



TB IN SAN FRANCISCO: INNOVATIONS & COLLABORATIONS



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Flu and Infectious Disease Forum

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POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

Outline

- Background / TB elimination
- TB Testing / Screening
- LTBI Treatment



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Global Tuberculosis, WHO 2015 report

10.4 million new cases*

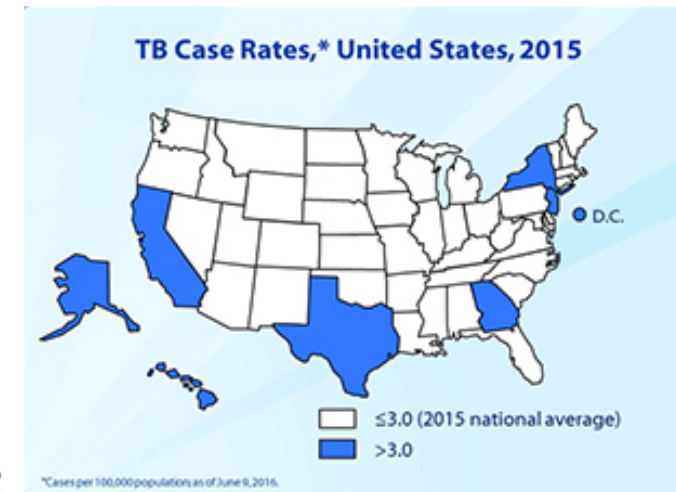
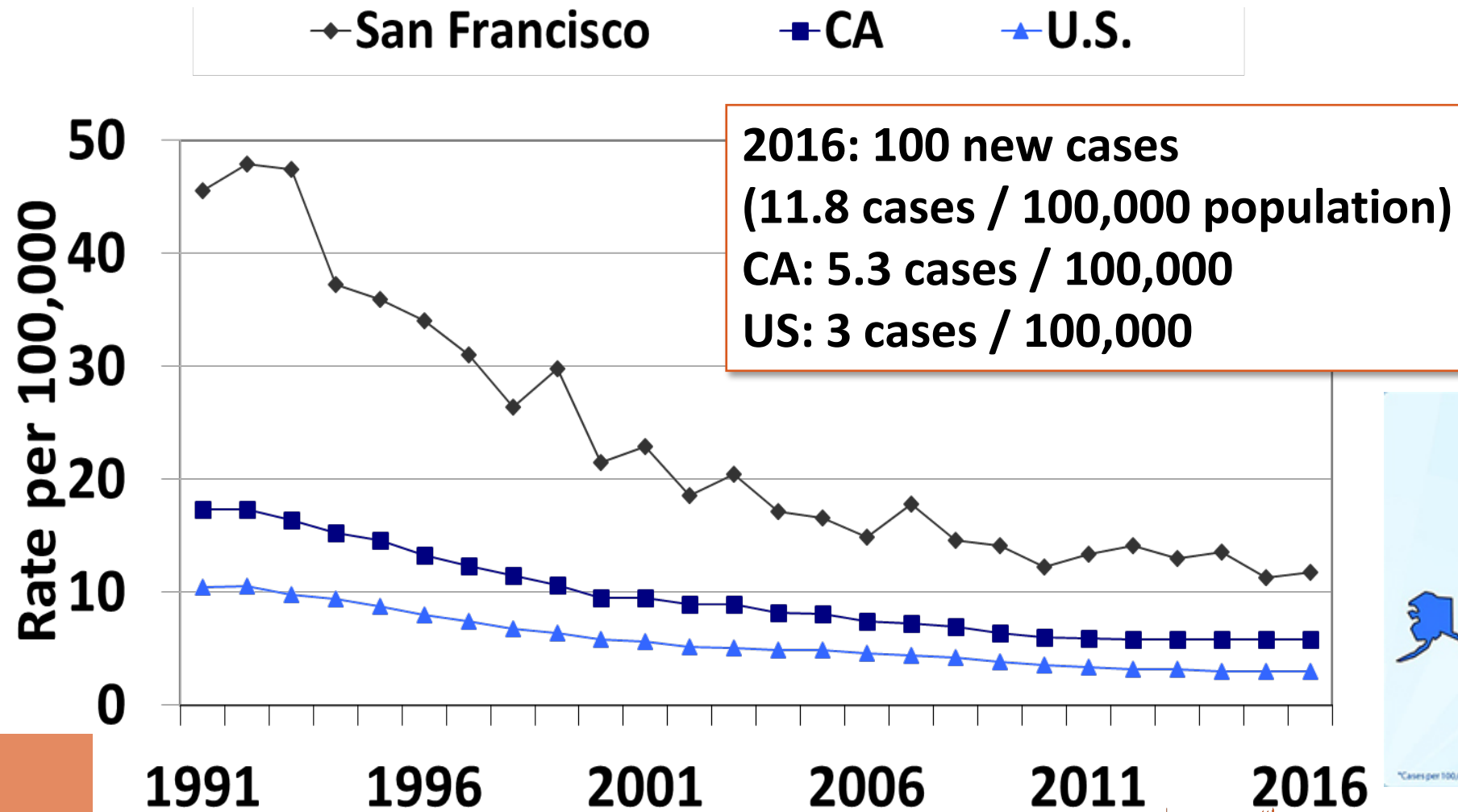
1.8 million deaths

**Leading Infectious Killer in the
World and Leading Killer of
People Living with HIV**

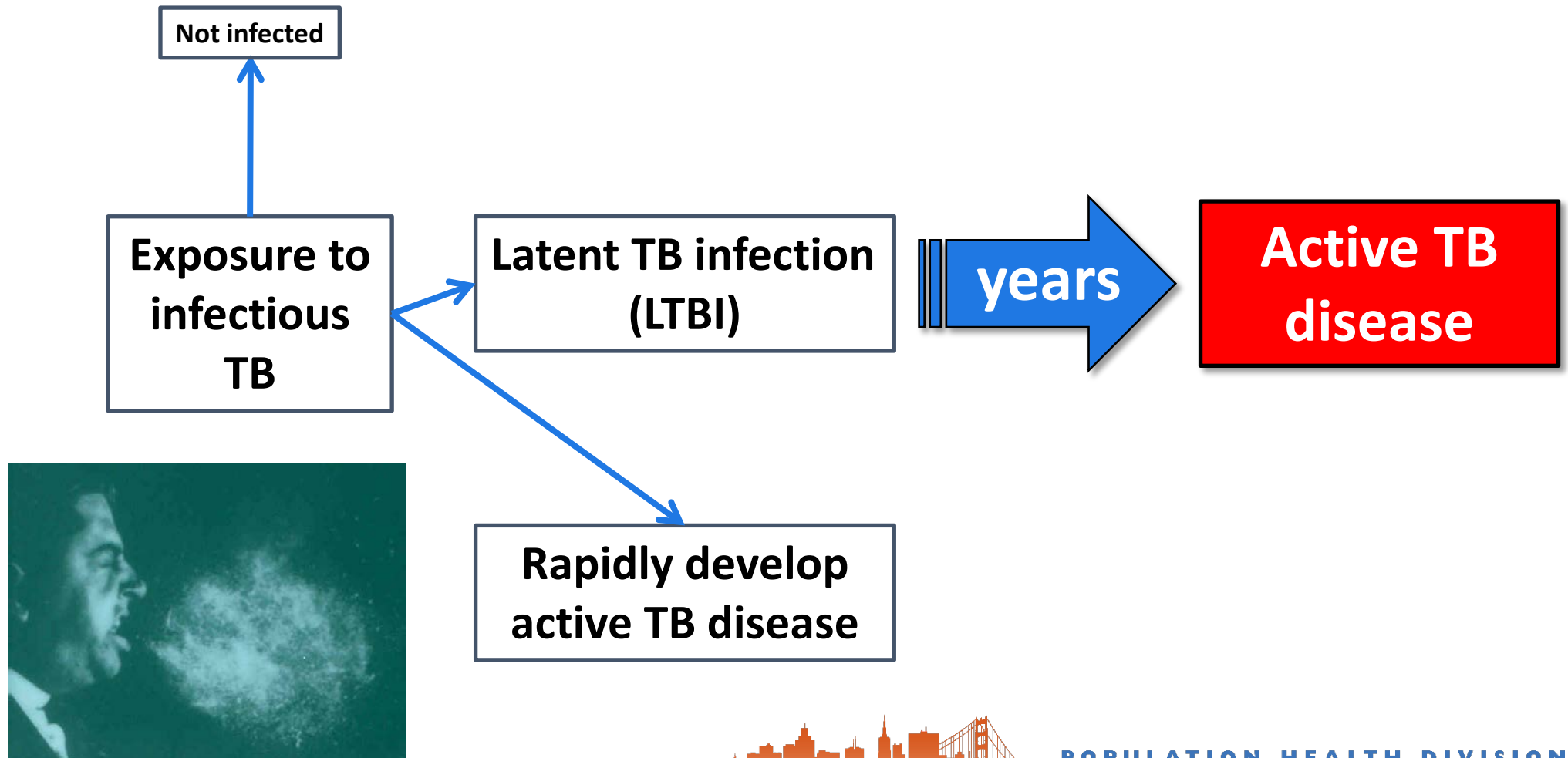


*** Additional one-third of the world's population are infected**

San Francisco TB Case Rate



Natural History of TB



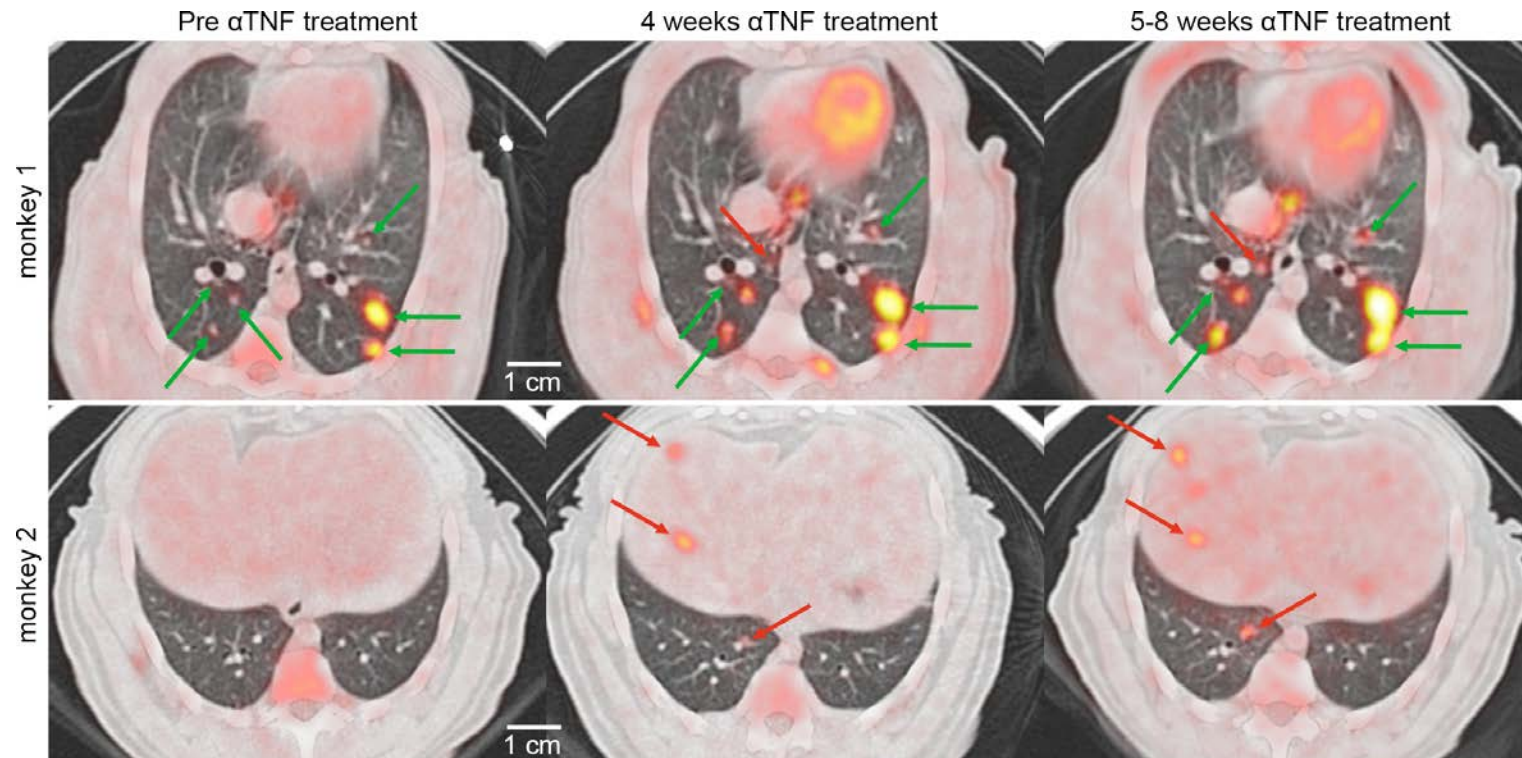
TB Disease vs. (Latent) Tuberculosis Infection (LTBI)

Active TB disease	Latent TB infection
Cough, fever, weight loss, night sweats	No symptoms
Abnormal chest x-ray	Normal chest x-ray
Infectious	Not infectious
	May progress to active TB disease



TB as a spectrum of disease

- Evidence of progression / regression of FDG-avid granulomas in non-human primates
- Re-think binary definitions: LTBI vs Active Disease
- Nomenclature change?: (Latent) Tuberculosis Infection



TB in the U.S.- what lies beneath



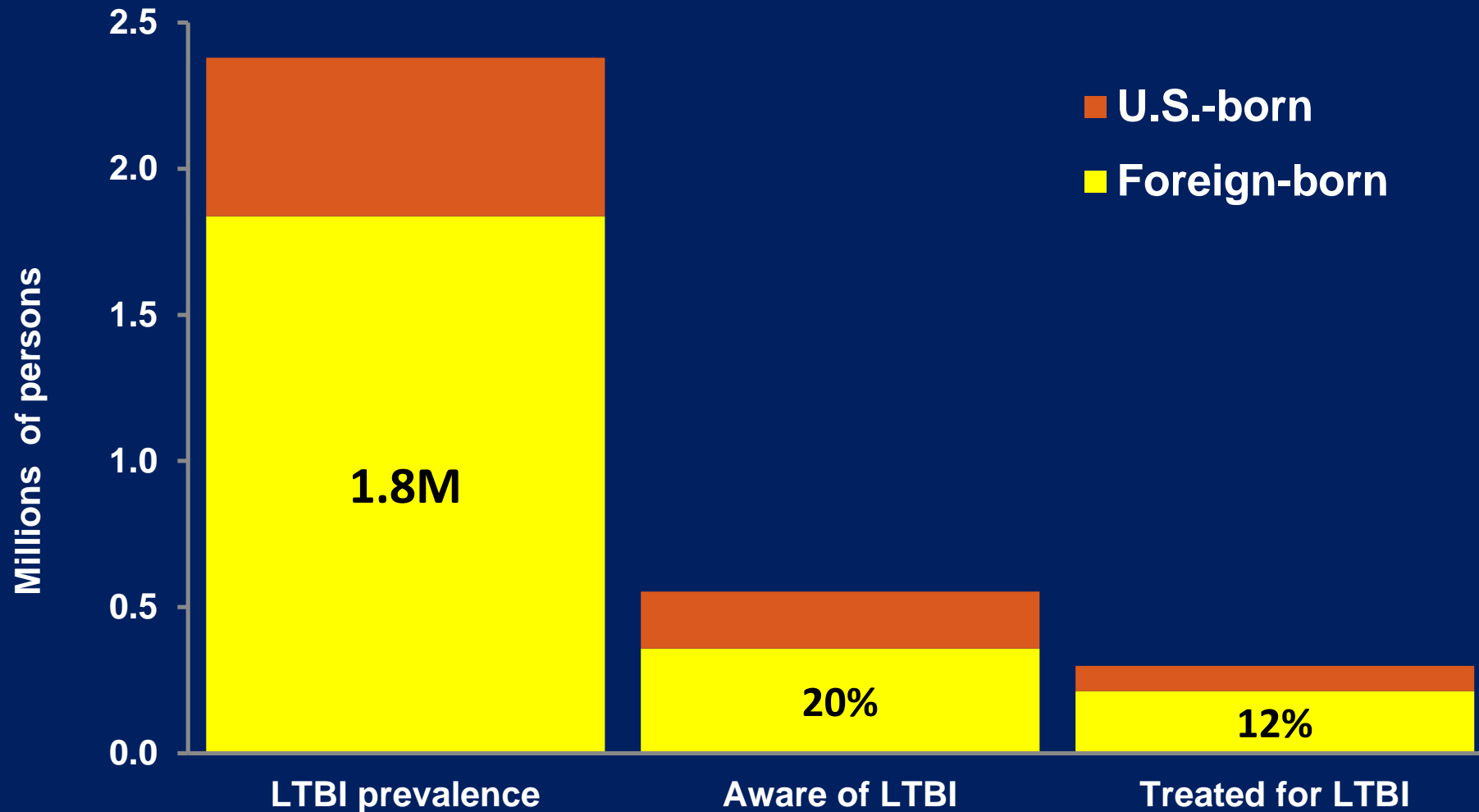
9557 cases

10-15 million
persons with LTBI

**1 out of 5 non-U.S.
born has LTBI**

**1 out of 7 Asian-born
has LTBI**

2.4 Californians with latent TB infection- most are unaware and untreated



NHANES 2011-2012 applied to California population

How far are we from elimination?

TB elimination: <1 case per million

United States, 2015

30 cases per million (all)

12 cases per million (U.S.-born)

151 cases per million (non-U.S.-born)

San Francisco, 2016

116 cases per million (all)

23 cases per million (U.S. born)

291 cases per million (non-U.S.-born)



TB elimination: Key Points

- 1) TB disease remains a substantial contributor to morbidity and mortality
- 2) Most TB cases in California are due to progression of LTBI and are therefore preventable
- 3) In order to move forward in elimination, LTBI needs to be diagnosed and treated



TB Testing / Screening



TB Skin Test (TST)



Interferon-gamma release assays (IGRAs,
e.g. Quantiferon, T-spot)



USPSTF, Update for LTBI 2016

Screening for Latent Tuberculosis Infection in Adults US Preventive Services Task Force Recommendation Statement

Recommendation:

Screen for latent tuberculosis infection in asymptomatic adults at increased risk of infection

Grade:

B



Check appropriate risk factor boxes below.

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

If LTBI test result is positive and active TB disease is ruled out, LTBI treatment is recommended.

☐ **Foreign-born** person from a country with an elevated TB rate

- Includes countries other than the United States, Canada, Australia, New Zealand, or Western and North European countries.
- If resources require prioritization within this group, **prioritize** patients with at least one medical risk for progression (see Fact Sheet for list)
- Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for foreign-born persons

☐ **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 at any time

See the **California Tuberculosis Risk Assessment Fact Sheet** for more information about using this tool.

LTBI Testing and Treatment Guidelines for SF

- **High Priority:** Focus on risk factors for progression
 - Foreign born with **diabetes**
 - Foreign born with **active tobacco** use
 - Foreign born with **ESRD**
 - Foreign born / US born with **immune suppression**
 - Medications (biologics, organ transplant)
 - Cancer
 - HIV
 - Converters
 - Contacts
- **Medium Priority:** Foreign Born < 50

* Recent arriver criteria has been eliminated



Tuberculin Skin Test (TST)

- **How to read:**
 - Measure induration (not erythema) at 48-72 hrs
 - Record millimeters
- **Positive test:**
 - $\geq 5\text{mm}$ for immunosuppressed including HIV, recent contacts
 - $\geq 10\text{mm}$ for all others with TB risk



Interferon-Gamma Release Assays (IGRAs)

- **QuantiFERON[®]-TB Gold (QFT)**
 - Reported as positive, negative, or indeterminate
- **QuantiFERON[®]-PLUS is replacing QFT-Gold**
- **T-SPOT.TB (T-Spot)**
 - Reported as positive, borderline, negative, or indeterminate



TST vs IGRA

TST (e.g. PPD)	IGRA (e.g. QFT, T-spot)
Potential for false positive in BCG vaccinated individuals	Preferred in prior BCG vaccinated individuals
Subjective	Less subjective (although issue with indeterminate)
Booster effect	No booster effect
Injection, ≥ 2 visits	Blood draw, single visit
	Limited in young (2-5 yo)



Diagnosing Latent TB Infection

- **TSTs and IGRAs cannot distinguish between latent TB infection and active TB disease**
- **Patients with positive TST or IGRA must be evaluated for active TB disease**



Case

- 35 yo US-born nurse works in a long term care facility
- Contact to active TB cases 3 years ago → TST positive → completed 9 mo of INH
- Now
 - Smear positive, cavitary, INH resistant TB
 - Review of prior CXR shows “faint irregular 1cm density” in area of current cavity
- Genotype matches prior cases (INH sens)



RULE OUT ACTIVE DISEASE BEFORE STARTING LTBI TREATMENT!!

- **Symptom screen + chest radiograph**
- **If abnormal collect sputum:**
 1. **AFB smear and culture**
 2. **TB PCR/NAAT**
- **If sputum collected:**
 - **Either start empiric treatment for active disease**
 - **Or await final culture results before starting LTBI Rx**



TST / IGRA Interpreter

www.TSTin3d.com

- ◆ Estimates risk of active TB
- ◆ Limited to up to age 80
- ◆ Accounts for risk factors

TST Size: TST Not Done

IGRA Result: Positive

Age: 70

Age at immigration (if person immigrated to a low TB incidence country): N/A

Country of birth: United States of America

BCG status: Never vaccinated or unknown
For more info, visit: [BCG World Atlas](#).

Recent contact with active TB: No Contact

Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

<input type="checkbox"/> AIDS	<input type="checkbox"/> Abnormal chest x-ray: granuloma
<input type="checkbox"/> Abnormal chest x-ray: fibronodular disease	<input type="checkbox"/> Carcinoma of head and neck
<input checked="" type="checkbox"/> Chronic renal failure requiring hemodialysis	<input type="checkbox"/> Cigarette smoker(>1 pack/day)
<input checked="" type="checkbox"/> Diabetes Mellitus (all types)	<input type="checkbox"/> HIV infection
<input type="checkbox"/> Recent TB infection (TST conversion \leq 2 years ago)	<input type="checkbox"/> Transplantation (requiring immune-suppressant therapy)
<input type="checkbox"/> Silicosis	<input type="checkbox"/> Treatment with glucocorticoids
<input type="checkbox"/> Tumor Necrosis Factor (TNF)-alpha inhibitors(e.g. Infliximab/Etanercept)	<input type="checkbox"/> Underweight (< 90 per cent ideal body weight or a body mass index (BMI) \leq 20)
<input type="checkbox"/> Young age when infected (0-4 years)	

Submit

The likelihood that this is a true positive test (PPV) is: 98%

The annual risk of development of active tuberculosis disease is estimated to be 1.99%

The cumulative risk of active tuberculosis disease, up to the age of 80, is: 19.89%

If treated with INH, the probability of clinically significant drug-induced hepatitis is 5%, and the associated probability of hospitalization related to drug-induced hepatitis is 2.4%.

Results



Testing: Key Points

- 1) Use a risk based approach to testing
- 2) Patients should be evaluated for TB risk factors regardless of age or time since entry into the U.S.
- 3) Either IGRA or TST can aid in the diagnosis of latent TB infection
- 4) Neither test can distinguish between LTBI and active TB disease
- 5) IGRAs have advantages over TST in certain situations



LTBI Treatment Options



- Isoniazid
- Isoniazid + Rifapentine (3HP)
- Rifampin



Treatment Regimens for Latent TB Infection

Medication(s)	Frequency	Duration	Doses
Isonizaid (INH)	Daily	6–9 months	180 - 270
INH + Rifapentine (RPT)	Weekly	3 months	12
Rifampin	Daily	4 months	120



Isoniazid (INH)

- **Advantages**
 - Efficacy is 60%–90%, depending on duration of treatment
 - Fewer drug-drug interactions
- **Disadvantages**
 - Adherence: Completion rates <50%
 - Hepatotoxicity: Incidence 0.1%, but increases with age
 - Clinic time required for 6-9 monthly visits



3HP (INH+RPT)

- INH + Rifapentine, Qweek x 12 weeks
- Recommended as an equal alternative to INH x 9 mo in healthy patients ≥ 12 yo
- Not recommended in the following:
 - Children <2 yo
 - HIV-infected patients on any ART
 - Pregnant or planning to become pregnant
 - Contact to INH/RIF resistant cases
 - Prior adverse events / hypersensitivity to INH/RIF



Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653



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Prevent TB Study Results

	INH-RPT	INH	P-value
Effectiveness	1.9 per 1,000	4.3 per 1,000	Non- inferior
Completion rate	82.1%	69.0%	P<0.001
Hepatotoxicity	0.4%	2.7%	P<0.001

Sterling TR, et al; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66.



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3HP- Adverse Reactions



- Possible hypersensitivity (3.8%)
 - Rash (0.8%)
 - Hepatotoxicity (0.4%)
 - Thrombocytopenia (rare)
 - Other toxicities (3.2%)
-
- Monitoring- similar to INH or RIF
 - RFP drug-drug interactions similar to RIF

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653

<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-INH-RIF-LTBI-fact-sheet.pdf>



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3HP

- **Advantages:**
 - Less hepatotoxicity (~ 7x less than INH)
 - Greater adherence (82% INH-RPT vs. 69% INH)
- **Disadvantages:**
 - Multiple drug interactions
 - Pill burden
 - Flu-like / hypersensitivity syndrome (2.2%)
 - Directly Observed Therapy



Video Directly Observed Therapy

- Observation of medication ingestion by video
 - Live vs Recorded
 - Smartphone application, cloud based
- Can be used for active disease and LTBI
- Cost-effective and ensures adherence



<http://www.calit2.net/newsroom/release.php?id=2211>



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Rifampin

- **Advantages:**
 - Less hepatotoxicity (~5x less than INH)
 - Greater adherence (78% RIF vs. 60% INH)
 - Cost effective
 - **Disadvantages:**
 - Less evidence of efficacy
 - Multiple drug interactions
 - Warfarin, oral contraceptives, methadone, protease inhibitors, tenofovir alafenamide, and more
- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000; 49 (No. RR-6)
 - Guidelines on the management of latent tuberculosis infection, WHO, 2015
 - American Academy of Pediatrics, Red Book 2015
 - Fresard, et al. Swiss Med Wkly. 2011 Aug 15;141:w13240.
 - Esfahani, et al. Int J Tuberc Lung Dis. 2011. Oct;15(10):1340-6



Rifampin- Adverse reactions



- Hepatotoxicity
 - Rare severe hepatitis, more common when combined with other medications
- Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritis, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
- Orange discoloration of body fluids



Rifampin- Need for additional data

- Cost
- Efficacy
- Adverse events
- Development of resistance
- HIV
- Pediatrics



Monitoring

ATS/CDC LTBI guidelines, 2000

- Routine baseline / follow-up laboratory testing

→ Not needed

- Except for:
 - HIV infection
 - Pregnancy / Early postpartum (<3mo)
 - History of liver disease / hepatitis
 - Regular EtOH use

Also consider for: Statin/other hepatotoxic meds,
age >50



Monitoring

Evaluate monthly for:

- Adherence
- Symptoms of hepatitis or other side effects
 - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
 - Fatigue or weakness
 - Dark urine
 - Rash
 - Persistent numbness in hands or feet



Management of side effects: Drug-induced liver injury

- Review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- HOLD Treatment if:
 - AST/ALT > 3 times the upper limit of normal + symptoms of hepatotoxicity
 - AST/ALT > 5 times the upper limit of normal + asymptomatic
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks.
- Depending on above, consider alternate therapy with close LFT monitoring.



LTBI Treatment: Key Points

- 1) INH has low treatment initiation and completion rates
- 2) Short course regimens have higher completion rates and are less hepatotoxic
- 3) INH-RPT (12 doses) is as efficacious as INH (9 months)
- 4) All patients should have at least a monthly symptom review for hepatotoxicity and adherence.



SFDPH TB Prevention & Control (Ward 94)



- Provide services to patients / providers within health network and the rest of SF, regardless of insurance or immigration status
- TB Clinic
 - Manage all cases of suspected / confirmed active TB cases
 - Perform Directly Observed Therapy
 - Complicated TB infection
 - TB program clearance for at-risk settings (shelters, methadone program, rehab, etc)
- TB Control
 - Contact investigations
 - Technical assistance and policies on TB screening, diagnosis, and treatment
 - Research



Assistance is right around the corner...



- TB Control & Prevention, SFDPH
 - 415-206-8524
 - Report of confirmed/suspected case: 415-206-3398
- TB Warmline Consultation (Curry International TB Center): 1-877-390-6682
- California Dept of Public Health, TB Control Branch,
<https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TBCB.aspx> (510) 620-3000





THANK YOU!

Special thanks to CDPH/TBCB for additional slides

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