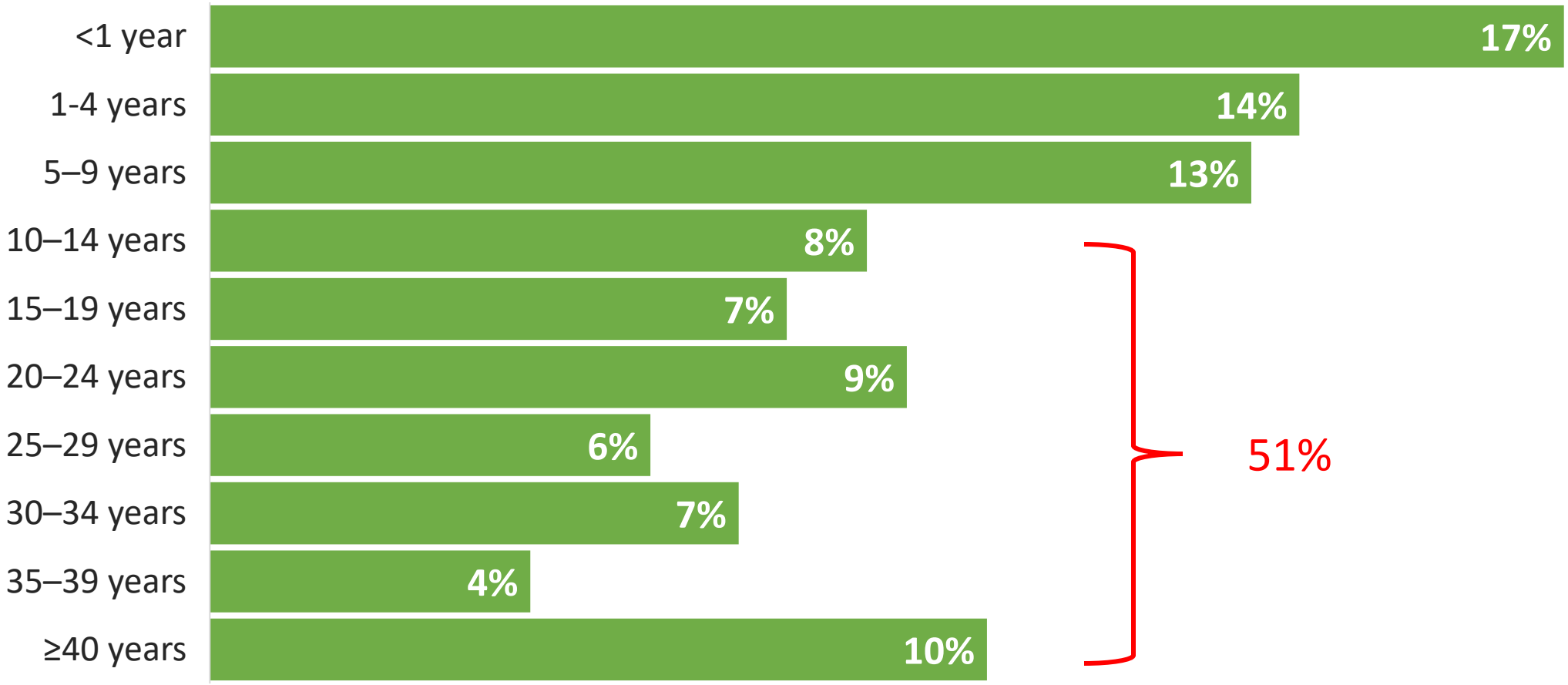
- 50-year-old man from Honduras, immigrated to the US 20 years ago. He recently changed jobs and they require an IGRA for employment. He tests positive.
- He had a positive TST in the past that he attributed to being BCG vaccinated. He is currently without symptoms and has a negative CXR.
- What is your messaging to this man regarding LTBI treatment?

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



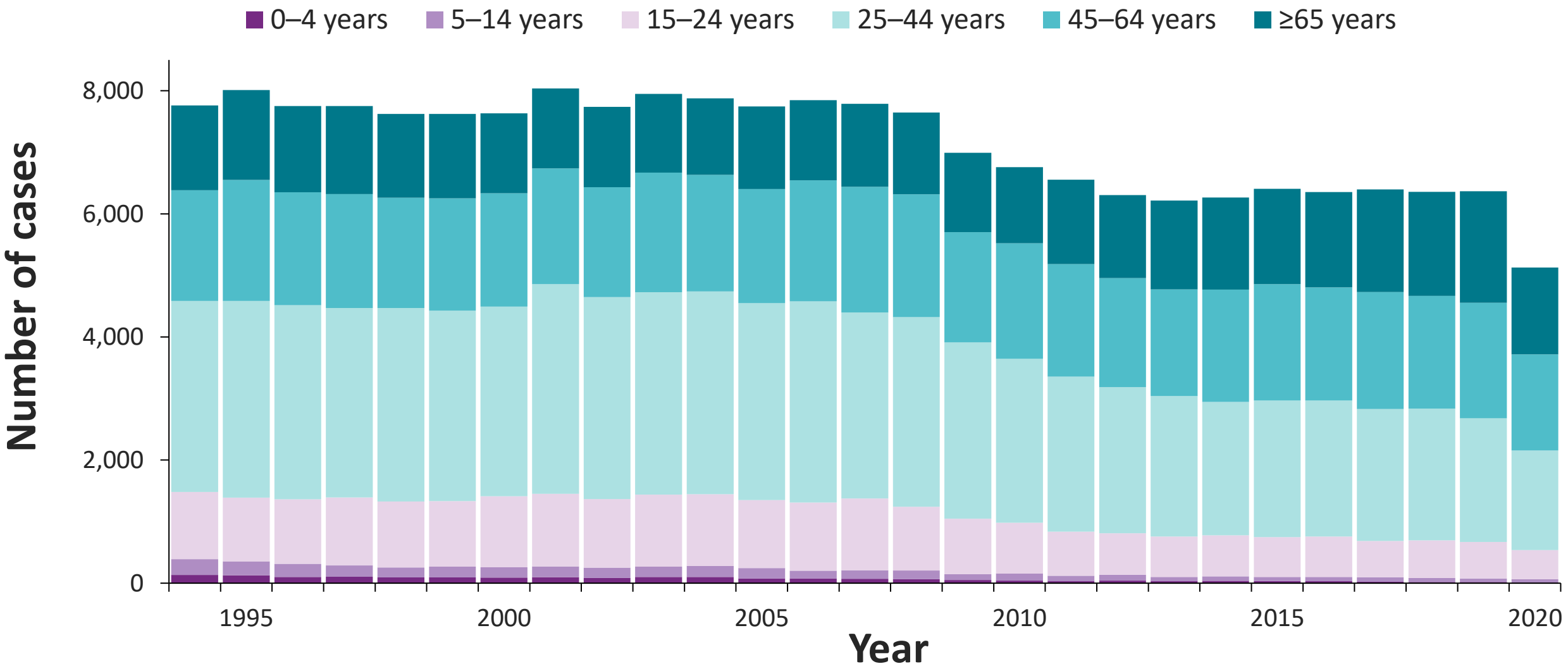
* Years since arrival was missing/unknown for 585 cases (11.4%).

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)



*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.
†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.

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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

Active TB disease: 7/3986 in 3 HP arm; 15 of 3745 in 9H arm
Completion of treatment: **82.1% 3HP arm**; **69% 9 H arm**
Hepatotoxicity: 0.4% 3HP arm; 2.7% 9 H arm.

Conclusion: Use of 3 HP x 3 months was as effective as 9 months of INH and had a higher treatment completion rate.

Dosing for 3 HP

Rifapentine is available only as a 150 mg tablet for oral administration. It can be crushed for pediatric dosing

Adults and children > 45 kg

- 900 mg INH once weekly
- 900 mg Rifapentine once weekly
- Vitamin B 6 50 mg once weekly

- **Completion** - 11 to 12 doses in 16 weeks

Children 2 – 12 years*

- INH 25 mg/kg (round to nearest 50 or 100 mg tablet)
- Rifapentine
  - 10-14 kg: 300 mg
  - 14.1-25 kg: 450 mg
  - 25.1-32 kg: 600 mg
  - 32.1-49.9 kg: 750 mg
  - ≥ 50 kg: 900 mg

* Especially when short course is desirable; pill burden may be a problem

INH + RPT (3HP) is NOT Recommended For:

- Children under 2 y/o
- HIV infected persons on Antiretroviral Therapy with drug drug interactions
- Presumed INH or Rifampin Resistance in the source case
- Pregnant women

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.

- Open label trial in 9 countries comparing 4 months rifampin vs 9 months INH:
  - study endpoint: prevalence of TB 28 months after randomization
- Rifampin: 3443 patients:
  - 4 active TB, 4 clinical TB
- INH: 3416 patients:
  - 4 active TB, 5 clinical TB

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 Dosing for TB Infection

- Adults
  - 600 mg daily x 4 months

- Children:
  - 10 – 20 mg/kg daily x 4 months
  - Capsules 150mg/300 mg round up - use higher range
  - Higher rifampin doses well tolerated

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

Rifampin (rifamycin) Drug Interactions

- Interactions due to induction of hepatic microsomal enzymes (cytochrome P-450, CYP, enzyme system) that accelerate metabolism of multiple drugs
- Major concern is reduction in serum concentrations of common drugs (OCP's, warfarin, etc.) to ineffective levels
- Bidirectional interactions between rifamycins, INH and antiretroviral agents

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 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

Isoniazid (INH) Dosing

- Adults: 300 mg single daily dose or 900 mg twice weekly*
- Children: 10-15 mg/kg single daily dose (max dose 300 mg daily)
  - 20-30 mg/kg twice weekly*
- Duration of treatment for TB Infection: 6 - 9 months
  - 9 month regimen more effective
  - 9 month regimen is very difficult to complete
  - 6 months is considered adequate therapy by ATS/IDSA/CDC guidelines

* **twice weekly treatment must be given by directly observed therapy through health department**

Duration of Therapy

• INH	• 9 months (270 doses)
• Rifampin	• 4 months (120 doses)
• INH + Rifampin	• 3 months (90 doses)
• INH +RPT	• 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!

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.

TB Prevention After Exposure

- Household contact with contagious person
  - Teen or adult with pulmonary TB disease
  - Usually ≥ 4 hours of contact
- Initial TST negative
  - ❖Window period for TST conversion (8-10 weeks)
- 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

- Repeat TST 8-10 wks after exposure
- May stop INH if 2nd TST negative <5mm in immunocompetent patients

Slide shamelessly stolen from Dr. Kim Smith

Should Pregnant Women Be Treated for TB Infection during Pregnancy?

- Treatment usually only given to those with recent contact to a person with active TB disease, HIV positive women or those with other immunosuppressive conditions. This is being reconsidered
- A pregnant woman with tuberculosis can transmit to her unborn child which can have devastating consequences.
- Active disease during delivery can expose medical staff to additional risk
- Multiple medications required for treatment of active TB disease adds additional risk to the pregnancy

Should Pregnant Women Be Treated for TB Infection during Pregnancy?

- A prior study showed increased risk of serious, even fatal hepatotoxicity with INH during pregnancy and the immediate post-partum period (3 months following delivery)
- No study has shown increased risk of hepatotoxicity with daily rifampin
- In pregnant persons who have reason for treatment of LTBI, consider daily rifampin
- Monitoring should be close
  - Blood work for any symptoms and hold medication
  - Monitor liver enzymes and patient at every monthly visit.

Treatment for LTBI in contacts of MDR-TB patients, Federated States ofMicronesia, 2009-2012.

Bamrah S. Int J Tuberc Lung Dis. 2014;18:912.

- 119 contacts of MDR-TB patients
- 12 mos daily FQ-based treatment of MDR TBI by DOT.
  - Moxi (45%), Levo (4%), Moxi + EMB, Levo + EMB, Levo + ETH
- 119 infected contacts, 104 began treatment, 15 refused
- Of the 104 who initiated treatment:
  - 93 (89%) completed treatment, 4 discontinued due to AE's.
  - None of the 104 contacts who undertook MDR LTBI treatment of any duration developed MDR-TB disease;
  - 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB disease.

Conclusions

- The most important step to treating LTBI is to rule out active disease first
- Treatment for LTBI can be done safely in most populations
- Shorter, rifamycin-based regimens are preferred

Thank you for being here.

Thank you for all that you do every single day.

You make a difference.

Questions?

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