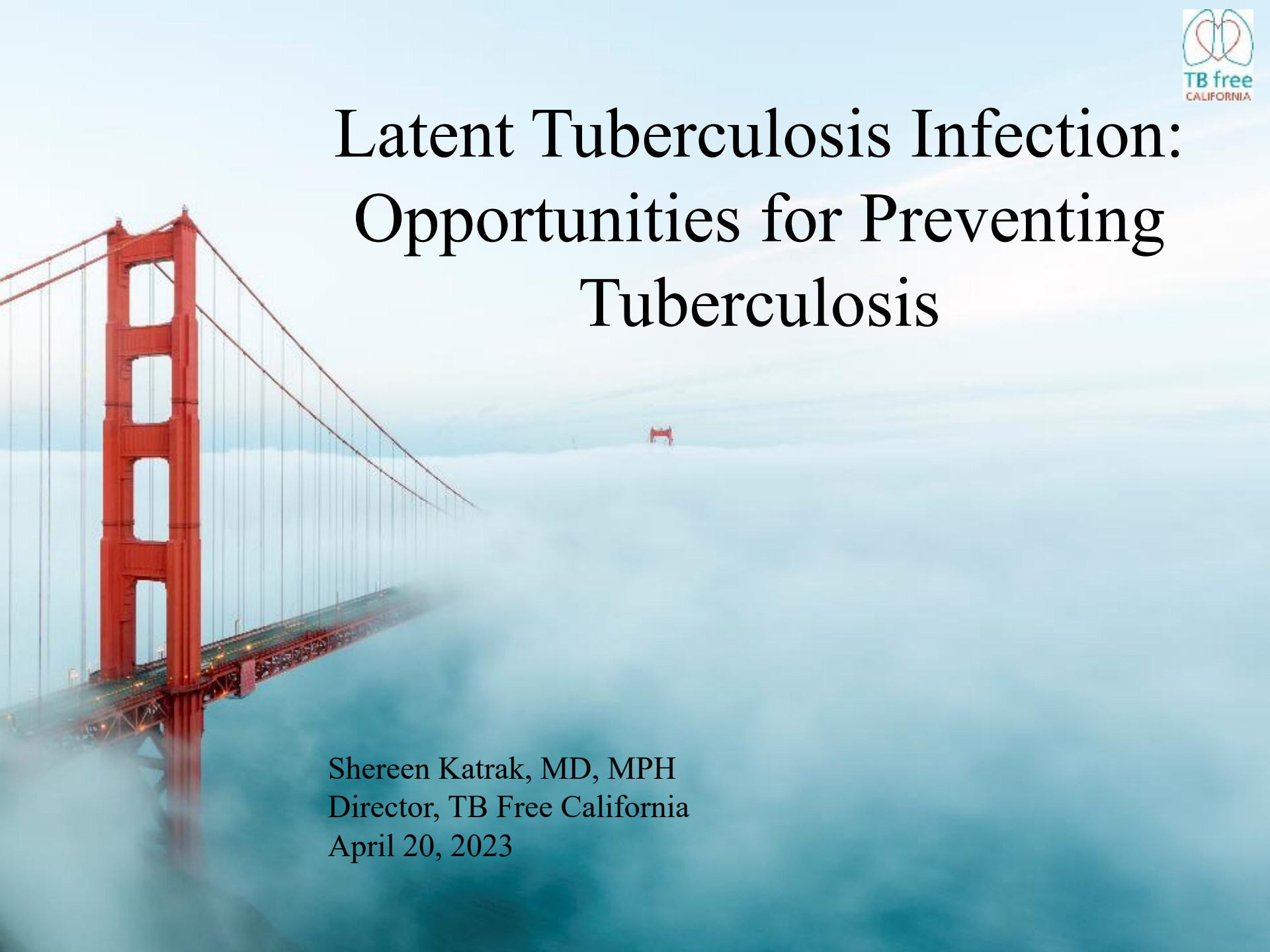
Latent Tuberculosis Infection: Opportunities for Preventing Tuberculosis



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Director, TB Free California
April 20, 2023

Disclosures

- During the past 24 months, I have not had any relevant financial relationships or conflicts of interest with commercial interests that may have a bearing on the subject matter

Objectives

1. Understand the importance of latent TB infection (LTBI) in preventing TB disease
2. Know who is at risk of TB infection, and how to test for TB infection
3. Know how to work up and exclude (active) TB disease before treating LTBI
4. Name preferred regimens used for LTBI treatment

Case 1

53 M, with positive IGRA. Born in China, in U.S. since 1980s. IGRA sent by Derm during workup for Erythema nodosum. He has CAD s/p stenting and DM2, but is otherwise healthy with no personal hx of TB or TB contacts.

What do you do?

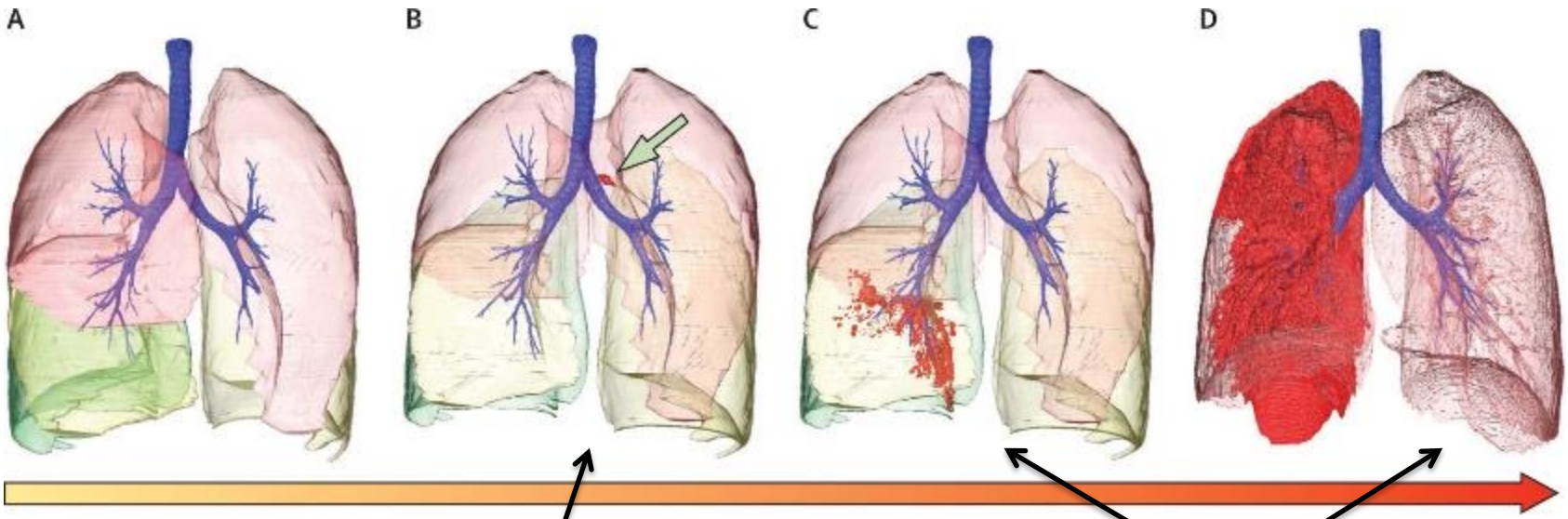
- Nothing – he's had sufficient evaluation
- Additional workup is needed
- Offer treatment for LTBI
- Encourage treatment for LTBI
- Other

Key points

Screen	Screen to identify patients experiencing risk (non-U.S.-born, immune compromise, TB contact)
Test	Test using an IGRA, if risk is present
Treat	Treat with 3- to 4-month rifamycin-based regimens

Spectrum of TB disease

A – Clearance
B – Latent infection
C – Pulmonary infection (active)
D – Disseminated infection (active)



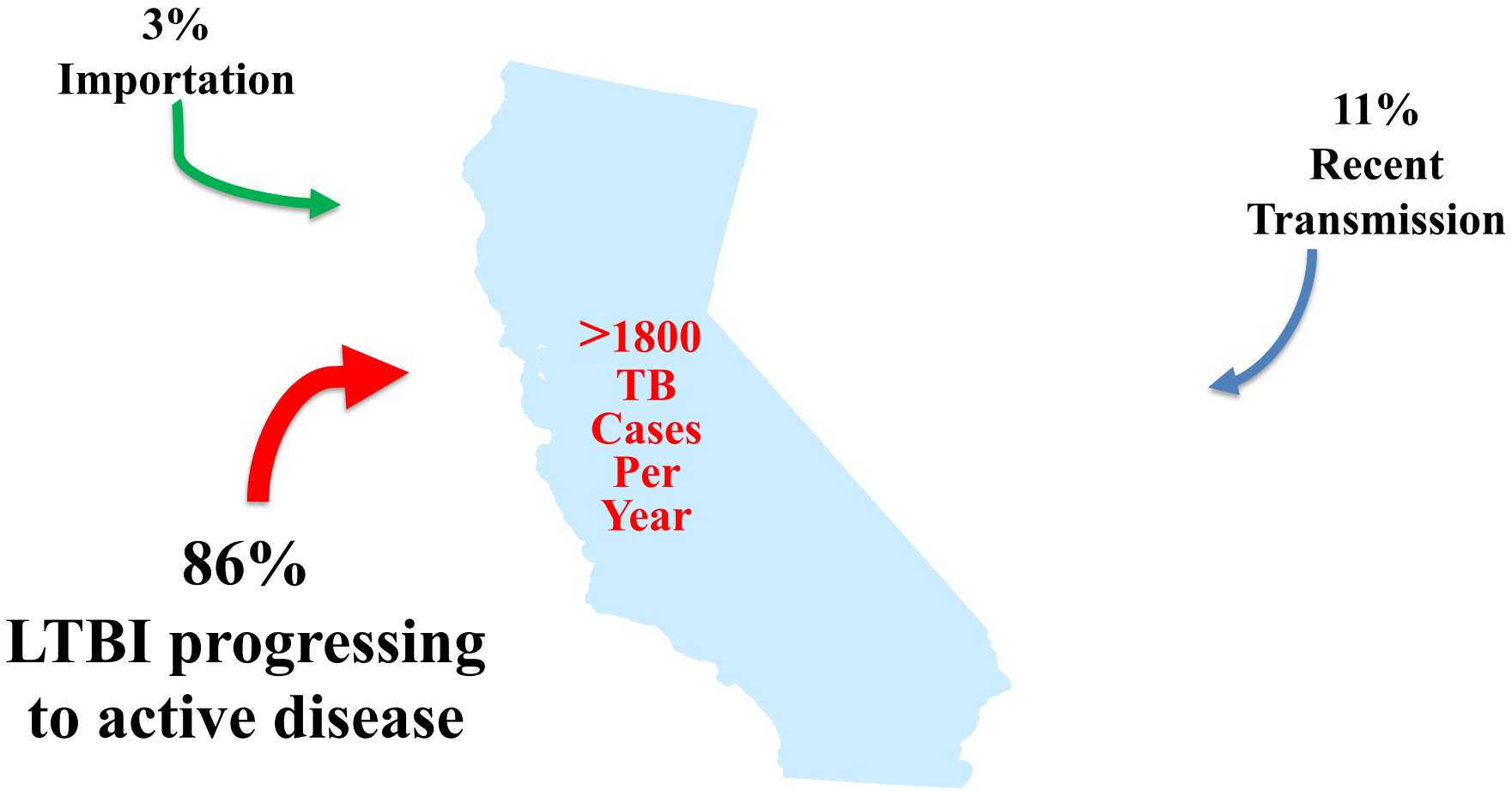
Latent TB Infection
- ***Absence of TB symptoms***
- Positive TST[1] or IGRA[2] result
- Chest radiograph normal
- Not infectious

[1]TB skin test
[2]Interferon gamma release assay

Active TB Disease
- ***Symptoms such as cough, fever***
- TST or IGRA is usually positive
- Chest radiograph is usually abnormal
- Respiratory specimens usually culture positive (smear positive in about 50% of patients)

Image: Dheda K. Lancet, 2016

LTBI is the primary cause of TB disease in California



Tuberculosis Control Branch. California Department of Public Health, Feb 2022.

TB is a health disparity in California

In 2022 in California:

- **Nearly half (49%)** of all TB cases occurred in Asians
- The rates of TB in **Asians born outside the U.S. were 70x higher** than those of U.S.-born whites
- For TB cases in persons born outside the U.S., half of TB cases occurred **≥ 20 years after arrival** to the U.S.

Tuberculosis Control Branch. California Department of Public Health, March 2023.

Who to test for TB infection

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Test patients who have “TB risk factors”

- Risk of exposure and/or risk of progression

Testing populations with low prevalence will result in many false-positive results

Most persons with a positive test for LTBI should be treated, after TB disease ruled out

1. CDC, MMWR, 2000, 2. Miramontes, PLOS One, 2015

TB Risk Factors

Exposure	Progression
• Non-U.S.-born*	• HIV/AIDS
• Known contact to infectious case (highest risk within 2 years)	• Transplant
• Homeless	• TNF-alpha inhibitors
• Corrections	• Steroids
• IV drug abuse	• Cancer (head/neck, leukemia/lymphoma)
• Long term care facilities	• ESRD on dialysis
• Healthcare workers	• Recent infection
	• Silicosis
	• Diabetes mellitus
	• Underweight, malabsorption
	• Smoking
	• Children age < 5

*From a country with elevated TB rate

California Tuberculosis Risk Assessment

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.

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-CA-TB-Risk-Assessment-and-Fact-Sheet.pdf

What about LTBI testing and treatment in these populations?

Congregate settings or homeless?	At risk, but regulatory mandates and routine screening programs exist
Pregnant?	Rule out TB disease immediately. If high risk of progression treat immediately, otherwise consider delaying LTBI treatment until ~3 months postpartum.
Kids <5?	Use risk-based testing, rule out TB disease immediately. At high risk of progression, prioritize LTBI treatment!
Older adults?	No upper age cutoff for LTBI screening and treatment. Consider overall health and risks/benefit tradeoff, like any screening for older adults.

Quick poll in the chat

1) Which patient(s) should be tested for TB infection?

a) 40 F, grew up in Modesto, CA. PMHx GERD. Works as an accountant in SF. Requests TB testing bc she takes public transportation.

b) 40 F, grew up in Philippines. PMHx GERD. Works as accountant.

c) 20 M, grew up in Modesto, CA. PMHx HIV on ART, meth use. Employed as a food service worker.

d) 20 F, grew up Guatemala. No PMHx, currently pregnant. OB asking about TB testing as part of prenatal labs.

e) 40 M, grew up in Modesto, CA. PMHx of rheumatoid arthritis, soon to start infliximab.

f) None of the above

Who should you test for TB infection?

Birth, travel or residence (>1 month) in a country with an elevated TB rate

Immunosuppression

Close contact to someone with infectious TB disease during lifetime

Testing for TB infection: Interferon-Gamma Release Assays (IGRAs)

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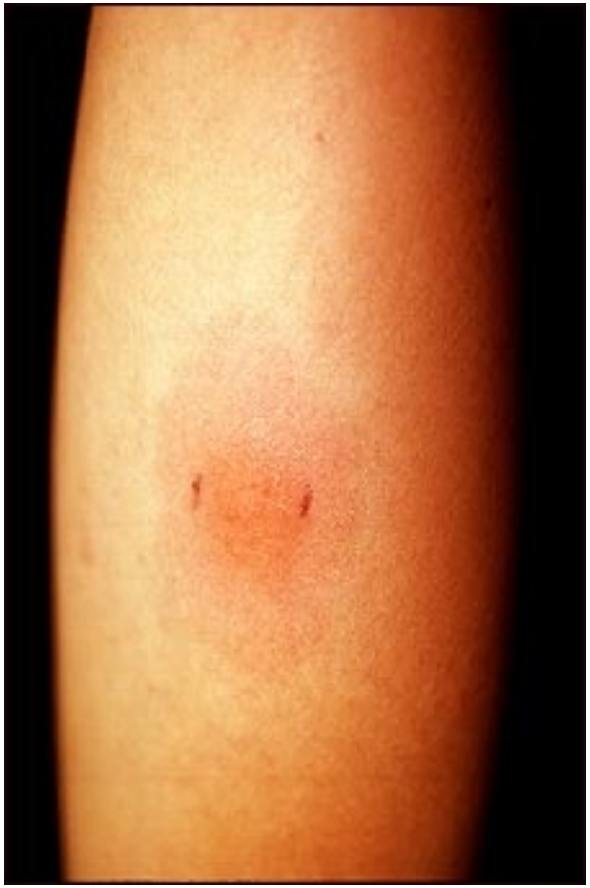
- **Measures**
  - Cellular response (interferon gamma production) to TB-specific antigens, with positive and negative controls
- Requires heparin-anticoagulated whole blood
- **Several commercial tests, including:**
  - **QuantiFERON Gold-PLUS (QFT)**
    - Reported as positive, negative, or indeterminate
  - **T-SPOT.TB (T-Spot)**
    - Reported as positive, borderline, negative, or indeterminate

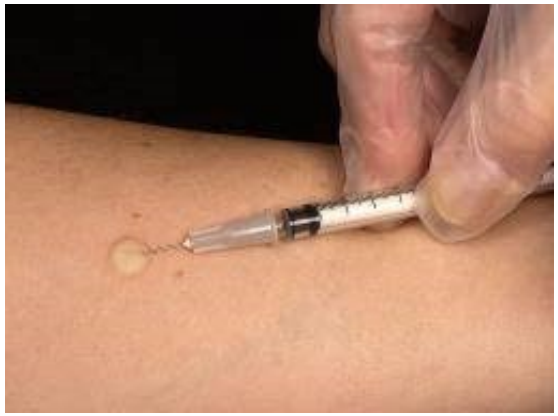
Testing for TB infection: Tuberculin Skin Test (TST)

- **Measures:**
  - Cellular immunity/response to antigens secreted by M. tuberculosis-complex organisms
- **How to read:**
  - Measure induration (not erythema) at 48-72 hrs
  - Record millimeters
- **Positive test:**
  - ≥ 5mm for immunosuppressed including HIV, recent contacts
  - ≥ 10mm for all others with TB risk



Advantages of testing type for TB infection?

1. **TB skin test (TST)**
    1. Intradermal
    2. Cheap
    3. TB vaccine (BCG) can cause false positive



2. **Interferon-gamma release assay (IGRA)**
    1. Blood test
        a. Quantiferon (QFT) or T-SPOT
    2. No return visit needed
    3. More specific

Who should be tested for LTBI, and how?

- Use California Risk Assessment
- Test people with risk factors:
  1. People **born outside the U.S.**
  2. **Contacts** of TB cases
  3. **Immune-compromised** patients
- Do not test if TB risks absent
- IGRA is preferred test for patients ≥2, especially if born outside the U.S.

Quick poll in the chat

2) Which test is a "direct" test for MTB bacilli?

a) IGRA
b) TST
c) AFB culture from sputum
d) All of the above

Quick poll in the chat

3) Which test distinguishes "active" TB disease from latent TB infection?

a) IGRA
b) TST
c) Both
d) Neither

Rule out active disease before LTBI treatment

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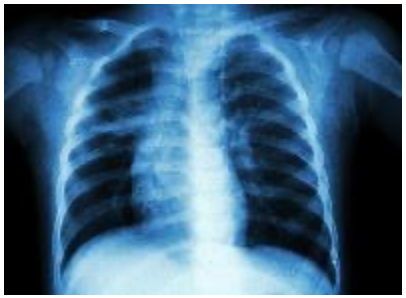
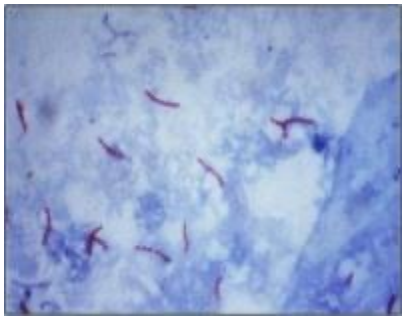
1. Symptom screen

- Cough
- Hemoptysis
- Weight loss
- Fevers/sweats
- Extreme fatigue



2. Chest x-ray

- Infiltrate
- Cavitary lesion
- Nodule
- Effusion
- Hilar LAD



3. Sputum collection

- AFB smear & culture
- MTB PCR (Xprt)

Images: 1. MedlinePlus.gov 2. Adobe Stock Images 3. CDC.gov, TB 101 for Healthcare Workers

Treatment Regimens for Latent TB Infection

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Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Recommendations and Reports / February 14, 2020 / 69(1);1–11

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TB Prevention Treatment Options

STRONGLY PREFFERED

3 Months

Isoniazid (INH) & Rifapentine (RPT)

Treatment taken once a week for 3 months.

Recommended for adults and children >2 years old, and can be used by people living with HIV.

4 Months

Rifampin (RIF)

Treatment taken every day for 4 months.

Recommended for adults and children of all ages. Not recommended for people living with HIV.

3 Months

Isoniazid (INH) & Rifampin (RIF)

Treatment is taken every day for 3 months.

This is recommended for adults, children of all ages, and can be used by people living with HIV.

6 Months OR **9 Months**

Isoniazid (INH)

Treatment is taken every day for 6 or 9 months.

Recommended for adults and children of all ages. Sometimes recommended for people living with HIV.

4R = Rifampin 600 mg daily x 4 months

- First line, suitable for most patients
  - Adults (including pregnant) and children
  - Avoid in most people living with HIV
- Clinical considerations include:
  - Rifampin **drug interactions** (rifampin lowers plasma levels of drugs including dabigatran, oral contraceptives, methadone, most HIV medications and cancer chemotherapy)
  - Adverse drug reactions including hepatotoxicity (although risk is lower than with 9 months of INH), rash, GI upset, orange discoloration of body fluids.

3HP = Rifapentine 900 mg po + isoniazid 900 mg once weekly x 12 weeks

- First line, suitable for some patients
  - ideally those who are able to take a weekly medication
  - motivated to finish treatment in the shortest time possible
  - okay for kids ≥ 2, adults, people living with HIV*
- Clinical considerations include:
  - Ability to remember a weekly (rather than daily) dose
  - High pill burden (usually 11 individual pills at once) and higher dose of drugs when dosed weekly
  - Drug interactions (rifapentine drug interactions generally milder than those of rifampin)
  - Hypersensitivity or flu-like reaction, rash, hepatotoxicity
  - Safety and PK not established for kids <2

***not on ART, or no significant drug interactions**

Rifamycin drug interactions

- Many rifampin and rifapentine drug interactions can be **managed with clinical monitoring and/or dose adjustment**!
- Find your favorite resource:
  - Lexicomp
  - Micromedex
  - Rifamycin Drug-Drug Interactions
  - Heartland: Tuberculosis Medication Drug and Food Interactions
  - DHHS AIDS-info (HIV specific)

UCSF University of California San Francisco

Curry International Tuberculosis Center

CDPH California Department of Public Health

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Rutgers Global Tuberculosis Institute

Rutgers Ernest Mario School of Pharmacy

Rifamycin Drug-Drug Interactions

A Guide for Primary Care Providers Treating Latent Tuberculosis Infection

How should patients be treated for LTBI?

- **Always exclude TB disease before treating LTBI**
- 3- or 4- month regimens are preferred
- **Strongly preferred regimens** for LTBI are:
  - ***rifampin daily*** for 4 months (4R)
  - ***isoniazid*** + ***rifapentine weekly*** for 12 doses (3HP)

- Isoniazid is a second line regimen
  - isoniazid daily for 9 or 6 months (9H or 6H)
  - BUT lower completion rates and higher risks of hepatotoxicity than first line therapies

Case 1 – respond in chat

53 M, with positive IGRA. Born in China, in U.S. since 1980s, he thinks he received BCG as a child. IGRA sent by workplace. He has CAD s/p stenting and DM2, but is otherwise healthy with no personal hx of TB or TB contacts.

What do you do next?

a) Nothing – this is likely a false positive related to BCG
b) Offer treatment for LTBI
c) Symptom screen and chest x-ray
d) Refer to health department for treatment of TB disease
e) Other

Case 1, part 2

53 M, born in Mexico, with positive IGRA. Your evaluation for TB disease, including symptoms screen and CXR, is negative.

PMHx: CAD s/p stent in 2011, DM2

Meds: ASA, metoprolol, metformin, lisinopril and statin

What do you do?

a) Encourage treatment with 9 months of INH
b) Encourage treatment with 4 months of Rifampin
c) Encourage treatment with 3 months of 3HP
d) Other

How do I counsel my patients about LTBI therapy?

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Common concerns

- "Why should I take medication if I am not sick?"
- "Why do I have to take medications for so long?"
- "I had the vaccine when I was a child, how can I get TB?"
- "What will happen to me if people find out I have LTBI?"

Talking points

- TB germs can hide in the body for years. People with hidden ("latent") TB do not feel sick. However, latent infection can eventually become active and make you ill.
- TB is a slow-growing bacteria, so treatment of TB infection takes longer than antibiotics you take for other infections. But it is ***easier to treat latent TB infection*** than TB disease, which is why we recommend getting tested and treated for LTBI if you are at risk.
- The TB vaccine (called BCG) does not work in all cases, and it ***does not protect you for your whole life.*** It is most effective in young children against more severe forms of TB.
- Your test results will be confidential. People with LTBI cannot be forced to leave the United States. They also cannot be fired from a job or forced to leave school.
- ***Protect your family from exposure to TB*** by taking LTBI treatment

Case 1, part 3

53 M, born in China, with positive QFT+. Your evaluation for TB disease is negative.
PMHx: CAD s/p stent in 2011, DM2
Meds: ASA, metoprolol, metformin, lisinopril and pravastatin

You counsel him about LTBI treatment, and he agrees to take 3HP, with careful monitoring of his blood pressure and glucose.

Does he need LFT monitoring?

a) Yes
b) No
c) Maybe

Monitoring for patients on LTBI treatment

Evaluate all patients 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

*Does not have to be in-person visit

Who needs baseline labs (LFTs, CBC)?

- People living with HIV
- Pregnancy / Early postpartum (<3mo)
- Liver disease (hepatitis B or C, alcoholic hepatitis or cirrhosis)
- Regular EtOH use or currently injecting drugs
- Consider for others based on clinical discretion:
  - Statin/other hepatotoxic meds
  - Age >50
  - Other comorbidities (DM, renal disease, etc)

Case 2

26 F born in Guatemala, referred to you with positive QFT.

She is G2P1, and 13 weeks pregnant. QFT was performed with prenatal labs, and she was referred to you by obstetrics. She is healthy, asymptomatic, and has no known contact to a patient with TB disease.

What will you do next?

a) Wait on doing CXR and symptom screen until she is 6 months postpartum
b) CXR and symptom screen now – if negative she's done
c) CXR and symptom screen now – if negative, offer LTBI treatment immediately
d) CXR and symptom screen now – if negative, offer LTBI treatment at 3-6 months postpartum
e) Other

Treating LTBI in pregnancy

- Always **exclude TB disease immediately**
- If immune-compromised or recent contact/converter within 2 years, treat for LTBI immediately
- If not immune-compromised or recent contact, discuss risk/benefit of immediate treatment vs deferred treatment (3 months postpartum)
  - <20% actually complete LTBI therapy after delivery[1]
- If treatment needed, 4 months of RIF or 9 months of INH preferred
  - 3HP regimen not extensively studied in pregnancy
  - B6 supplementation recommended with INH
  - Breastfeeding <u>not</u> contraindication:
    - Infant will get small amount of INH (sub-therapeutic)
- Don't suspend LTBI therapy if patient gets pregnant!

1. Cruz CA. Am J Obstet Gynecol, 2005 2. American Thoracic Society. MMWR Recomm Rep, 2000 3. Am Academy Pediatrics & Am College of Obstetricians and Gyn. Guidelines for Perinatal Care, 2017.

Case 3

20 M with ongoing meth use. PMHx includes +HIV testing in 2022; he was lost from care and never received ART. Born in Modesto. One week ago he was a close contact to a TB case; his IGRA testing today is negative. Besides starting ART, what do you do next?

a) Nothing – evaluation is complete
b) Retest with IGRA in 8-10 weeks
c) Evaluate for TB disease, retest with IGRA in 8-10 weeks
d) Evaluate for TB disease, if no e/o disease start LTBI therapy, retest with IGRA in 8-10 weeks
e) Something else

Window prophylaxis protects high risk contacts

- IGRA and TST may take 8-10 weeks to become positive after exposure
- "Window prophylaxis" = treating contacts at high risk of progression with LTBI therapy when they are ***IGRA/TST negative***
  - Purpose is to abort early TB infection / progression
  - Need to exclude TB disease first (sx and CXR)
  - Consider window ppx for:
    - immune-compromised (including PLHIV)
    - children <5
  - Follow up: repeat IGRA/TST 8-10 weeks after exposure

LTBI in TB Contacts

- Remember that recent (within 2 years) contacts are at highest risk of progression
- Make sure you adjust treatment based on drug-susceptibility testing (DST) of source case!
  - i.e., a contact of a case of rifampin-resistant TB should not receive 4R
- For contacts of ***multi-drug resistant (MDR)*** TB:
  - limited data supports 12 months Fluroquinolone (FQ) +/- EMB for 6-12 months

1. Bamrah S, et al. Int J Tuberc Lung Dis. 2014

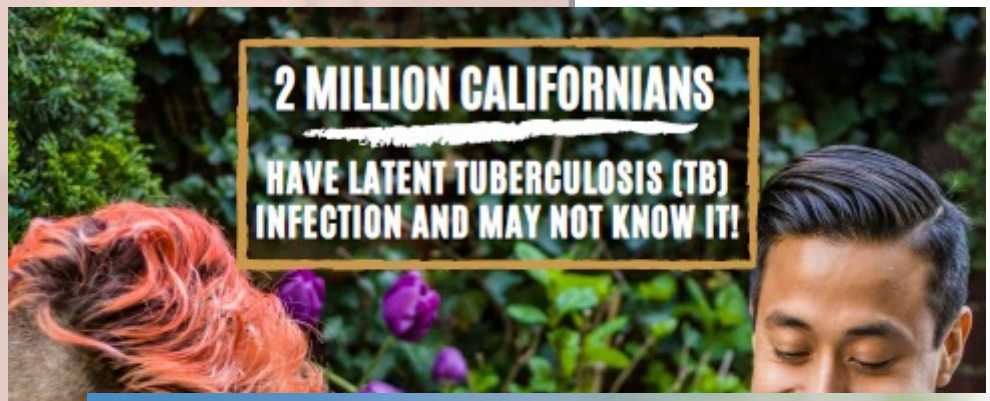
TB Free California

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB_Provider_Resources.aspx

California Department of Public Health
Tuberculosis Control Branch
850 Marina Bay Parkway
Building P, 2nd floor
Richmond, CA 94804
Phone: (510) 620-3000
TBCB@cdph.ca.gov

Clinical support for LTBI, including:

- Provider education tools
- Patient handouts
- Drug fact sheets
- Resources for counseling patients
- Expert consultation on cases



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您知道嗎？

在加州，每7名亞裔就有1名患有潛伏性肺結核感染（LTBI）.

如果沒有及時治療，
感染就可能會發展成活動性肺結核疾病，
從而令患者變得十分虛弱，
或傳染病菌給他們的家人

請和您的醫生談談潛伏性肺結核的篩檢，
這樣您就可以照顧好您自己，
以及保護您的家人.

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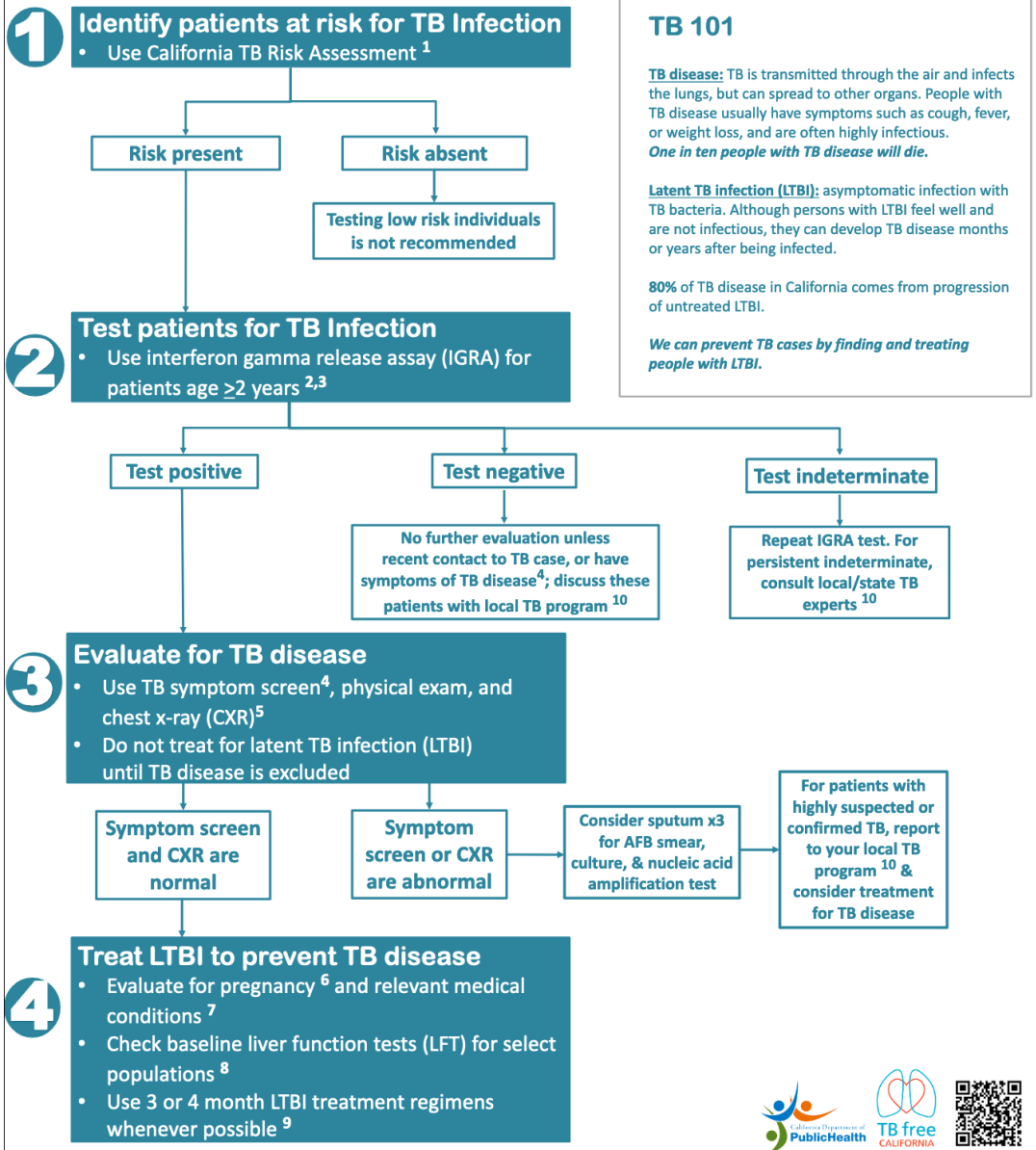
LEARN MORE
ABOUT 潛伏性肺結核
bit.ly/CDPHTB

Prevent Tuberculosis (TB) in 4 Steps: A Guide for Medical Providers



TB 101

TB disease: TB is transmitted through the air and infects the lungs, but can spread to other organs. People with TB disease usually have symptoms such as cough, fever, or weight loss, and are often highly infectious.
One in ten people with TB disease will die.

Latent TB infection (LTBI): asymptomatic infection with TB bacteria. Although persons with LTBI feel well and are not infectious, they can develop TB disease months or years after being infected.

80% of TB disease in California comes from progression of untreated LTBI.

We can prevent TB cases by finding and treating people with LTBI.

January 2020

More LTBI Provider Resources

1. TB Free California (email tbcb@cdph.ca.gov)
2. NTCA LTBI clinical guidelines https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/
3. Rifamycin Drug Interaction Guide https://www.currytbcenter.ucsf.edu/products/view/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis
4. CDC LTBI patient+ provider resources https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm

TB PREVENTION GUIDEBOOK

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TBCB@cdph.ca.gov

Summary

1. Many TB cases could be prevented by treating LTBI
2. Test people with risk factors
   - Birth/residence outside the U.S.
   - Immune compromise
   - Contact to TB case
3. Use IGRA (QFT-Plus or T-SPOT tests)
4. Neither TST nor IGRA can distinguish latent infection from TB disease
5. Treating LTBI with 3- or 4-month regimens (3HP or 4R) is strongly preferred

Image: Getty Images

Key points

Screen	Screen to identify patients experiencing risk (non-U.S.-born, immune compromise, TB contact)
Test	Test using an IGRA, if risk is present
Treat	Treat with 3- to 4-month rifamycin-based regimens

”.

ACOG guidelines

Which pregnant women should be tested for TB?

- Women at high risk of TB (for example, women who are infected with HIV or who live in close contact with someone who has TB) should be tested for this infection

- Approaches might include:
  - Use risk assessment for all pregnant patients, order TB testing (IGRA) if risk factor is present

American College of Obstetricians and Gynecologists, Routine Tests During Pregnancy. FAQ133, September 2017

IGRA (Quantiferon) interpretation

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NIL IU/mL	TB Antigen minus NIL IU/mL	Mitogen minus NIL IU/mL	Result	Interpretation
<=8.0	>=0.35 and >=25% of Nil value	Any	Positive	M. tuberculosis infection likely
<=8.0	<0.35	>=0.5	Negative	M. tuberculosis infection not likely
<=8.0	>=0.35 and <25% of Nil value	>=0.5	Negative	
<=8.0	<0.35	<0.5	Indeterminate	Results are Indeterminate for TB Antigen responsiveness
<=8.0	>=0.35 and <25% of Nil value	<0.5	Indeterminate	
>8.0	Any	Any	Indeterminate	

Nil = negative control **Mitogen = positive control**

Rifamycins and Nitrosamine

U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Drug Safety and Availability / FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities

FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities

- FDA has set new limits on nitrosamine levels in drugs, including RIF and RPT
- Manufacturers may need to adjust drug making processes to limit nitrosamine contamination (in process)
- Over last several months, small voluntary recalls have been issued by one manufacturer after after post-distribution testing identified “out of specification” results
  - Follow manufacturer/FDA guidance if you have a recalled lot; consult your pharmacist if the guidance is not clear
- There are no restrictions on use of rifamycins currently available on the US market because of nitrosamines