Latent Tuberculosis Infection:
The Basics

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Focus on LTBI, Seattle, July 2023

Latent Tuberculosis Infection (LTBI): The Basics - Overview

NTCA/CDC LTBI Guidelines: Guidelines for the Treatment of Latent Tuberculosis infection *(February 2020 MMWR; prior 2000!)*

Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations (February 2021, NTCA)

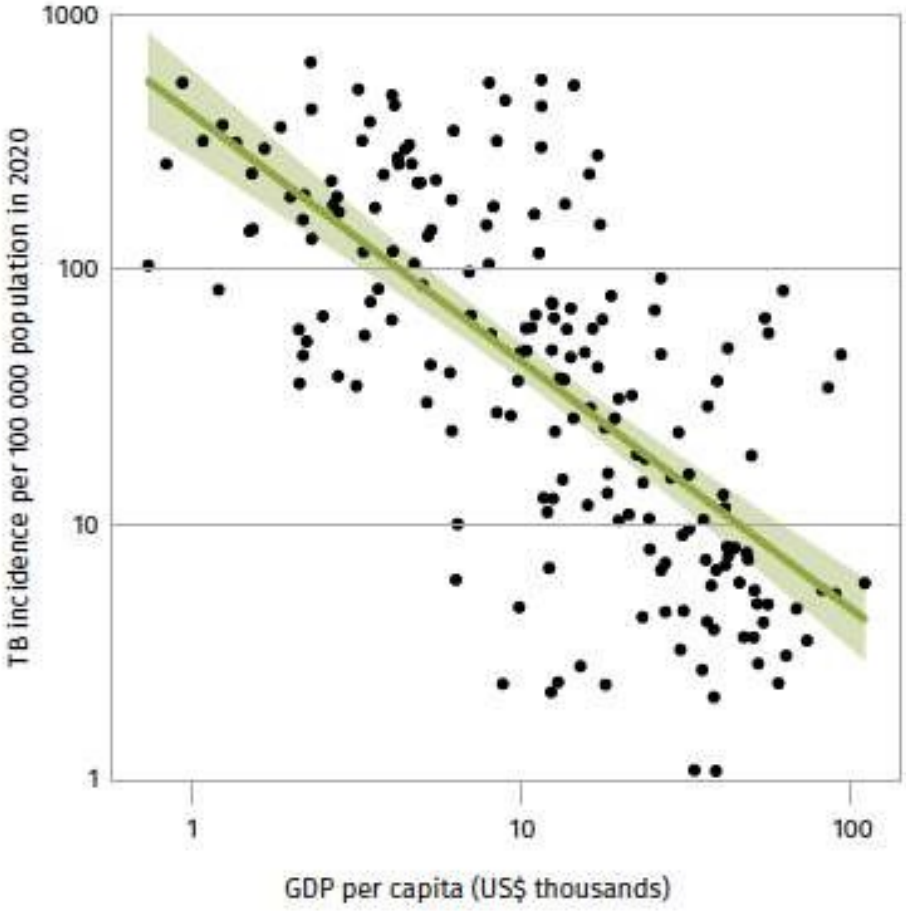
- LTBI epidemiology
- (Words we use matter)
- Pathophysiology
- Who to prioritize for testing:
  TB risk groups

TB is Global

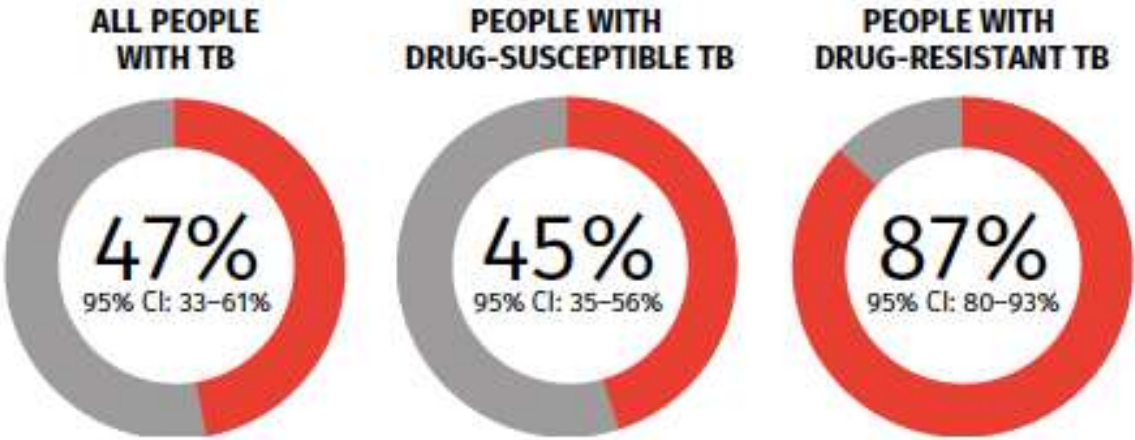
- Approx. one-quarter of the world's population is infected with TB
- 9.9 million cases active TB/yr
- 1.5 million TB deaths/yr

WHO 2021 Global Tuberculosis Report (2020 data)

Relationship between wealth and TB: higher GDP, lower TB incidence but TB associated with catastrophic costs



Average percentage of people with TB and their households facing catastrophic costs in 23 national surveys completed since 2015



Global TB Report, 2021

Addressing the negative impact of low income and expanding social protection could drastically decrease TB incidence globally

- Ending extreme poverty: reduces global TB incidence by 33% by 2035
- Expanding social protection coverage: reduces TB incidence by 76%.
- Together, both estimated to reduce TB incidence by 84%

The Paraisópolis favela in São Paulo, Brazil, and the neighbouring district of Morumbi
Tuca Vieira

Carter DJ, et al. Lancet Glob Health. 2018 May;6(5):e514–22

Global TB Report, 2018

TB is Local: U.S.

Only the “tip of the iceberg” →

*TB in the United States – CDC 2022 data

8,300 people with active TB (a rate of 2.5 cases per 100,000 persons)

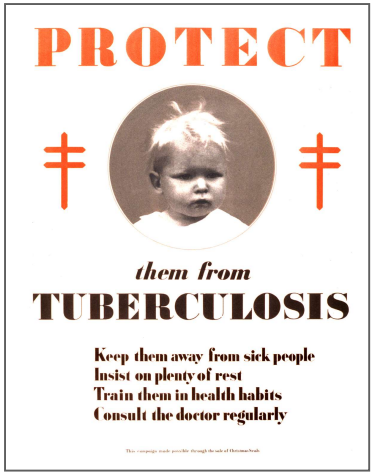
Estimated U.S. up to 13 million persons with Latent TB infection

(Mirzazadeh et al 2021: model w/ Nat. TB surv. syst. data 2013-2017; est. 2.7% prevalence)

Approx. 80% of active cases due to reactivation (*Shea KM et al, Am J Epidemiol 2014)*

Preventable!

Targeted Testing and Latent Tuberculosis Infection



Fundamental Principles:

- As a low incidence country, targeted testing and treatment of LTBI is an essential component of the strategic plan towards TB elimination in the US

 Focus on high-risk individuals

Goal: Reduce reservoir of latent TB

"A Decision to Test is a Decision to Treat (think)"

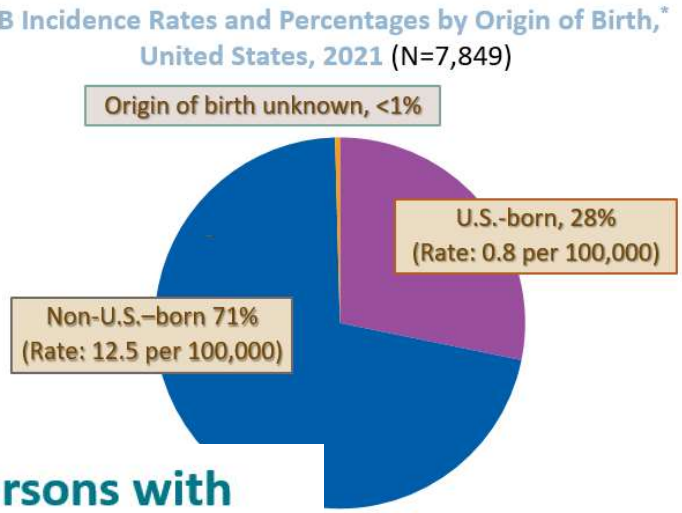
US Prevalence LTBI: Subgroups

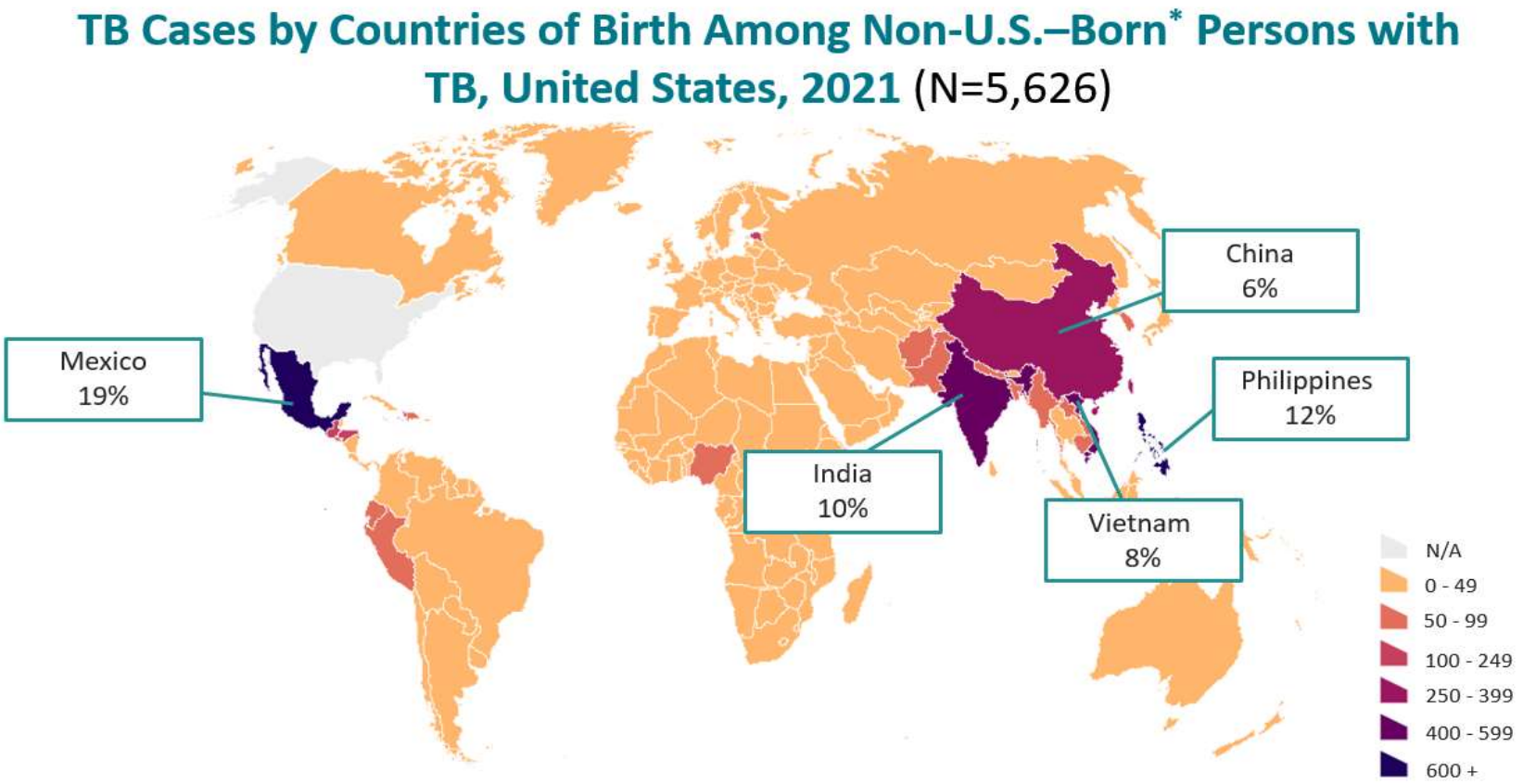
Horsburgh NEJM 2011

Table 1. Prevalence of Latent TB Infection among US residents as assessed by TB skin testing

Group and Study	Expected Prevalence (95% CI), %
Foreign-born persons	
Bennett et al.	**18.7** (13.5-25.2)
Close contacts of persons with infectious TB	
Marks et al.	**37.1** (35.7-38.5)
Homeless persons	
Kong et al.	12.8 (12.2-13.5)
Moss et al.	32.4 (30.5-34.4)
Injection drug users	
Riley et al.	16.1 (12.5-22.4)
Grimes et al.	27.7 (19.3-37.5)
Brassard et al.	22.4 (17.7-28.5)
Salomon et al.	14.0 (11.4-17.1)
Prisoners	
Lobato et al.	17.0 (16.8-17.1)
US-born, no other risk	
Bennett et al.	**1.8** (1.4-2.1)

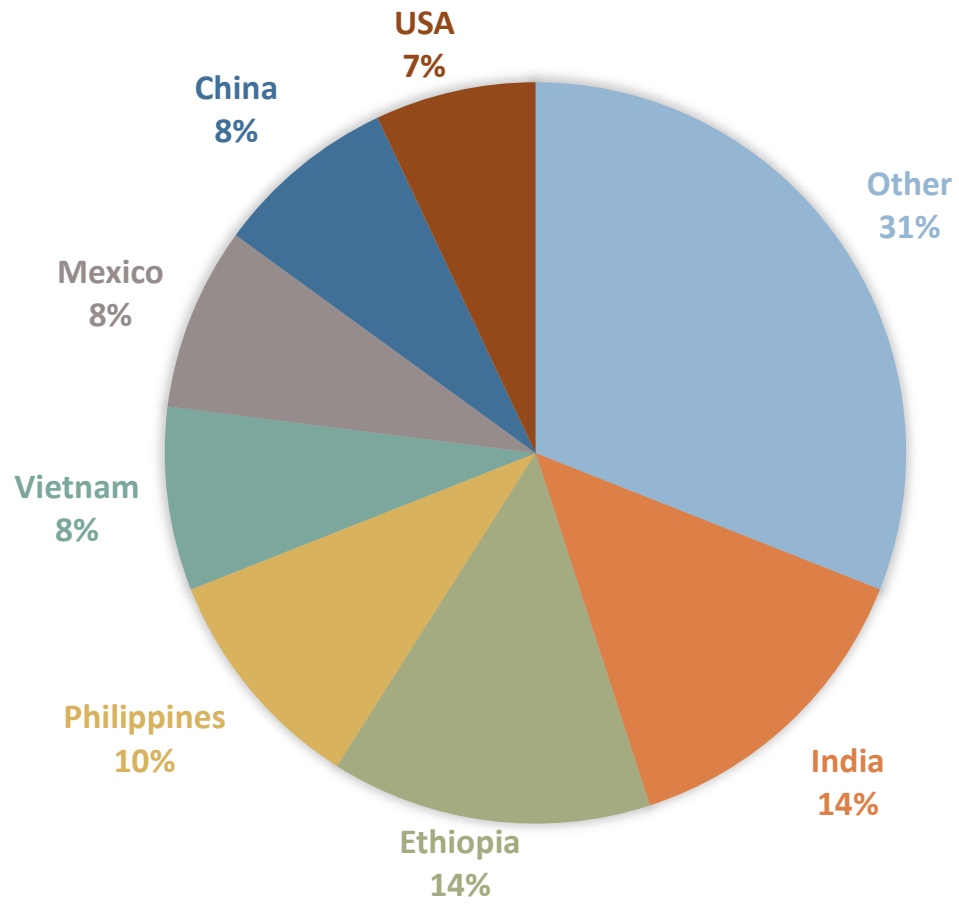
People with active TB by Origin of Birth



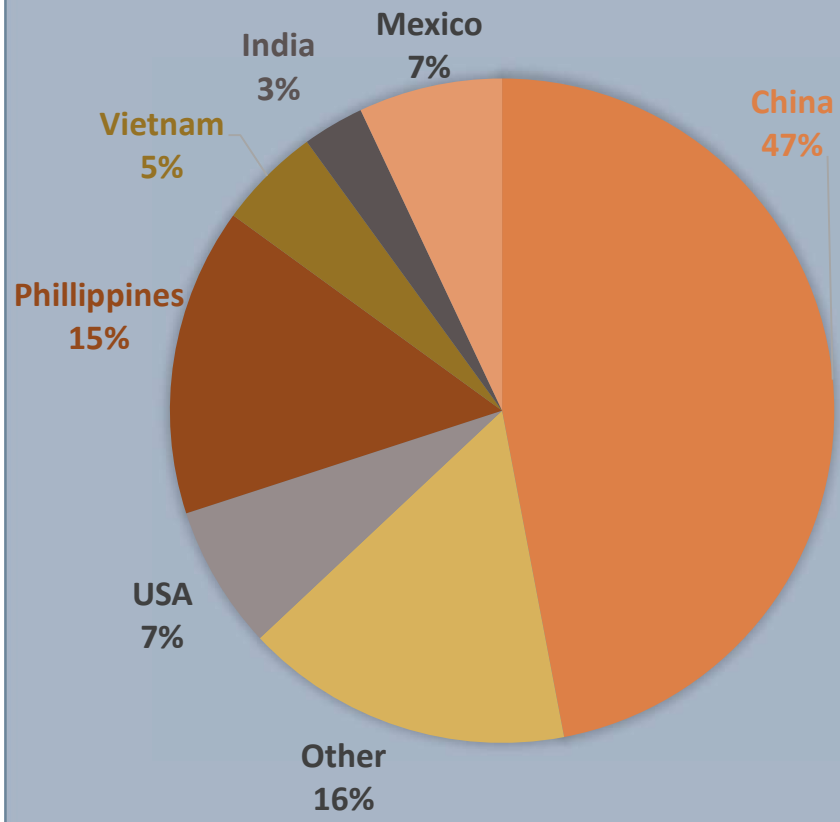


But look at what's happening in your own area……

Proportion of TB cases by country of origin, 2021 Seattle/King County, WA



….compared to 2021 San Francisco, CA



your home,

your priorities,

your practice….

Talking to patients about TB Screening

← **Scary**

- First—check yourself—how are you showing up today for your patients?
- "We aim to provide you care that is inclusive of and respects your lived experience."
- "Based on places you've lived or visited previously, it would be beneficial to your health to screen you for TB."
- "This is considered part of routine preventative care"
- "Your BCG vaccine, like many others, only protects against severe forms of TB. Its protection decreases over time and after childhood"

Clinical scenario: Is it something I said?

- Mr. X is a recent immigrant with LTBI. I tell him that his positive PPD means that he has been exposed to TB and I think that he should start preventive treatment.
- He explains to me that since he has only "been exposed" and doesn't have the disease that he graciously declines.

"Latent TB Infection" = TB infection

Rather than saying:

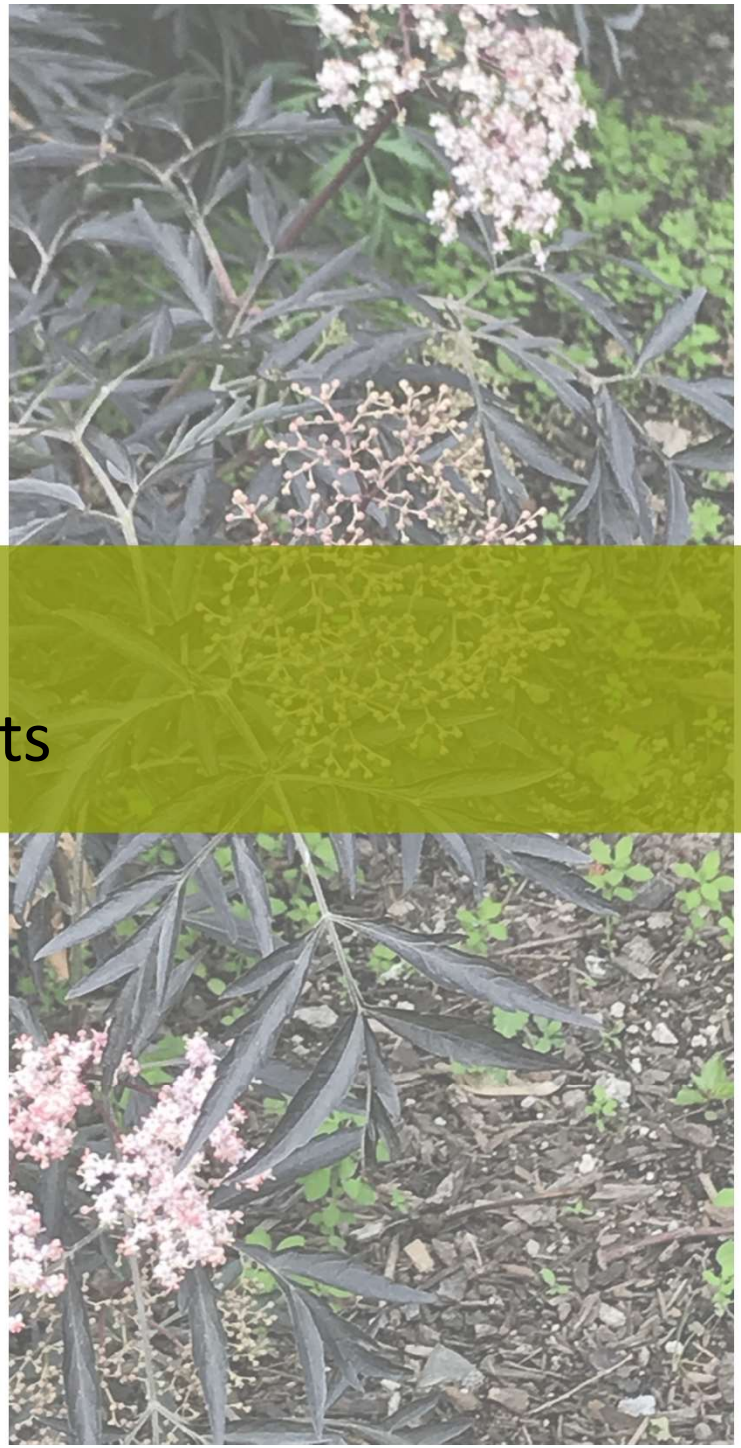
- "You have been exposed to TB…"
- "We would like to give you preventative/prophylactic treatment for TB…"

Say this:

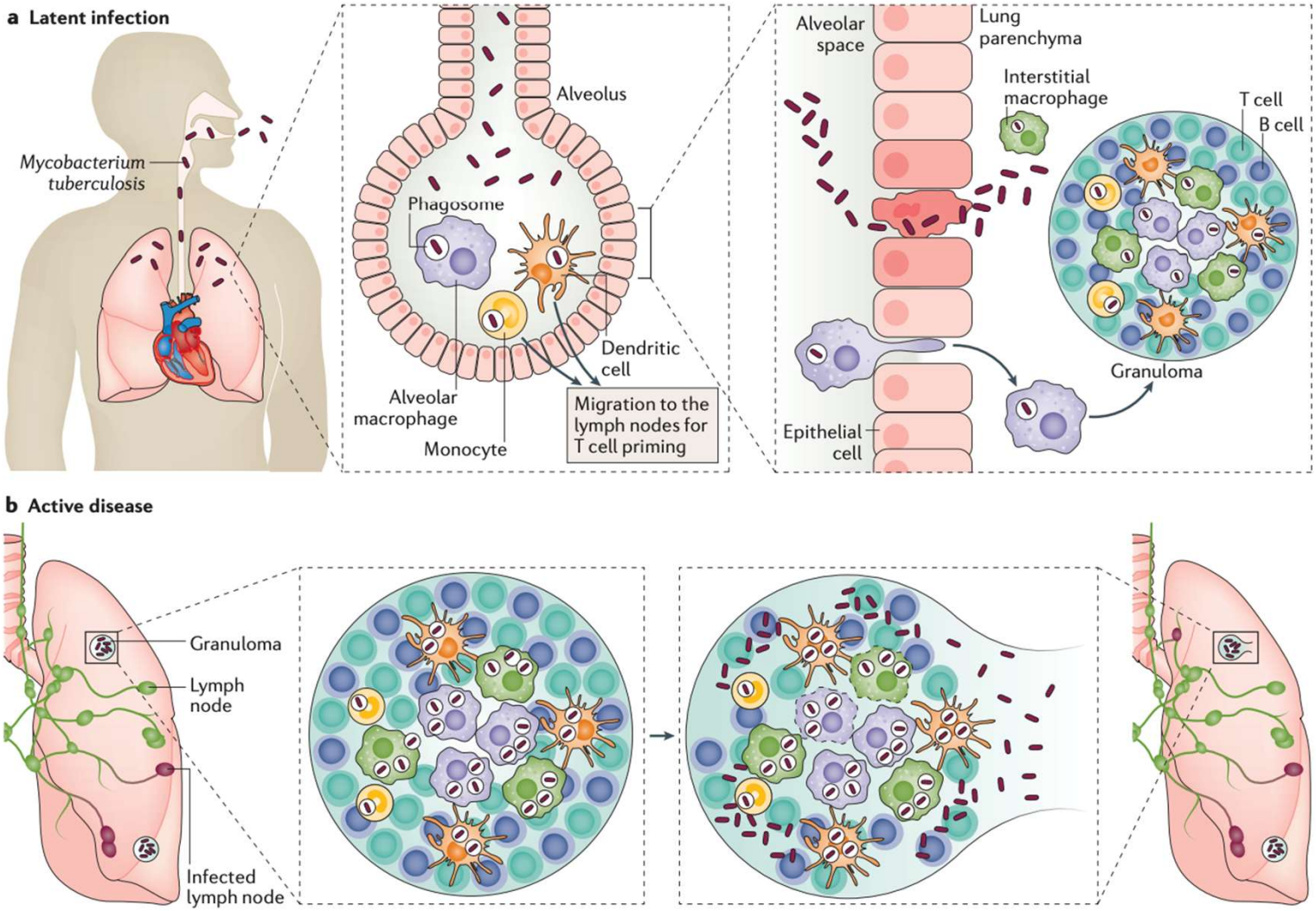
"You are infected with TB, but it is in a dormant state now ("sleeping TB" or what we call latent TB infection). We would like to treat the infection now before it has a chance to "wake-up" and become active…

Pair and share

What are your favorite words
to use to explain LTBI to your patients



TB Pathophysiology: from infection to active disease



TB Primer Nature Reviews, Pai 2016

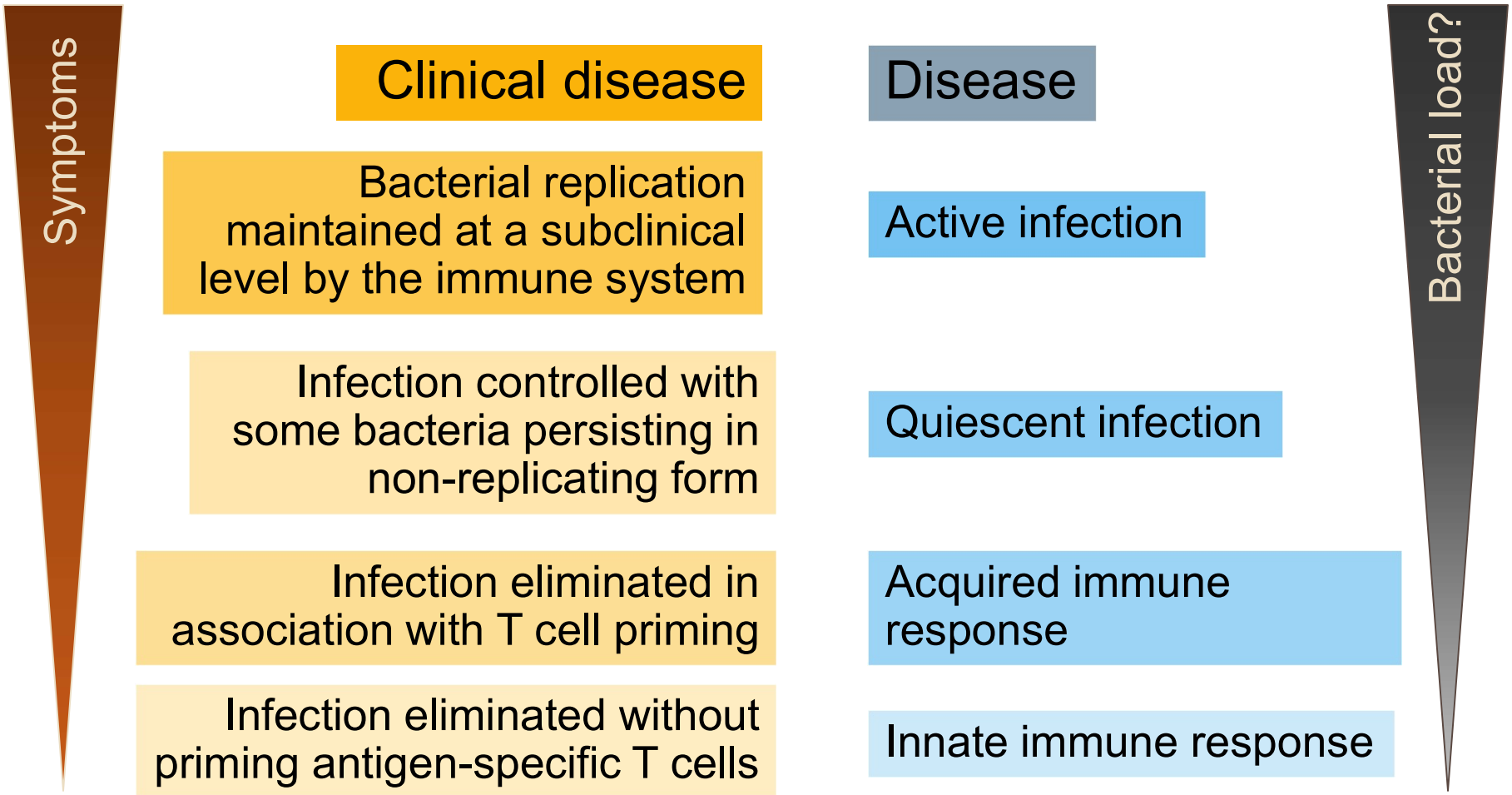
Compare LTBI vs Active TB

	Latent TB Infection	Active TB Disease
TST	Positive	Usually positive
IGRA	Positive	Usually positive
Culture	Negative	Positive (80%)
Sputum smear	Negative	Positive or negative
Infectious	No	Yes
Symptoms	None	Mild to severe
Preferred treatment	Preventive therapy	Multidrug therapy

Adapted: TB Primer Nature Reviews, Pai 2016

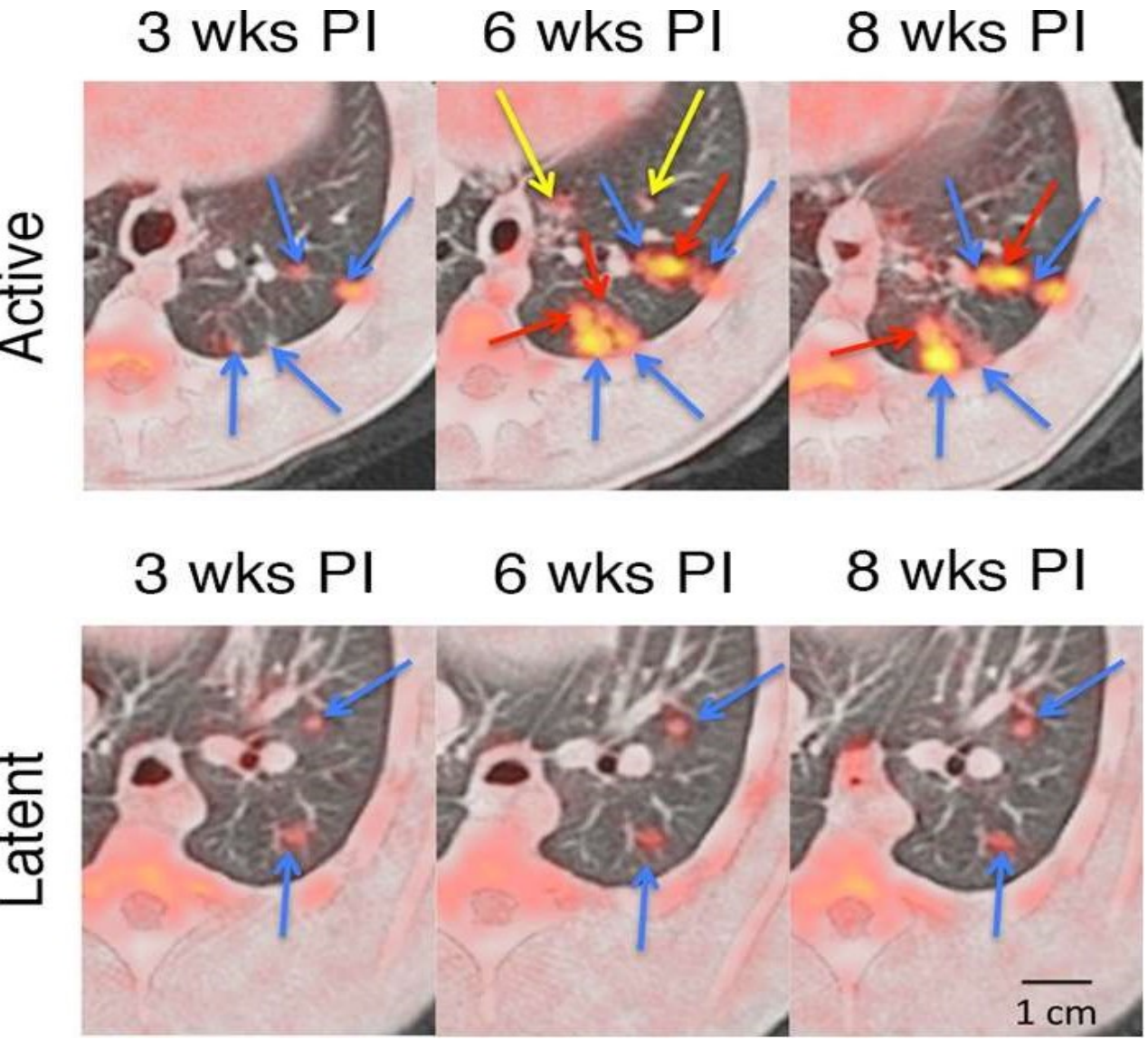
Are the bugs truly "sleeping"…….?

Probably not a true binary "latent vs. active"-----> SPECTRUM



Barry C et al. Nature Reviews 2010 (modified)

Evidence of activity: PET/CT LTBI vs active TB

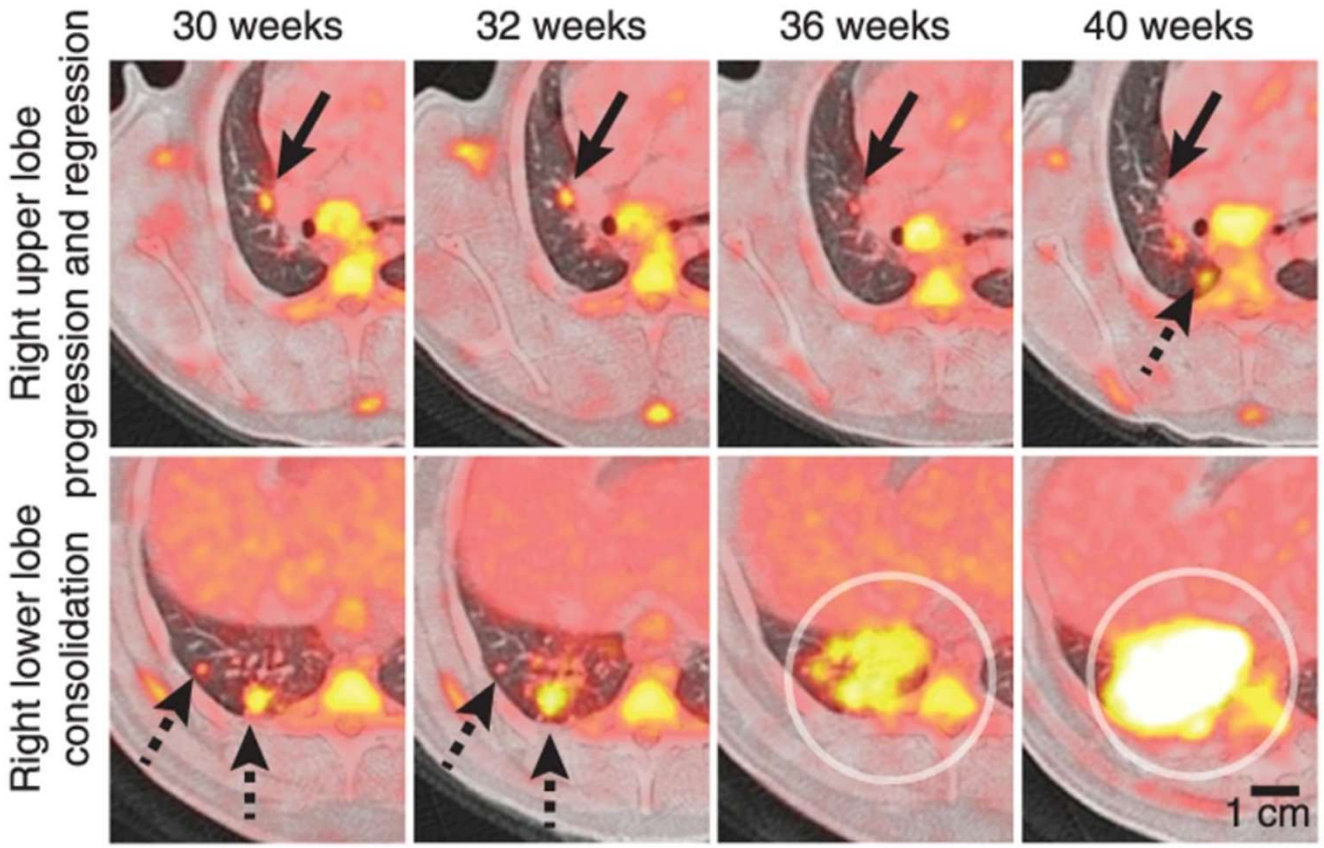


- Macaque monkey
- Inoculated with TB via bronchoscopy
- Followed with PET/CT over 6 mo.
- At 6 mo., classified as LTBI vs. TB disease
  - Clinical
  - Radiographic
  - Microbiologic (BAL)
  - Inflammatory markers (ESR)

Coleman. Infect Immun. 2014.

Moving forward – so much yet to learn….

Primate model: PET CT following active lesions: both grow/regress



Lin PL et al (JL Flynn) Nature Medicine 2013

Risk vs. benefit: what are the chances someone will develop active TB?

LTBI: Lifetime risk for (active) TB Disease

- In general: 5-10% lifetime risk of Active TB

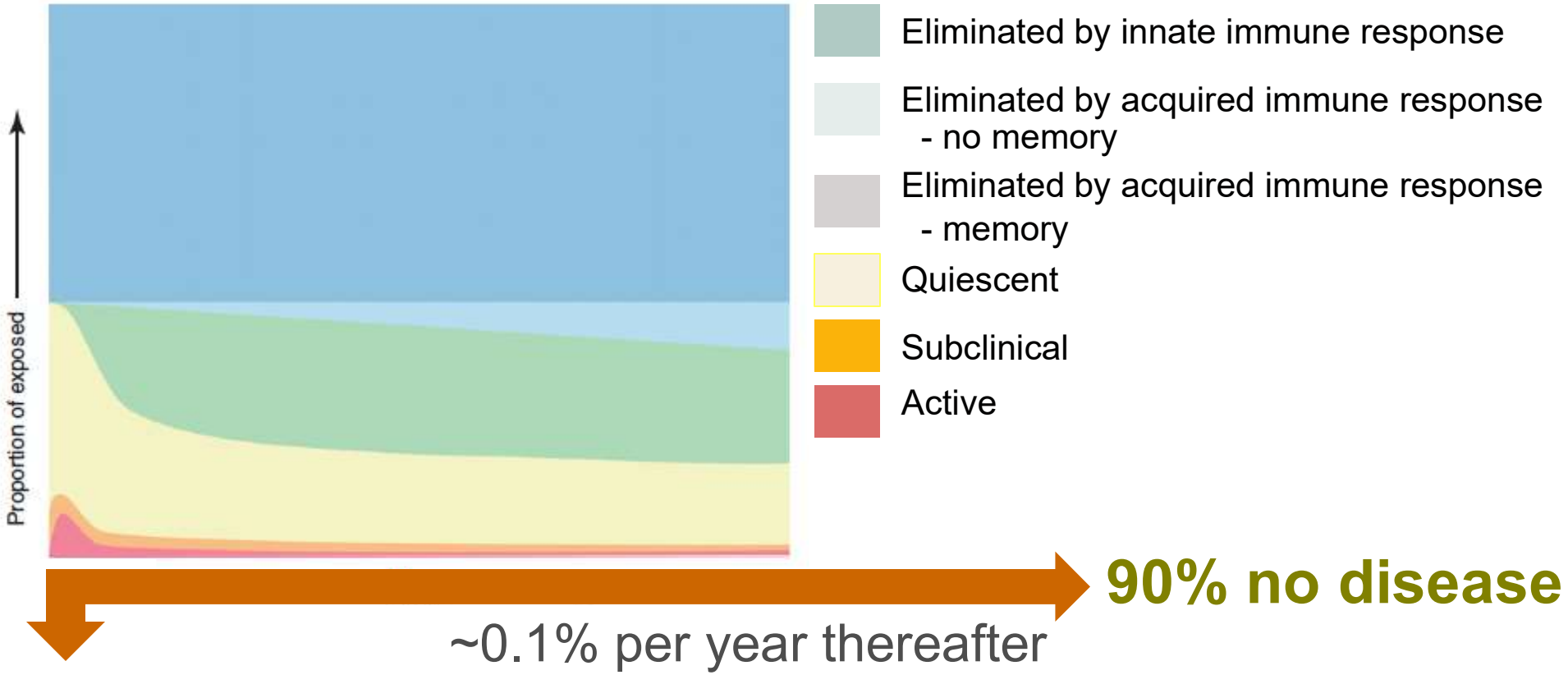


Figure: Esmial and Barry Drug discovery 2012

Lifetime risk: Age matters (non-converters)

Horsburgh NEJM 2004

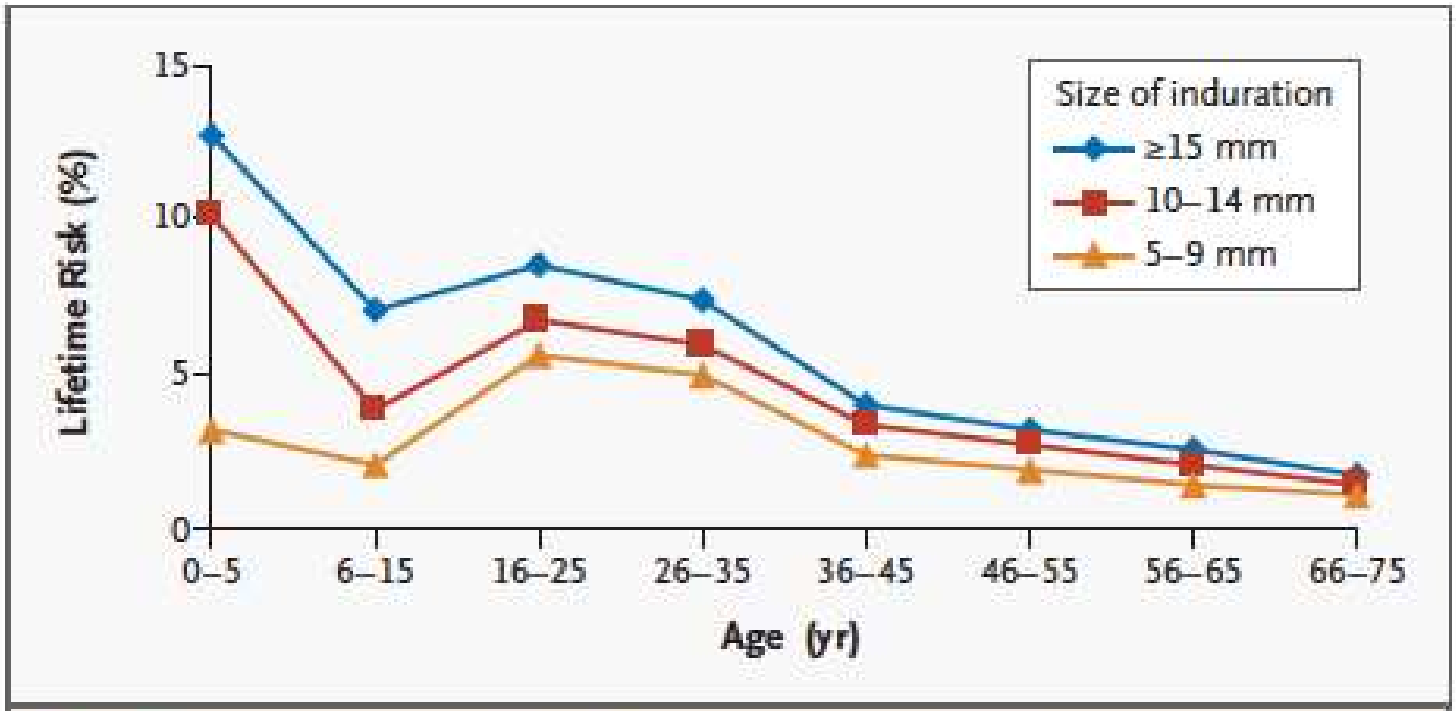


Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Non-conversion Positive Tuberculin Skin Test.

Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.

Lifetime Risk for TB: Effect of Age on Co-factors

Table 2. Lifetime Risk of Reactivation Tuberculosis.*

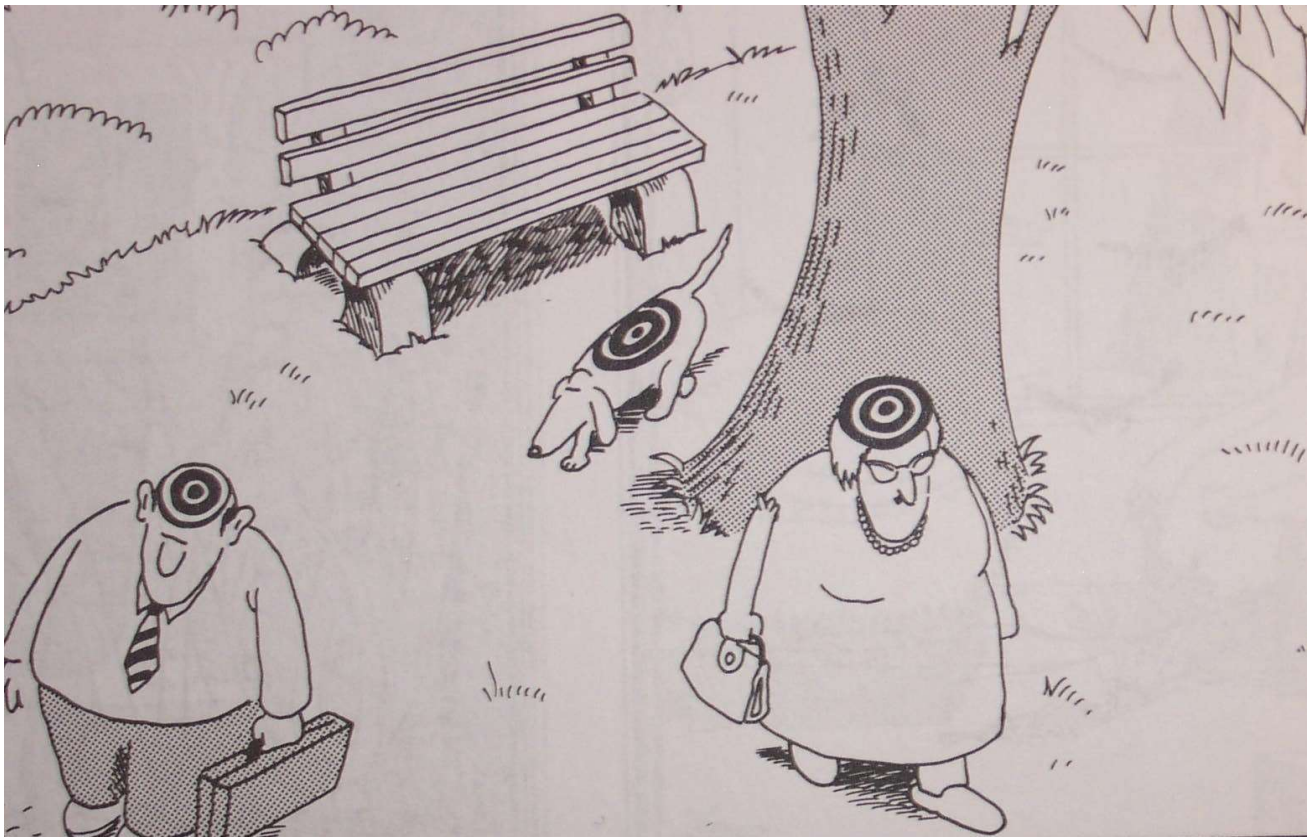
Size of Induration on Skin Test and Age	Nonconversion Positive Skin Test	Recent Conversion of Skin Test	Immunosuppressive Therapy	Old, Healed Tuberculosis	Advanced HIV Infection
	percent (95 percent confidence interval)				
Induration of ≥15 mm					
0–5 Yr	13 (10–16)	17 (12–24)	25 (7–87)	66 (34–100)	100 (88–100)
6–15 Yr	7 (6–8)	8 (6–10)	14 (4–46)	37 (21–67)	70 (52–92)
16–25 Yr	8 (5–15)	13 (8–21)	17 (3–84)	44 (15–100)	83 (39–100)
26–35 Yr	7 (4–13)	12 (8–19)	15 (3–74)	39 (14–100)	73 (35–100)
36–45 Yr	4 (2–7)	7 (5–12)	8 (2–39)	21 (8–57)	40 (20–79)
46–55 Yr	3 (2–6)	6 (4–10)	6 (1–32)	17 (6–46)	32 (16–44)
56–65 Yr	3 (2–4)	3 (1–7)	5 (1–23)	13 (5–33)	25 (14–46)
≥66 Yr	2 (1–3)	2 (1–5)	4 (1–17)	9 (4–24)	18 (10–33)

Horsburgh NEJM 2004

TARGETED TESTING…..

Should we just screen everyone?

Who to prioritize for Testing



TB preventionists

How ~~birds~~ see the world

PRIORITIZED TESTING…..

Only target if higher risk for TB

↑ higher risk for recent infection

↑ higher risk for progression

Prioritize: Risk of recent infection

- Close contacts of people with infectious TB
- Immigrants from countries where TB is endemic (20/100,000)
- Employees/residents of high-risk congregate settings
  - Shelters for people experiencing homelessness, correctional facilities, nursing homes, and residential homes for people living with HIV *[only where TB is more common]*
  - *[Healthcare Personnel -> see new HCP recommendations]*

➔ *Look at local data & demographic risk groups……*

CDC: Latent TB Infection Testing &Treatment: Summary of U.S. Recommendations; **Feb 2019;** online resources (updated June 2, 2022): https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm

[Note: *ATS/IDSA/CDC 2017 Guidelines: Diagnosis of TB* adds Mycobacteriology Lab personnel]

Prioritize: Risk of recent infection (2)

Foreign-born persons:

- ~70-80% of people with active TB in the U.S. are foreign-born
- Prioritize those born in or who frequently travel (>1mo) to countries with high TB prevalence
- High and intermediate incidence countries include: Mexico, Philippines, India, Vietnam, China, Guatemala & Honduras (countries of origin for ↑ cases in U.S.)

[Again, good to know local demographics & risk groups]

Prioritize: Risk of progression → immunocompromised

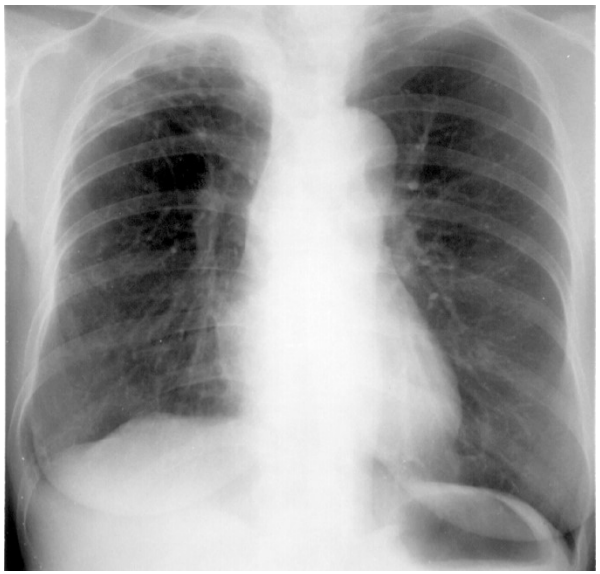
- HIV, immunosuppression - includes TNF-alpha inhibitors & corticosteroids (≥15mg/d for >2wks), organ transplants
  - Screen as early as possible
  - (anergy increases if HIV disease advances and/or immunosuppressive agents are started/escalated)
  - Screen as part of standard medical care - depends on TB exposure risks
  - Exceptionally high rate of reactivation in people with untreated HIV
    ➔rapid development to active disease

Prioritize: Risk of progression → TB4

TB4: Individuals with abnormal chest x-ray compatible with past TB. If untreated:

- Risk of active disease is 5x that of person with normal x-ray and no other risk factors
- Higher underlying bacillary load
- TB test and sputum part of initial screening in spite of stability of chest x-ray before LTBI treatment

➢ Must rule out active TB disease with cultures before starting LTBI treatment



Prioritize: Risk of progression → other

- Infants and young children < 5 yrs. age

  ("Sentinels of transmission")

- Specific medical conditions

  diabetes, renal failure, head & neck CA, silicosis, alcoholism, IVDU, tobacco use, gastrectomy/jejunoileal bypass, low body weight (BMI <20)

Risk of Developing Active TB

Horsburgh NEJM 2011

Risk Factor	Relative Risk (95% CI)
Advanced untreated HIV	9.9 (8.7-11)
Close Contacts	6.1 (5.5-6.8)
CXR c/w prior healed TB	5.2 (3.4-8.0)
Prednisone ≥15mg/day	2.8 (1.7-4.6)
Chronic Renal Failure	2.4 (2.1-2.8)
TNF alpha inhibitor	2.0 (1.1-3.5)
Poorly controlled diabetes	1.7 (1.5-2.2)
Weight <10% below normal	1.6 (1.1-2.2)
Smoking	1.5 (1.1-2.2)

Screening in Primary Care

U.S. Preventive Services Task Force March 2016 (USPSTF)

Recommendation	Grade
The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.	**B**

Population
Adults who are at increased risk for tuberculosis: • persons born in, or former residents of, countries with increased tuberculosis prevalence • persons who live in, or have lived in, high-risk congregate settings (such as homeless shelters and correctional facilities)

Screening Tools: Keep it Simple!

CA Risk Assessment Tool

(Adult, pediatric, school, university versions available)

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.

www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Risk-Assessment.aspx or Curry website

Frequency of HCP screening: 2019 Changes

Updated CDC/NTCA recommendations for US health care personnel (HCP) screening, testing & treatment; *MMWR, Sosa et al, May 17, 2019*

- Review of US Surveillance data: 1995-2007 HCP TB incidence rates similar to general population
- 2018 retrospective cohort study (40,000 HCP, low incidence state) found low rate TST conversion (0.3%) from 1998-2014; *Clin Inf Dis, Dobler et al, Feb 10, 2018*

HCP Retesting: *Need to correlate with local epidemiologic data*

- *Past wording: CDC Guidelines 12/05: Serial testing → "Institutional decision based on setting's risk classification" (Low, medium, or high ongoing risks);* *MMWR Dec. 30, 2005*

2019 - Frequency of testing HCP dependent on ongoing risk of TB exposure

In support of new HCP Recommendations:

- Relatively low proportion (3%–5%) of U.S. HCP test positive for *M. tuberculosis* at baseline
- <1% of U.S. HCP previously testing negative convert to a positive test result during serial testing
- Nearly 50% of U.S. HCP previously testing positive revert to a negative test result during serial testing
- Insufficient evidence to assess incidence and transmission of TB disease among HCP
  - No cases of TB disease reported among the ~64,000 U.S. HCP included in the studies reviewed

Slide credit: Lynn Sosa, Aug.2019 HCP Webinar

CDC/NTCA HCP Screening: May 2019

Category	2019 Recommendations
Baseline (pre-placement) screening and testing	TB screening of all HCP, including a symptom eval. and test (IGRA or TST) for those without documented prior TB disease or LTBI (unchanged); **individual TB risk assessment (new)**
Post-exposure screening and testing	Sx eval. for all HCP when an exposure is recognized. For HCP with a baseline neg TB test and no prior TB disease of LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative do another test 8-10 weeks after the last exposure (unchanged)
Serial screening and testing for HCP without LTBI	**Not routinely recommended (new)**; can consider for selected HCP groups (unchanged); recommend annual TB education for all HCP (unchanged) including information about TB exposure risks for all HCP (new emphasis)
Evaluation and treatment of positive test results	**Treatment is encouraged for all HCP** with untreated LTBI, unless medically contraindicated (new)

CDC/NTCA: HCP Baseline Risk assessment tool

Health care personnel should be considered to be at increased risk for TB if they answer "yes" to any of the following statements.

1. Temporary or permanent residence (for ≥1 month) in a country with a high TB rate (i.e., any country other than Australia, Canada, New Zealand, the United States, and those in western or northern Europe); Or

2. Current or planned immunosuppression, including human immunodeficiency virus infection, receipt of an organ transplant, treatment with a TNF-alpha antagonist, chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month), or other immunosuppressive medication; Or

3. Close contact with someone who has had infectious TB disease since the last TB test

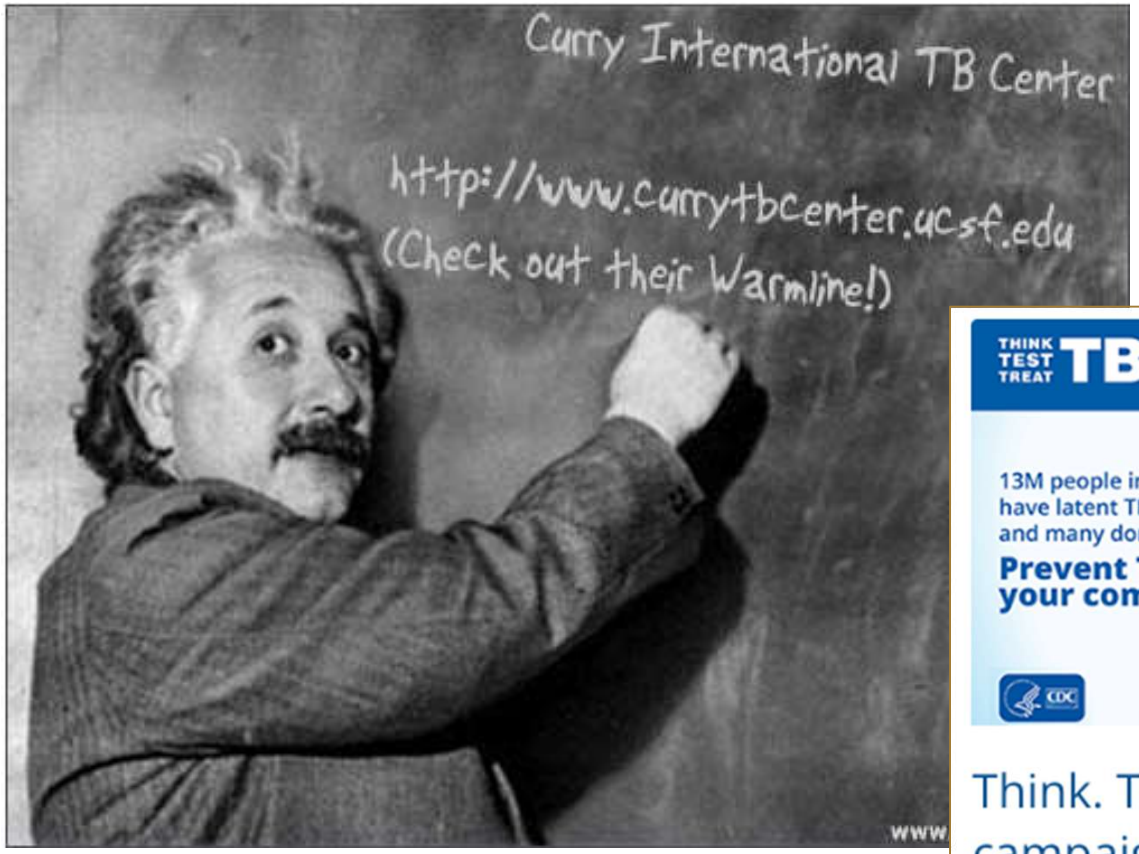
* Individual risk assessment information can be useful in interpreting TB test results. (Lewinsohn DM et al. ATS/IDSA/CDC and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infec Dis 2017)

† Adapted from a tuberculosis risk assessment form developed by the California Department of Public Health

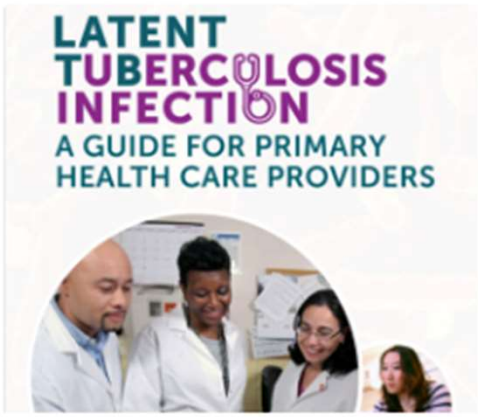
LTBI Basics: Summary

- LTBI identification and treatment is fundamental to US TB elimination strategy
- "Latency" may be dynamic process
- Identifying priority high risk groups is key

http://www.currytbcenter.ucsf.edu



Think. Test. Treat TB campaign



Latent TB Infection: A Guide for Primary Health Care Providers

https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm