Indian Country Infectious Disease ECHO Didactic

Atlanta June 15, 2023

Tuberculosis Basics: Treatment Management of Latent Infection and Active Disease

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Relevant Financial Disclosures

I have nothing to disclose

What will I cover?

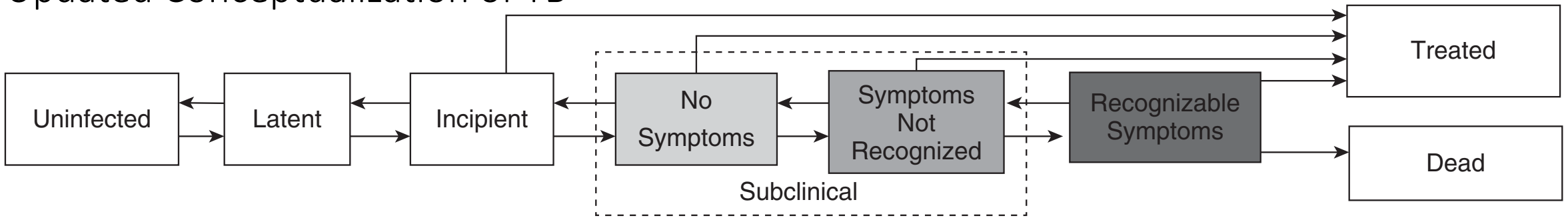
- Describe the conceptualization of the natural history of tuberculosis
- Review the epidemiology of LTBI and active TB disease
- Identify people at risk of progressing to TB disease & who to treat
- Review LTBI treatment guidelines
- Review Active TB disease guidelines
- Discuss alternative regimens and management needs in specific situations

Introduction

- It is estimated that 2 billion people are infected with Mycobacterium tuberculosis in the world
- Up to 13 million people in the United States are living with inactive TB and there are about 8000 TB cases reported annually in the US
- LTBI treatment is essential to maintain a continuous decrease in tuberculosis incidence rates

Classic Conceptualization of TB

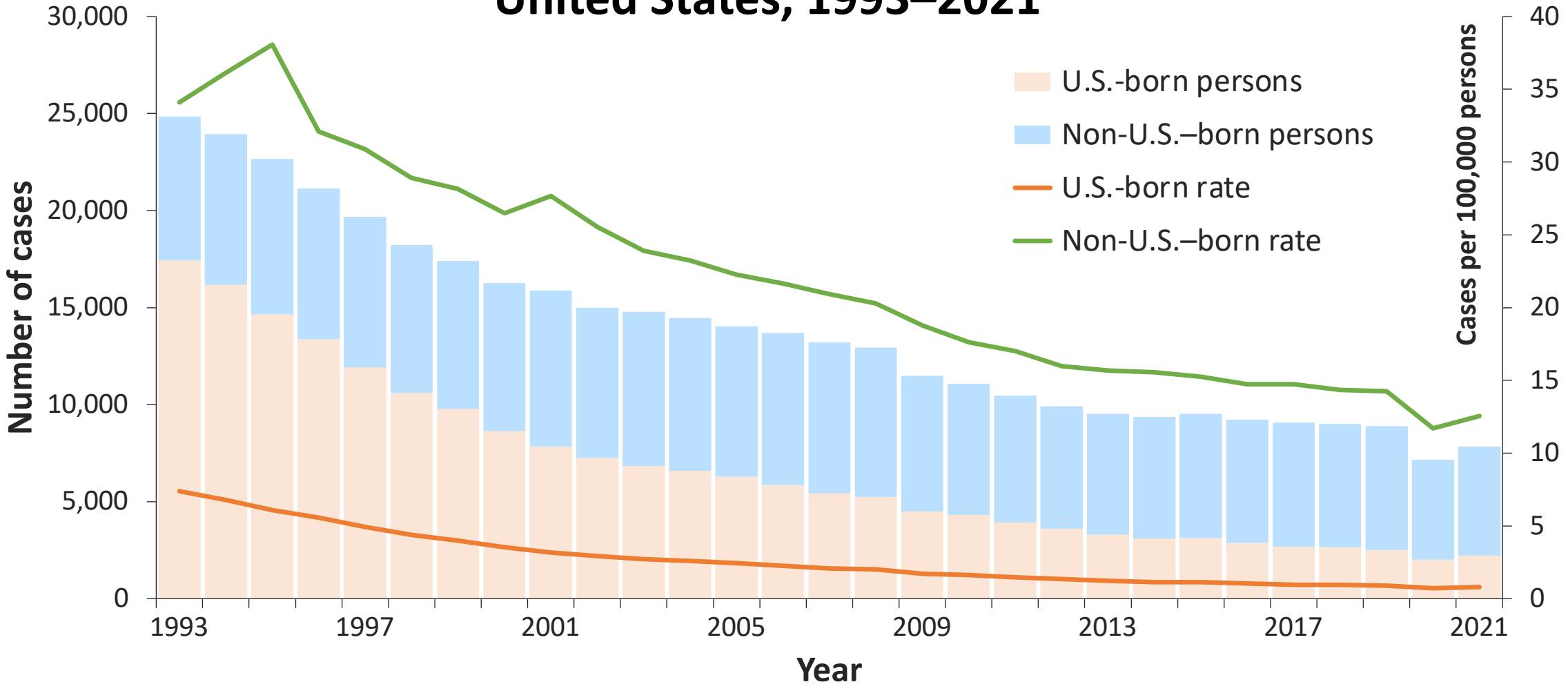
Updated Conceptualization of TB



- **Incipient TB**: An infection with viable MTB that is likely to progress to active TB disease
- It cannot currently be diagnosed by standard methods

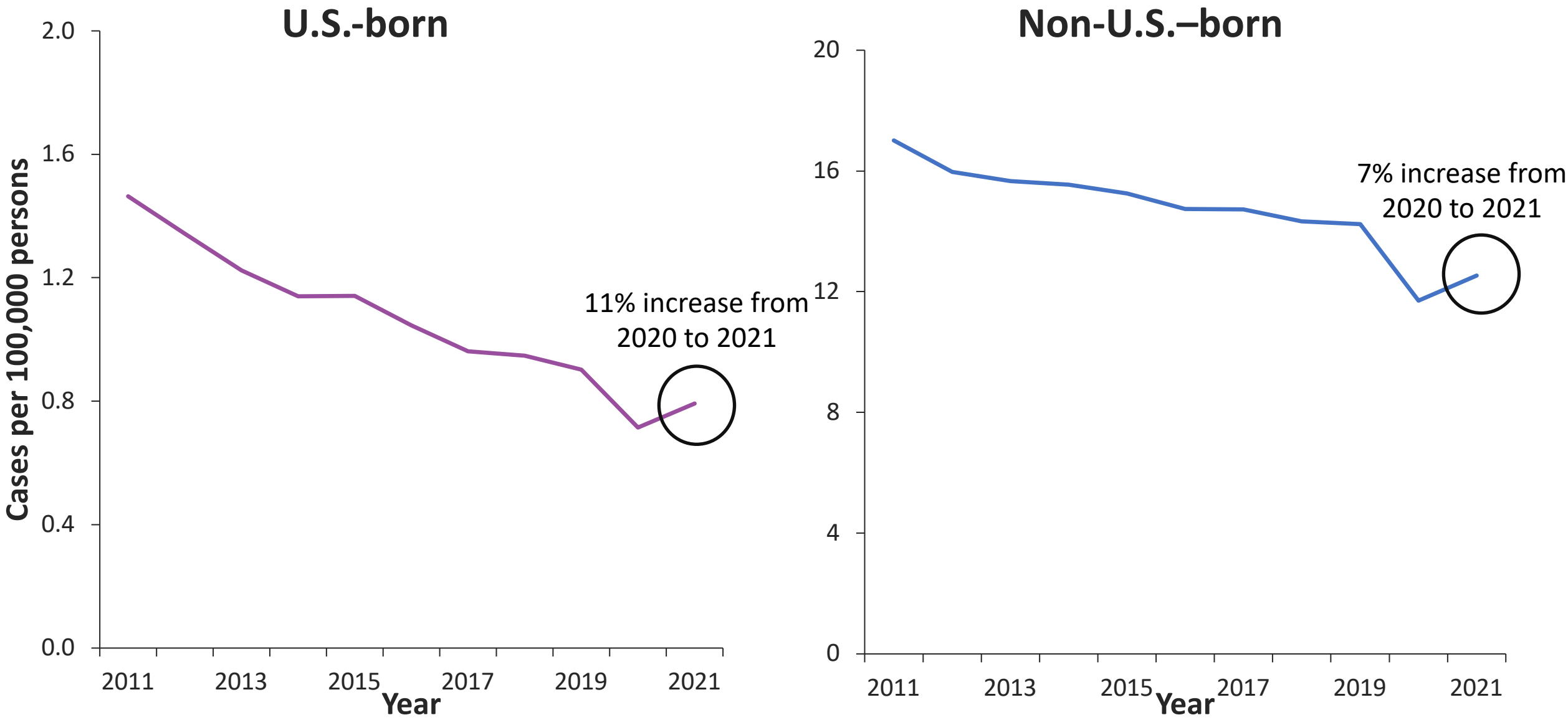
Kendall, Am J Resp Crit Care Med. 203: 2, Jan 2021

TB Cases and Incidence Rates by Origin of Birth,* United States, 1993–2021



*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.

TB Incidence Rates by Origin of Birth,* United States, 2011–2021



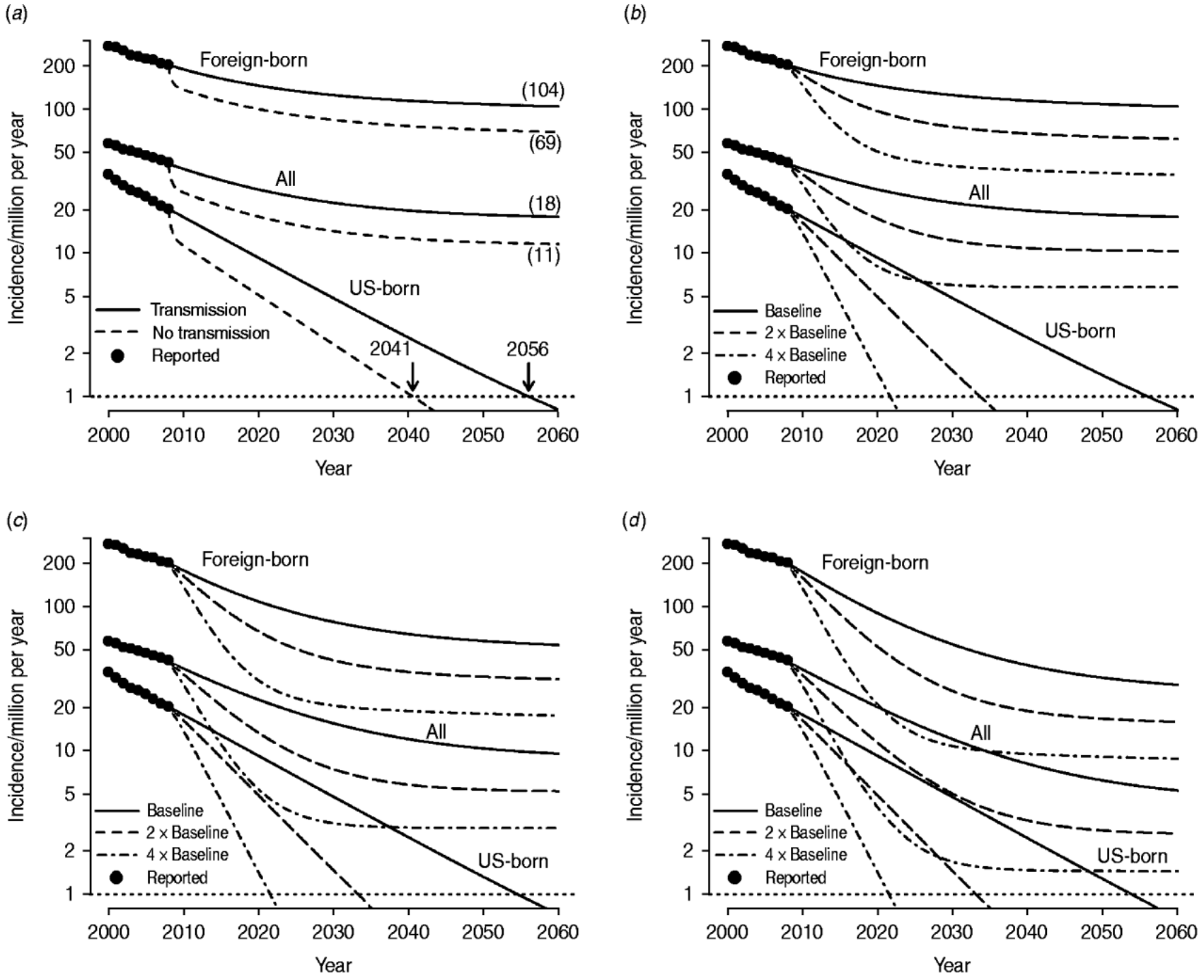
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

Modelling tuberculosis trends in the USA

Provided current efforts:

- Elimination in the US-born population end of this century.
- Elimination in the FB-born population would remain above the elimination target.

(elimination: <1 case/million).

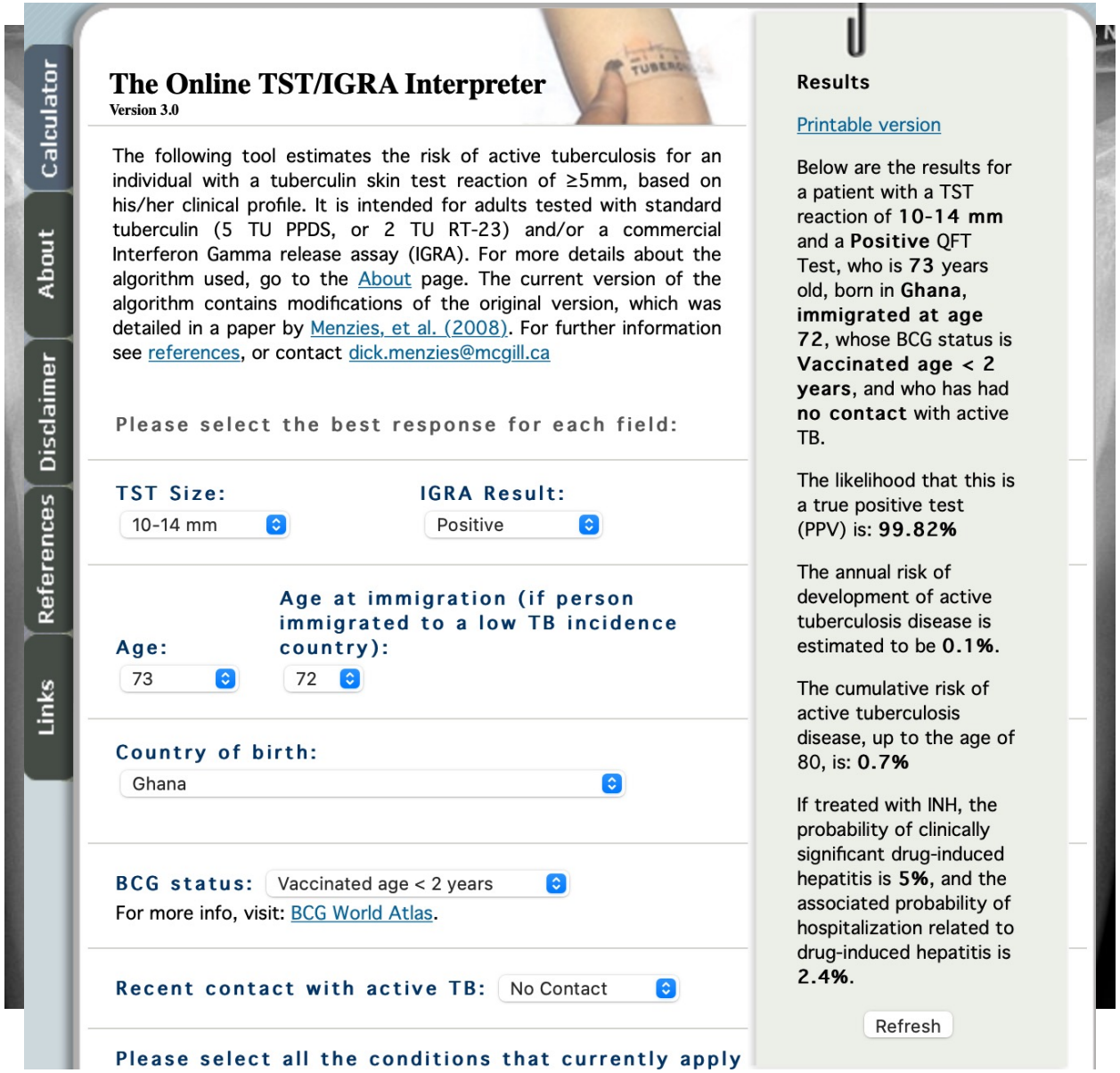


AN Hill, et al. Epidemiol. Infect. (2012), 140, 1862–1872.

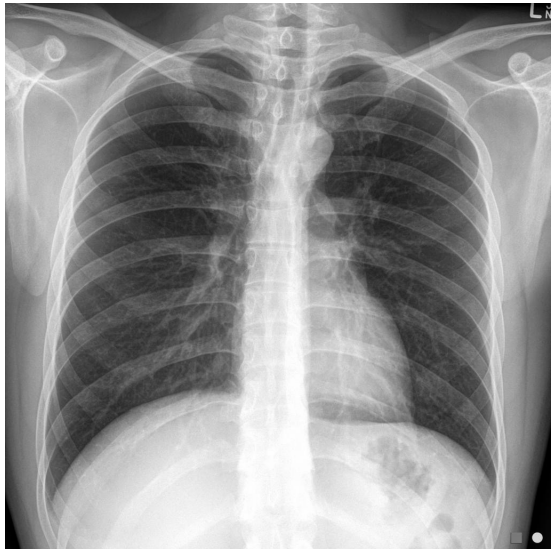
Case 1. 73-year-old female from Ghana

- Tested by PCP for LTBI, IGRA positive
- CXR normal
- HTN, no other comorbidities
- No known TB exposures

- Will you treat for LTBI?
- 1. Yes
- 2. No



Evaluation: Rule out TB disease



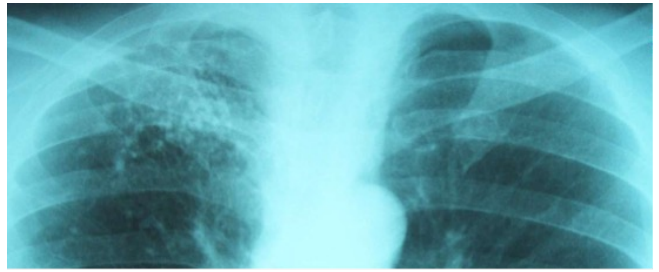
IGRA/TST positive

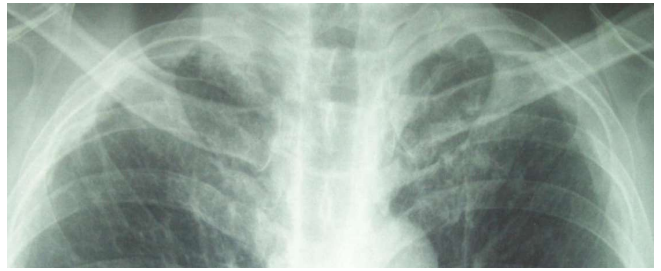
Evaluation of symptoms & physical examination

Chest-X-ray

normal

abnormal





Consider LTBI treatment

Develop a treatment plan to ensure adherence

sputum samples for AFB smear, culture & PCR

Estimated LTBI Prevalence and TB Reactivation Rates, Non-U.S.-Born, 2011–2012

- Woodruff RY, et al. J Immigr Minor Health. 2021 Aug; 23(4): 806–812.

Non-U.S.-born population[a]	LTBI prevalence % (95% confidence interval)	TB reactivation rate (95% confidence interval) per 100 person-years
India	31.7 (21.2, 44.5)	0.087 (0.062, 0.131)
China	30.3 (19.9, 43.1)	0.073 (0.051, 0.110)
Philippines	27.0 (17.8, 38.7)	0.148 (0.103, 0.224)
Vietnam	20.3 (12.2, 31.7)	0.183 (0.117, 0.303)
Mexico	15.3 (10.6, 21.6)	0.071 (0.050, 0.102)
Top 5 countries (Aggregate)[b]	20.0 (15.6, 25.2)	0.091 (0.072, 0.117)
Non-Hispanic Asian, Non-Hispanic Black, or Hispanic	19.1 (15.0, 23.9)	0.091 (0.073, 0.116)
Non-Hispanic White[c]	6.3 (1.9, 18.9)	0.062 (0.021, 0.203)
All non-U.S.-born	16.9 (13.1, 21.5)	0.088 (0.069, 0.114)

Open in a separate window

[a]Persons ≥ 6 years old

[b]Results for China, India, Mexico, Philippines, and Vietnam as a single population

[c]Relative standard error > 30% indicates an unreliable estimate

RR for TB Incidence by Country of Origin, US

Menzies NA, et al. The impact of immigration on tuberculosis in the United States. IJTBLD 2018.

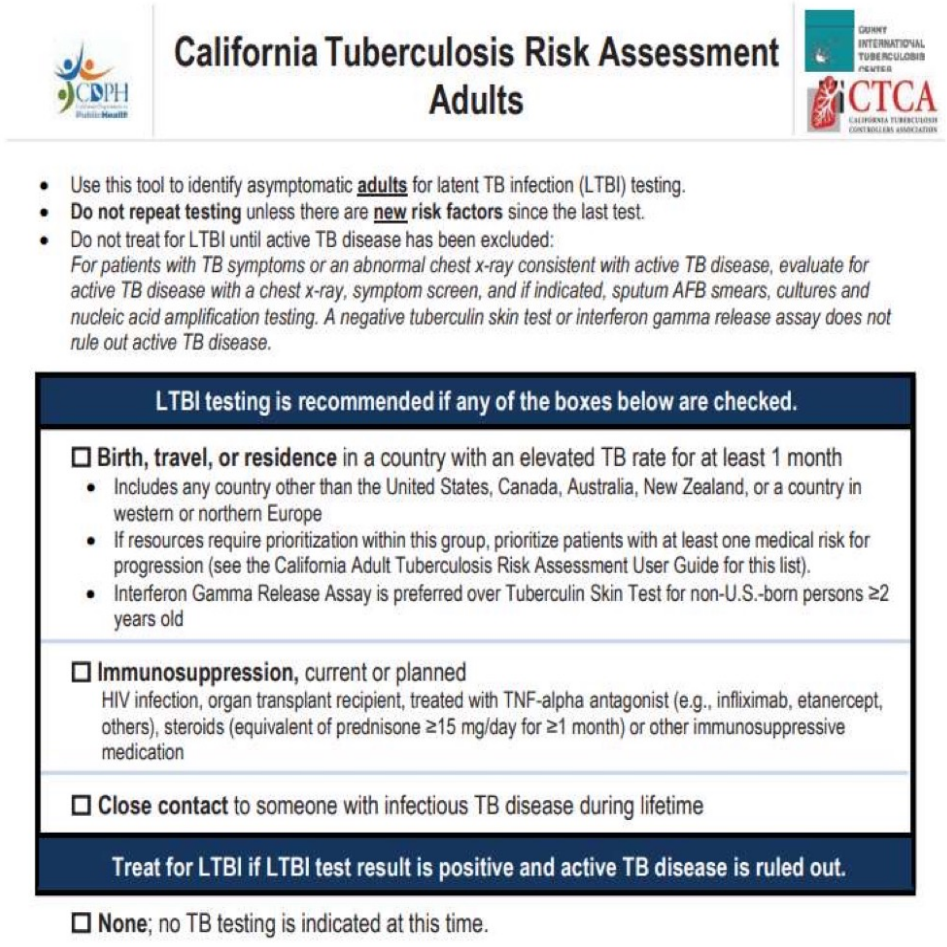
Country	aRR (95%CI)†	RR (95%CI)‡	Country	aRR (95%CI)†	RR (95%CI)‡
Cuba	0.20 (0.18–0.22)	0.27	Pakistan	1.73 (1.62–1.84)	1.99
Russia	0.39 (0.35–0.43)	0.52	Bangladesh	1.77 (1.63–1.91)	2.29
Colombia	0.40 (0.37–0.44)	0.49	Honduras	1.92 (1.83–2.01)	2.20
Taiwan	0.53 (0.48–0.59)	0.61	Haiti	2.24 (2.16–2.34)	2.65
Dominican Republic	0.61 (0.58–0.65)	0.69	Indonesia	2.54 (2.33–2.77)	3.19
El Salvador	0.70 (0.66–0.74)	0.74	Philippines	2.69 (2.62–2.75)	3.42
South Korea	0.82 (0.78–0.86)	0.98	Laos	2.95 (2.75–3.16)	2.65
Mexico (reference)	1.00 (1.00–1.00)	1.00	Viet Nam	3.03 (2.95–3.12)	3.32
China	1.17 (1.13–1.21)	1.79	Liberia	3.24 (2.96–3.54)	4.02
Nigeria	1.29 (1.19–1.39)	1.71	Cambodia	4.12 (3.88–4.39)	4.18
Thailand	1.59 (1.46–1.72)	1.58	Myanmar	4.57 (4.30–4.86)	7.32
India	1.66 (1.61–1.70)	2.36	Nepal	4.85 (4.52–5.21)	7.23
Ecuador	1.66 (1.57–1.76)	1.87	Ethiopia	5.85 (5.59–6.12)	7.59
Guatemala	1.70 (1.63–1.77)	1.85	Kenya	6.48 (6.05–6.94)	7.83
Peru	1.72 (1.63–1.81)	2.17	Somalia	9.58 (9.11–10.08)	13.18

Screening for LTBI in Adults: US Preventive Services Task Force Recommendation Statement

What does the USPSTF recommend?	**For asymptomatic adults at increased risk of latent tuberculosis infection (LTBI):** Screen for LTBI in populations at increased risk. **Grade: B** See "How to implement this recommendation" for additional information on adults at increased risk.
To whom does this recommendation apply?	This recommendation applies to asymptomatic adults 18 years or older at increased risk for tuberculosis (TB). It does not apply to adults with symptoms of TB or to children and adolescents.
What's new?	• This recommendation replaces and is consistent with the 2016 USPSTF recommendation on LTBI screening. • In 2016, the USPSTF recommended screening for LTBI in populations at increased risk (B recommendation).
How to implement this recommendation?	• **Populations at increased risk for LTBI,** based on increased prevalence of active disease and increased risk of exposure, include persons who were born in, or are former residents of, countries with high TB prevalence and persons who live in, or have lived in, high-risk congregate settings (eg, homeless shelters or correctional facilities). • Clinicians can consult their local or state health departments for more information about populations at increased risk in their community, since local demographic patterns may vary across the US. • Two types of screening tests for LTBI are currently available in the US: the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA). ° The TST requires trained personnel to administer intradermal purified protein derivative and interpret the response 48 to 72 hours later. ° The IGRA requires a single venous blood sample that measures the CD4 T-cell response to specific *Mycobacterium tuberculosis* antigens and laboratory processing within 8 to 30 hours after collection. ° Testing with IGRA may have advantages over TST for persons who have received a BCG vaccination, as IGRA does not cross-react with the vaccine, and for persons who may be unlikely to return for TST interpretation. • The USPSTF found no evidence on the optimal frequency of screening for LTBI. • In the absence of evidence, a reasonable approach is to repeat screening based on specific risk factors; screening frequency could range from 1-time-only screening among persons at low risk for future TB exposure to annual screening among those who are at continued risk of exposure. • Additional examinations, diagnostics, and tests (ie, medical history, physical examination, chest radiograph, and other laboratory tests) are essential to completing a diagnosis of LTBI. • Current recommendations for the treatment of LTBI are available from the Centers for Disease Control and Prevention (CDC).

JAMA. 2023;329(17):1487-1494. doi:10.1001/jama.2023.4899

Risk factors for developing Active TB



California Tuberculosis Risk Assessment Adults

- Use this tool to identify asymptomatic **adults** for latent TB infection (LTBI) testing.
- **Do not repeat testing** unless there are **new risk factors** since the last test.
- Do not treat for LTBI until active TB disease has been excluded:
  For patients with TB symptoms or an abnormal chest x-ray consistent with active TB disease, evaluate for active TB disease with a chest x-ray, symptom screen, and if indicated, sputum AFB smears, cultures and nucleic acid amplification testing. A negative tuberculin skin test or interferon gamma release assay does not rule out active TB disease.

LTBI testing is recommended if any of the 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
- If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see the California Adult Tuberculosis Risk Assessment User Guide for this list).
- Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for non-U.S.-born persons ≥2 years old

☐ **Immunosuppression,** current or planned
HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) 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.

☐ **None**; no TB testing is indicated at this time.

Risk Factor	Estimated risk for TB relative to persons with no known risk factor
HIV/AIDS	50-170
Transplantation and on immunosuppressant therapy	20-74
Silicosis	30
Chronic renal failure on hemodialysis	10-25
Carcinoma of head and neck	16
Recent TB infection (<2 years)	15
Abnormal CXR with upper lobe fibronodular disease consistent with old TB	6-19
TNF-alpha inhibitor therapy	1.9-9
Treatment with glucocorticoids	4.9
Diabetes mellitus	2-3.6
Young age when infected (0-4 years)	2.2-5
Underweight (BMI ≤ 20)	2-3
Cigarette smoker (1 pack/day)	2-3
Abnormal CXR- granuloma	2
Latent TB infection, normal CXR, no known risk factor	1

*Adapted from: Lobue P, Menzies D. Treatment of latent TB infection: An update. Respirology. 2010 May;15(4):603-22.

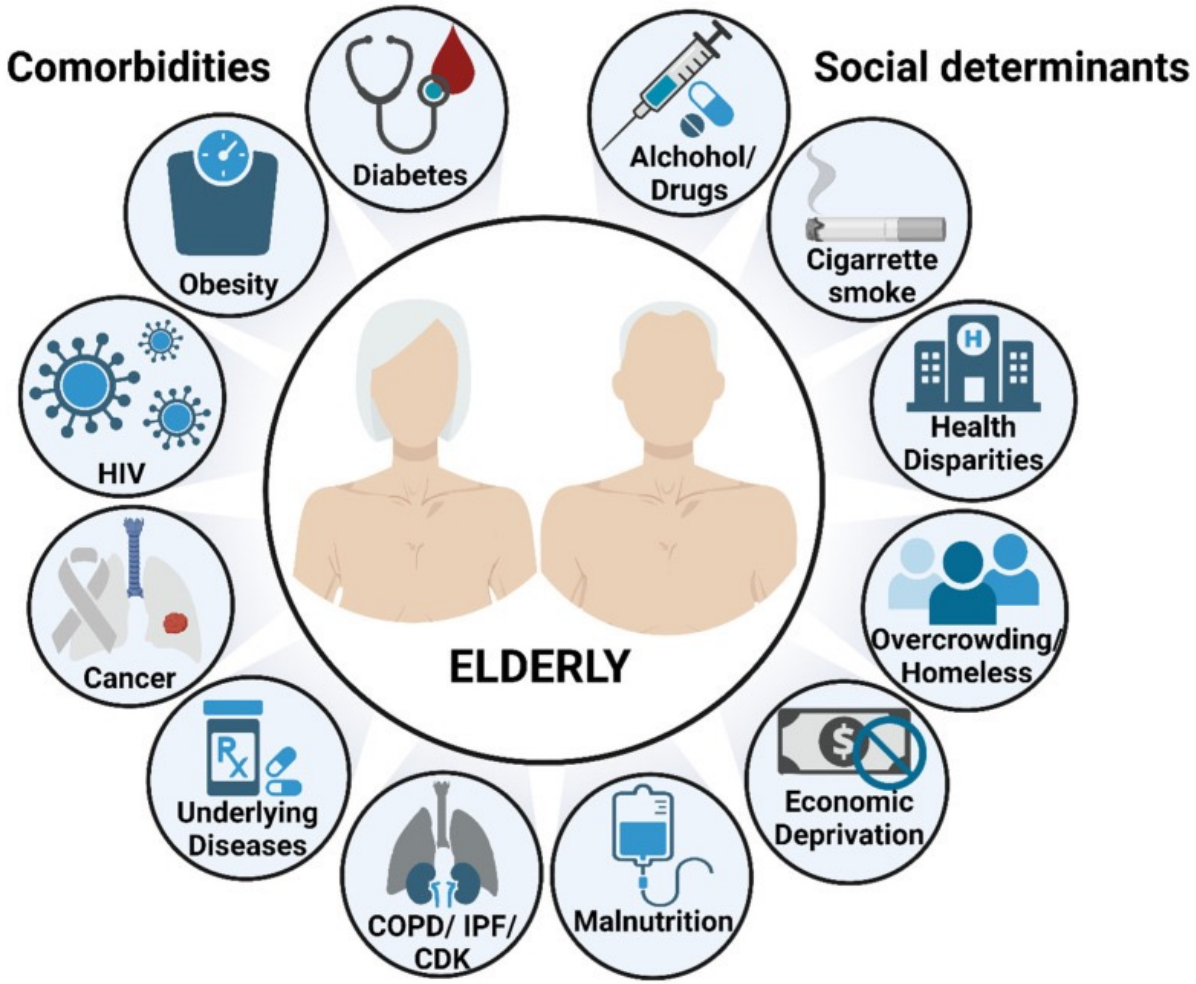
Risk factors of TB disease and mortality in the elderly

The elderly are a large reservoir of *M.tb*

Foreign- born older persons account for an increasing proportion of older TB cases

Additional risk factors, comorbidities and socioeconomic determinants may increase risk

>65 years of age a significant burden of TB cases in the US



Olmo-Fontanez A, et al. TB in the aging world. Pathogens. 2022 Sep 26;11(10):1101.

Options for Treatment of LTBI: CDC, 2020

Regimen	Priority Rank	Recommendation	Quality of Evidence (High, Moderate, Low, Very Low)
3HP	Preferred	Strong	Moderate
4R	Preferred	Strong	Moderate (HIV-negative)*
3HR	Preferred	Conditional	Very low (HIV-negative) Low (HIV-positive)
6H	Alternative	Strong^ Conditional	Moderate (HIV-negative) Moderate (HIV-positive)
9H	Alternative	Conditional	Moderate

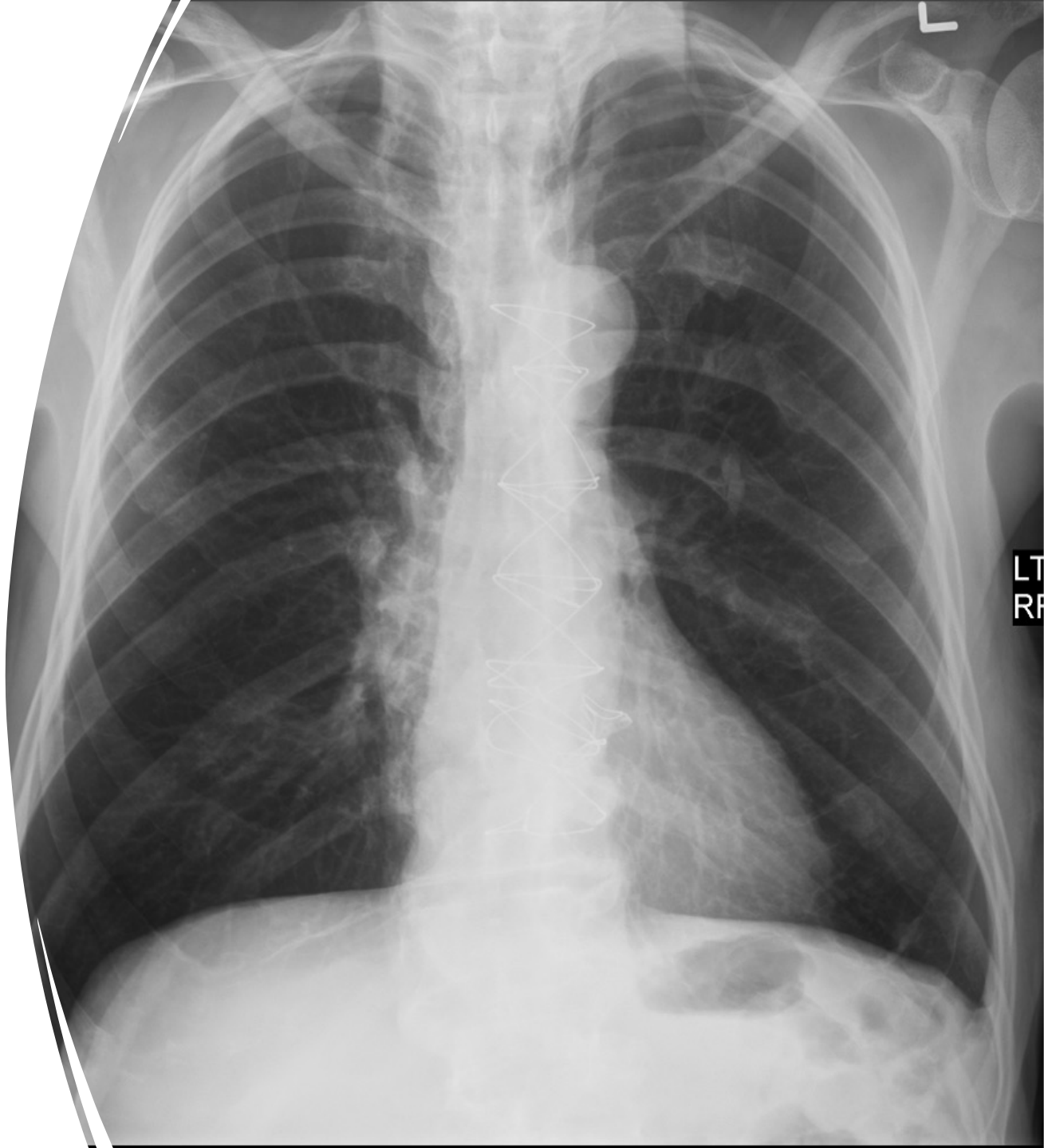
* No evidence reported in persons with HIV infection.

^ Strong recommendation for persons unable to take a preferred regimen (e.g., because of drug intolerability or drug-drug interactions)

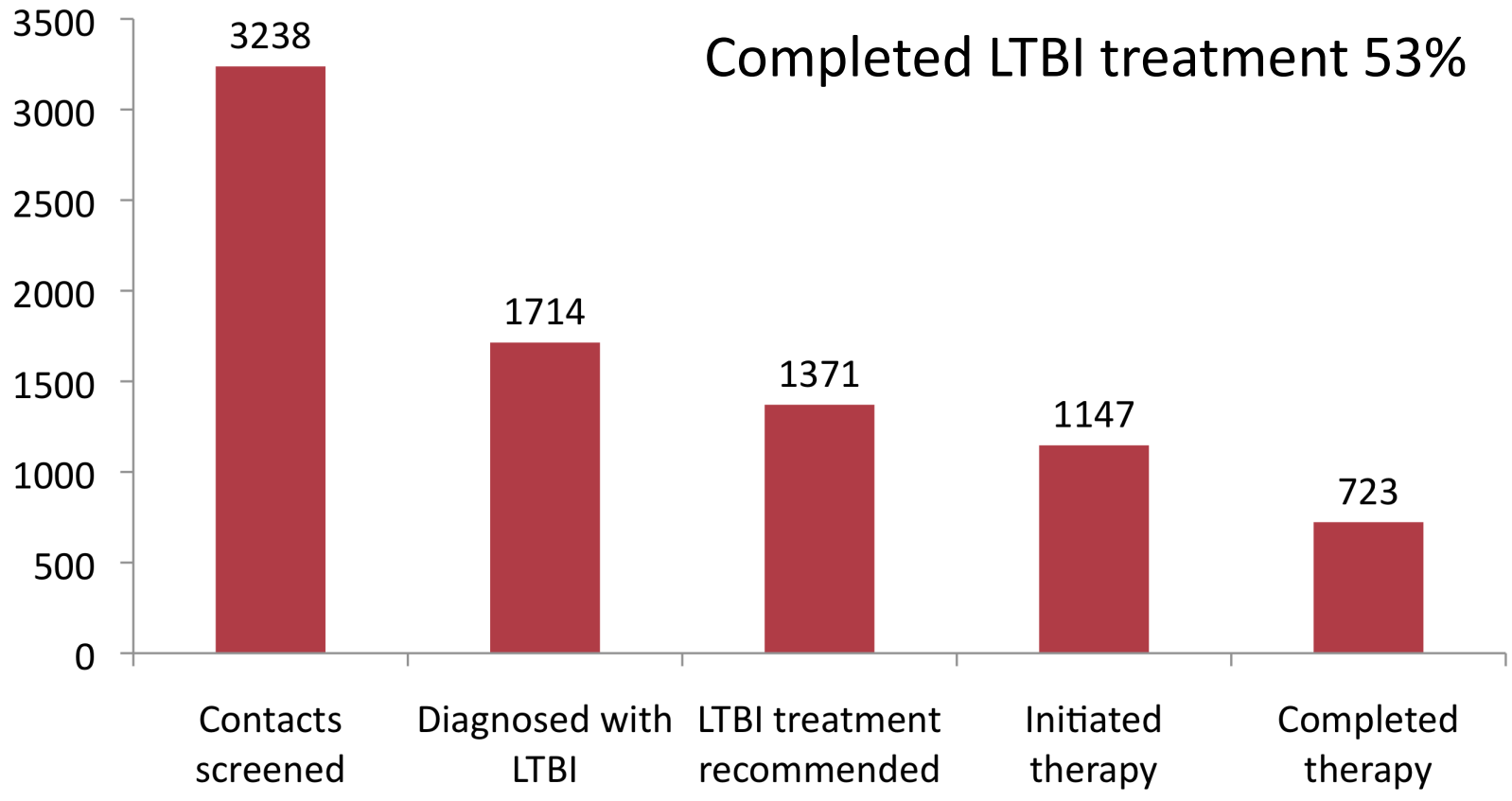
Source: Adapted from Sterling TR, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep.* 2020 Feb 14;69(1):1-11.

Case # 1

- 52-year-old white male with uncontrolled DM, US born, homeless, history of IVDU
- Exposed to an active TB case in a homeless shelter
- Denies any symptoms
- IGRA reactive/ CXR normal
- Started on INH, lost to follow 2 months

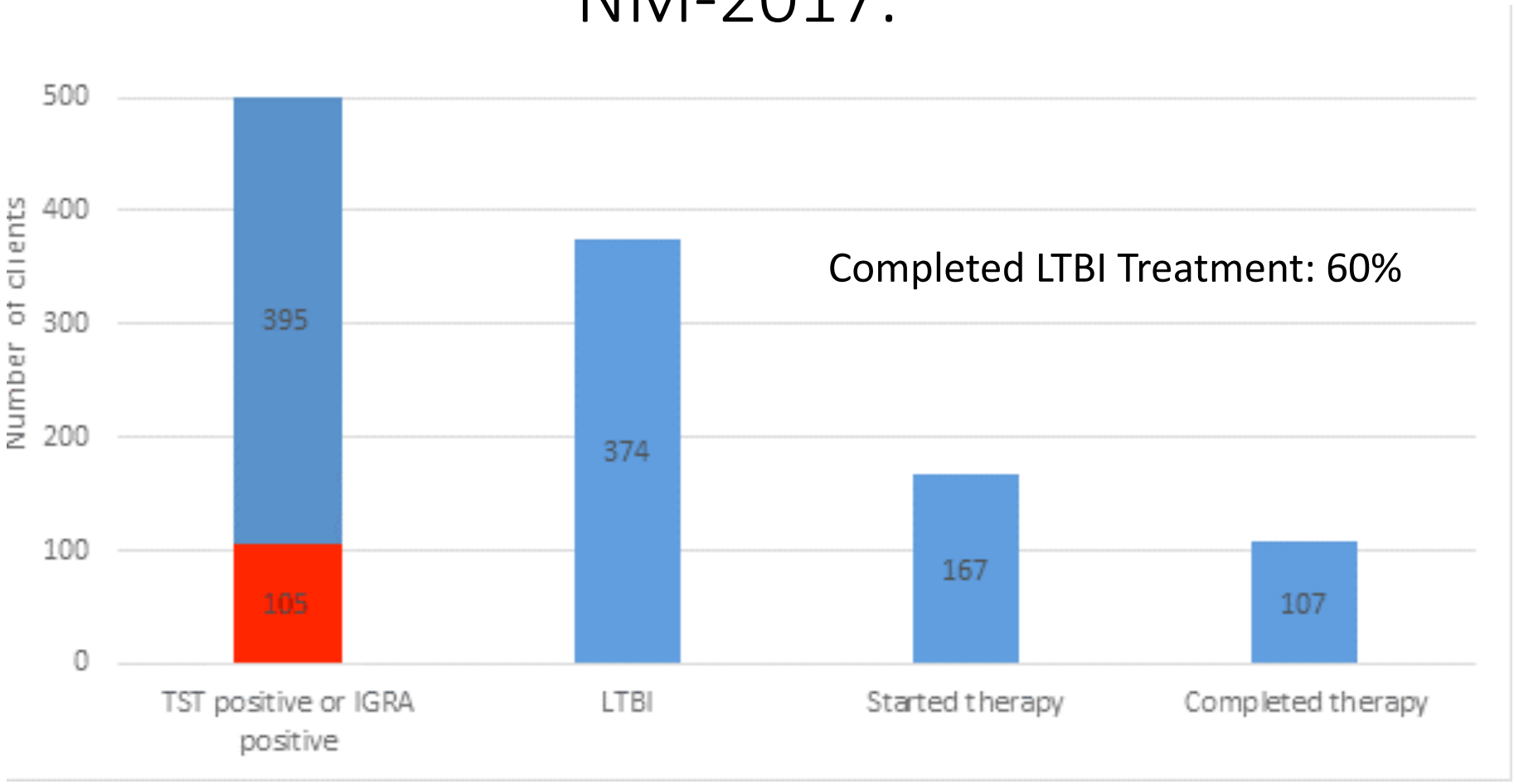


The clinical reality of TB screening cascade among contacts of AFB smear positive cases



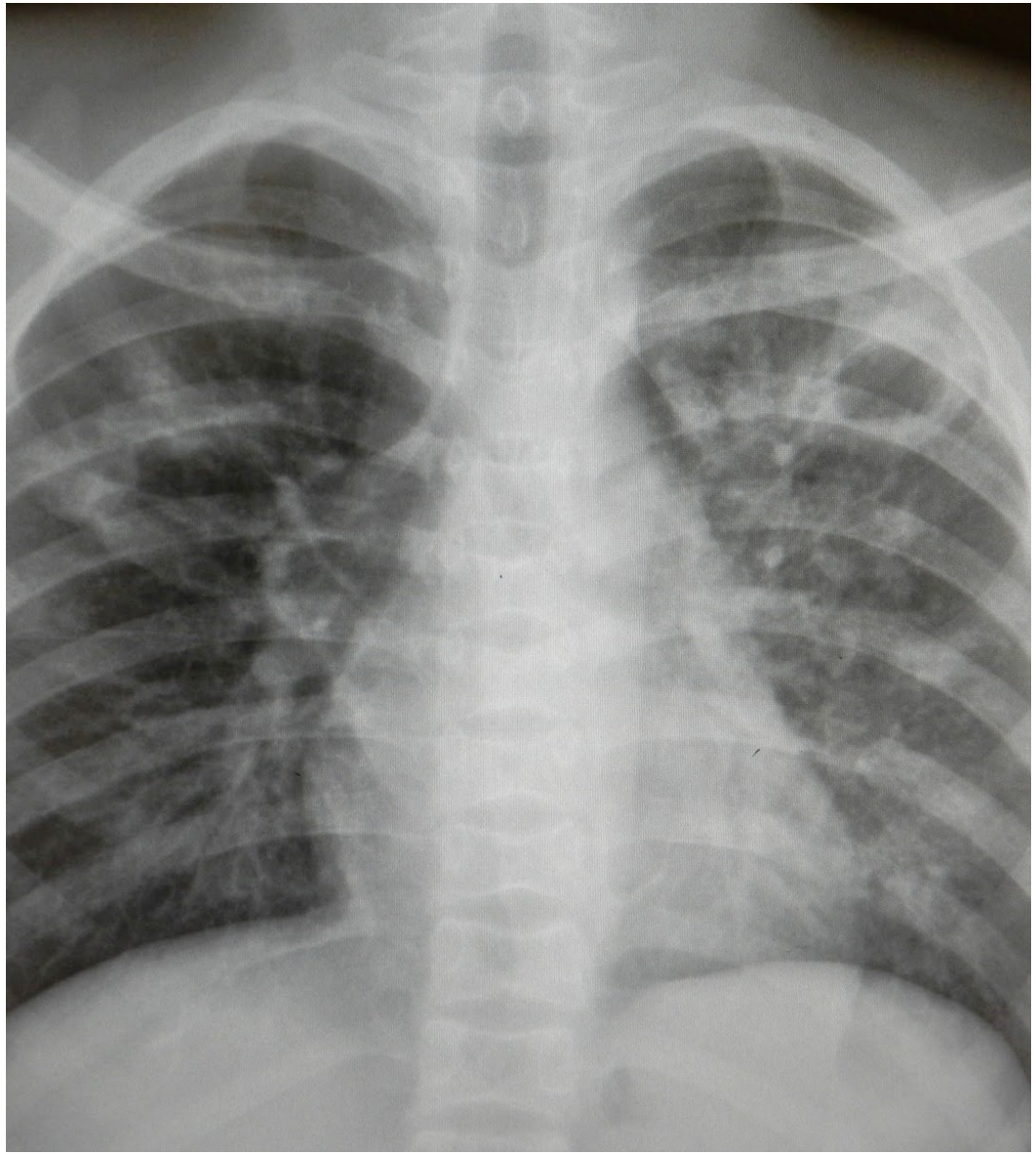
Int J Tuberc Lung Dis. 2014: 18(4)

Cascade of LTBI Diagnosis to Treatment Completion, NM-2017.



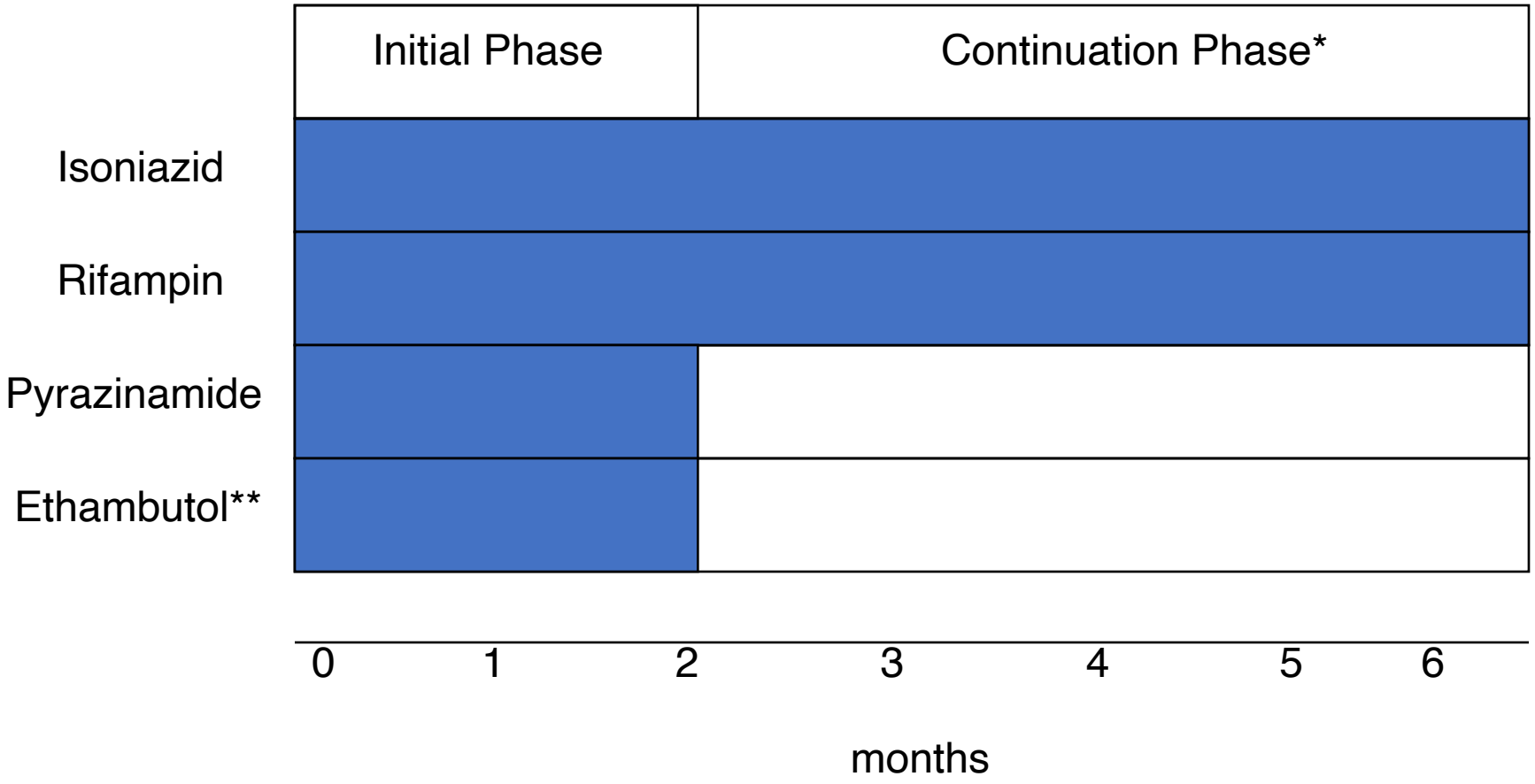
Case # 1 cont.

- A year later patient admitted with DKA and pneumonia
- He was treated for CAP and discharge to homeless shelter
- Persistent cough, CXR cavitary disease, HIV negative
- Sputum's smear positive 2 +, NAAT test positive for MTB complex



Treatment of Tuberculosis

Standard Regimen



*7 months for some patients

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[6]

[1]University of California, San Francisco; [2]Johns Hopkins University, Baltimore, Maryland; [3]California Department of Public Health, Richmond; [4]McMaster University, Hamilton, Ontario, Canada; [5]National Jewish Health, Denver, Colorado; [6]World Health Organization, Geneva, Switzerland; [7]Tuberculosis Control Section, San Francisco Department of Public Health, California; [8]Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [9]Harvard Medical School, Boston, Massachusetts; [10]McGill University, Montreal, Quebec, Canada; [11]WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri Care and Research Institute, Tradate, Italy; [12]Tuberculosis Control Program, Seattle and King County Public Health, and University of Washington, Seattle; [13]Ethics Advisory Group, International Union Against TB and Lung Disease, Paris, France; [14]University of Florida, Gainesville; [15]Boston University, Massachusetts; [16]Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [17]University of Sassari, Italy; and [18]Baylor College of Medicine, Houston, Texas

The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. *Mycobacterium tuberculosis*; HIV infections; antitubercular agents; case management; public health.

Preferred Regimens for Newly Diagnosed Pulmonary TB

Initial			Continuation	
Reg	Drugs	Interval/Dose	Drugs	Interval/Dose
1	INH RIF EMB PZA	7 days/wk (56) or 5 days/wk (40)	INH/RIF	7 days/wk (126) or 5 days/wk (90)
2	INH RIF EMB PZA	7 days/wk (56) or 5 days/wk (40)	INH/RIF	3 days/wk (54)

Effectiveness

ATS/CDC/IDSA. AJRCCM 2016 167:735

Objectives of the Treatment of Tuberculosis

01

Prevent the development of drug resistance with the use of combination of drugs

Two-month sputum culture conversion

Best biomarker of durable cure

Use to predict likelihood of relapse

Use as a marker of sterilizing activity of a drug regimen

Marker use in the accelerated approval of new tuberculosis drugs, potentially shortening the time needed for licensing of new drugs

Walis RS, The Lancet. Vol. 375, 2010.

Case # 1, cont.

- The patient management was individualized to incorporate measures that facilitate his adherence to treatment with a patient-centered approach
  - DOT
  - social service support
  - treatment incentives and enablers,
  - housing assistance
  - referral for treatment of substance abuse,
  - comanagement of comorbidities with PCP

DOT remains the standard of practice

- Evidence in support of this practice guideline showed that DOT was significantly associated with improved treatment outcomes in terms of patients cured and patients completing treatment
- However, the evidence did not find significant differences between SAT and DOT in terms of mortality, treatment completion and relapses
- DOT is not amenable to be study in conventional clinical trials

2016 ATS/CDC/IDSA TB treatment Guidelines

Treatment of Drug Susceptible TB Summary

Intermittent treatment Three times/week - from beginning has higher rates of failure and relapse, and ADR in multiple reviews
Daily initially (IP) then Twice weekly intermittent in continuation phase has higher rates of relapse
Daily initially, followed by Thrice weekly therapy has very good results

Treatment of Drug Susceptible TB Summary

- Treatment and its completion is the single most important factor in controlling TB in a population
- Treatment involves initiation of 4-drugs in the initial phase followed by two drugs during the continuation phase
- Duration of therapy is 6 months
  - Treatment should be extended to 9 months when cavitation is present on the xray AND the culture is still positive after 2 month of therapy.
- Patients with TB meningitis should be treated with adjunctive corticosteroids

Thank you!

Other relevant Sources

- Testing and Treatment of Latent Tuberculosis Infection in the United States http://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/
- Resources and continuing education activities on LTBI for clinicians (https://www.cdc.gov/tb/education/provider_edmaterials.htm), a guide for primary health care providers (https://www.cdc.gov/tb/publications/ltbi/pdf/LTBIbooklet508.pdf), and an online resource hub for information about LTBI (https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm).
- CDC's "Think.Test.Treat TB" campaign information to help inform and guide patient and clinician conversations (https://www.cdc.gov/thinktesttreattb/index.html).
- **American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America. 2016 Clinical Practice Guidelines AJRCCM 2016 167:735**
- **Effects of Intermittency on treatment outcomes in pulmonary tuberculosis: An Updated Systematic Review and Meta Analysis CID 2017; 64 May 1st.**