Treating Latent Tuberculosis: An opportunity to prevent disease

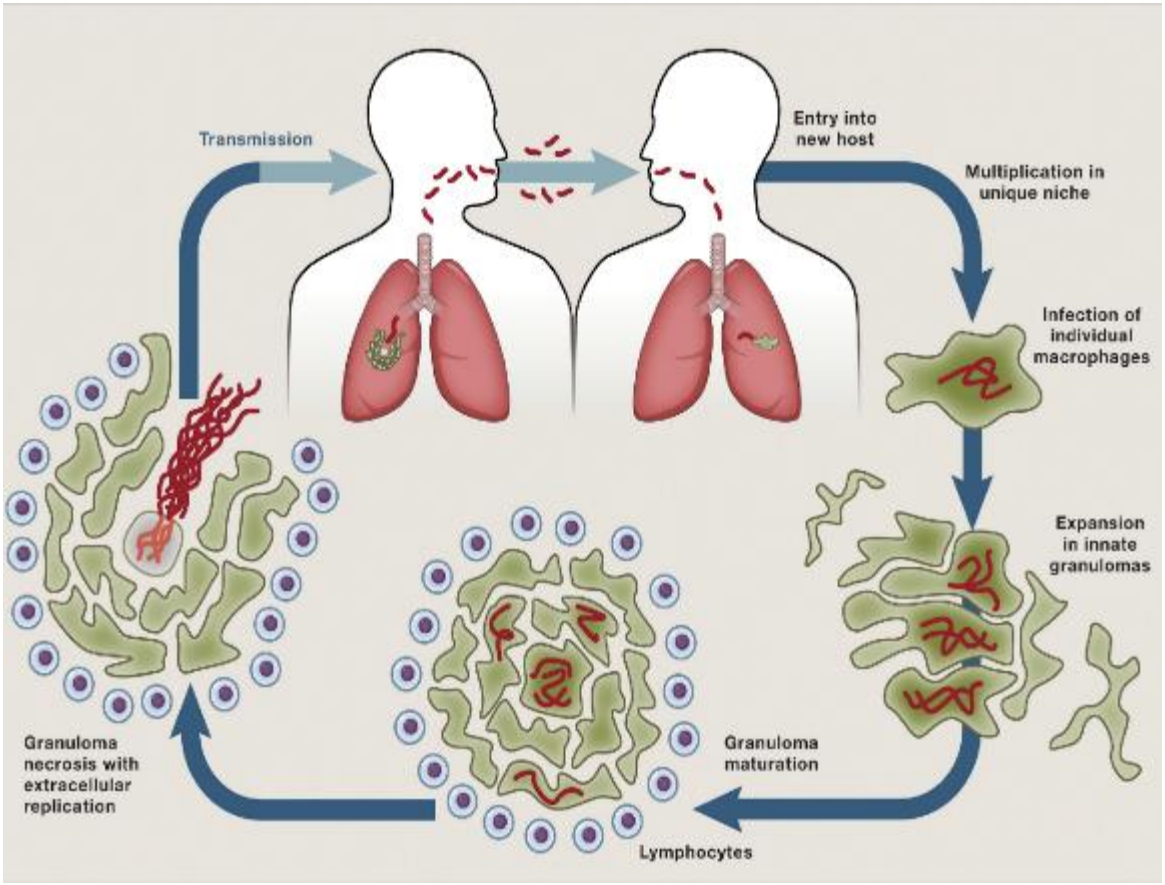
Shereen Katrak, MD, MPH
Assistant Clinical Professor, Division of Infectious Disease, UCSF

Phuong Luu, MD, MHS, FACP
Bi-County Health Officer, Sutter and Yuba Counties
TB Controller at Large, Executive Committee, CA TB Controllers Association

Disclosures

- No financial disclosures

Tuberculosis (TB) is transmitted person-to-person through the air



- Bacteria released into air when TB patient coughs, speaks, or sings
- Bacteria often contained in “latent state”, but can become active and cause disease
- TB causes disease in United States (>7000 cases in 2021)

1. Cambier CJ. Cell, 2014. 2. https://www.cdc.gov/tb/statistics/tbcases.htm

TB: a respiratory disease that is **preventable** and **you don't want to miss**

"Delayed or missed tuberculosis disease diagnoses are threatening the health of people with TB disease and the communities where they live. A delayed or missed TB diagnosis leads to TB disease progression and can result in hospitalization or death – and the risk of transmitting TB to others. The nation must ensure that healthcare providers understand how to diagnose and distinguish TB disease from potential cases of COVID-19."

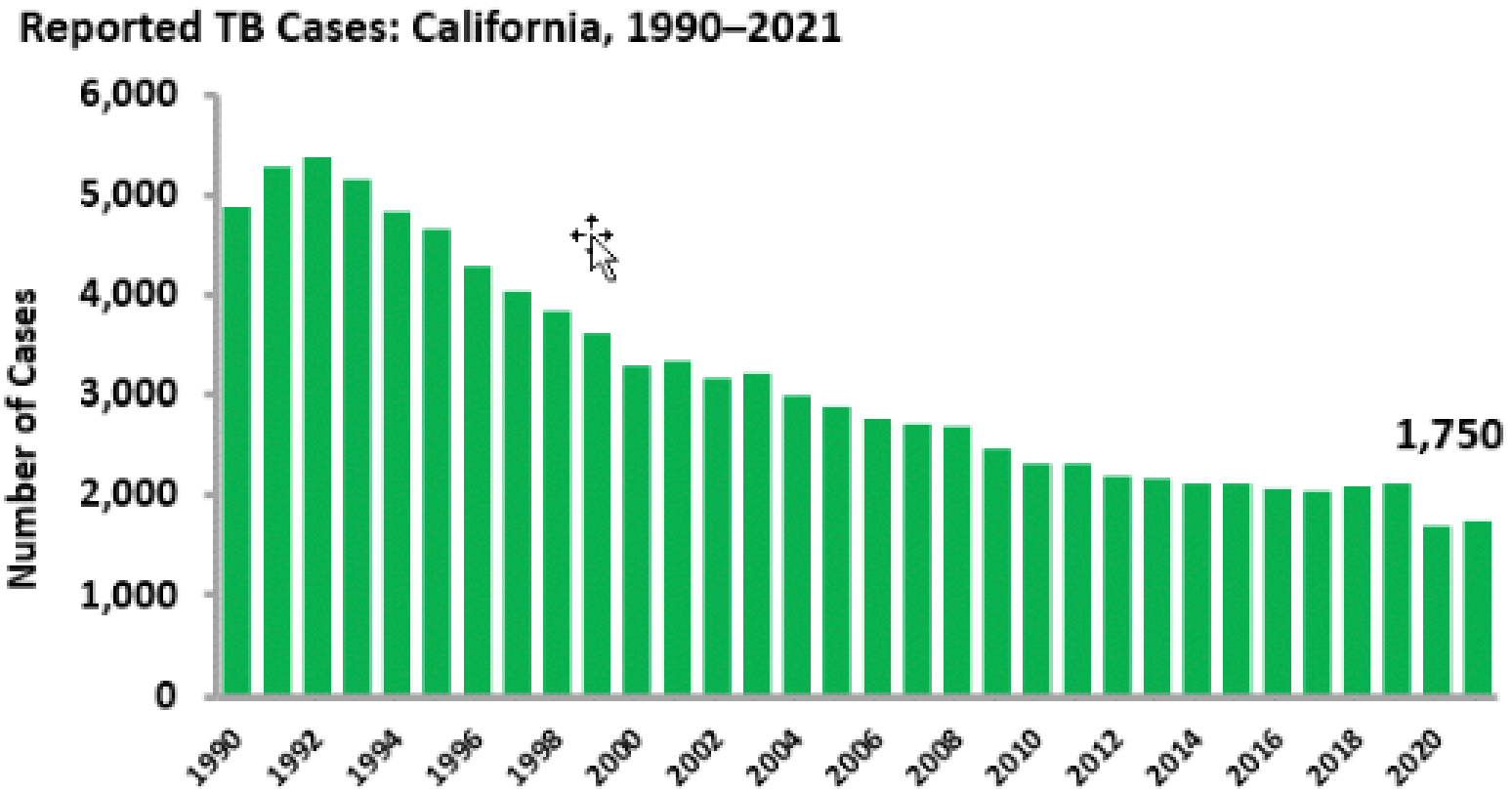
-Philip LoBue, MD, FACP, FCCP, Director of CDC's Division of Tuberculosis Elimination

Objectives

1. Understand the relevance of TB in California (treating latent TB can prevent TB!)
1. Understand who to test for TB infection, how to test, and work up of TB disease
2. Understand how to treat latent TB (LTBI)

PART 1: WHY TEST?

California continues to have a high rate of TB disease

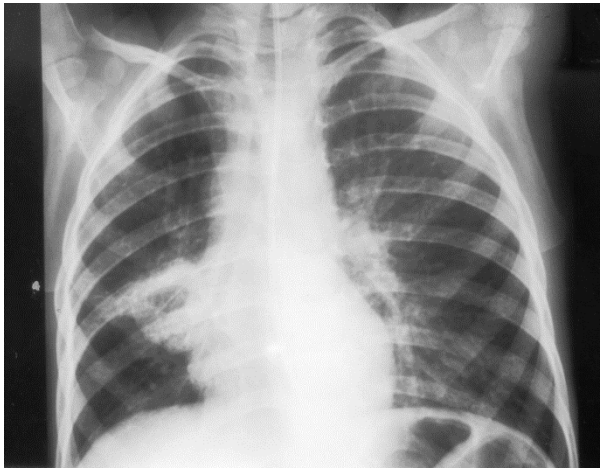


Tuberculosis Control Branch. California Department of Public Health , 2021
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-TB-Snapshot-2021.pdf

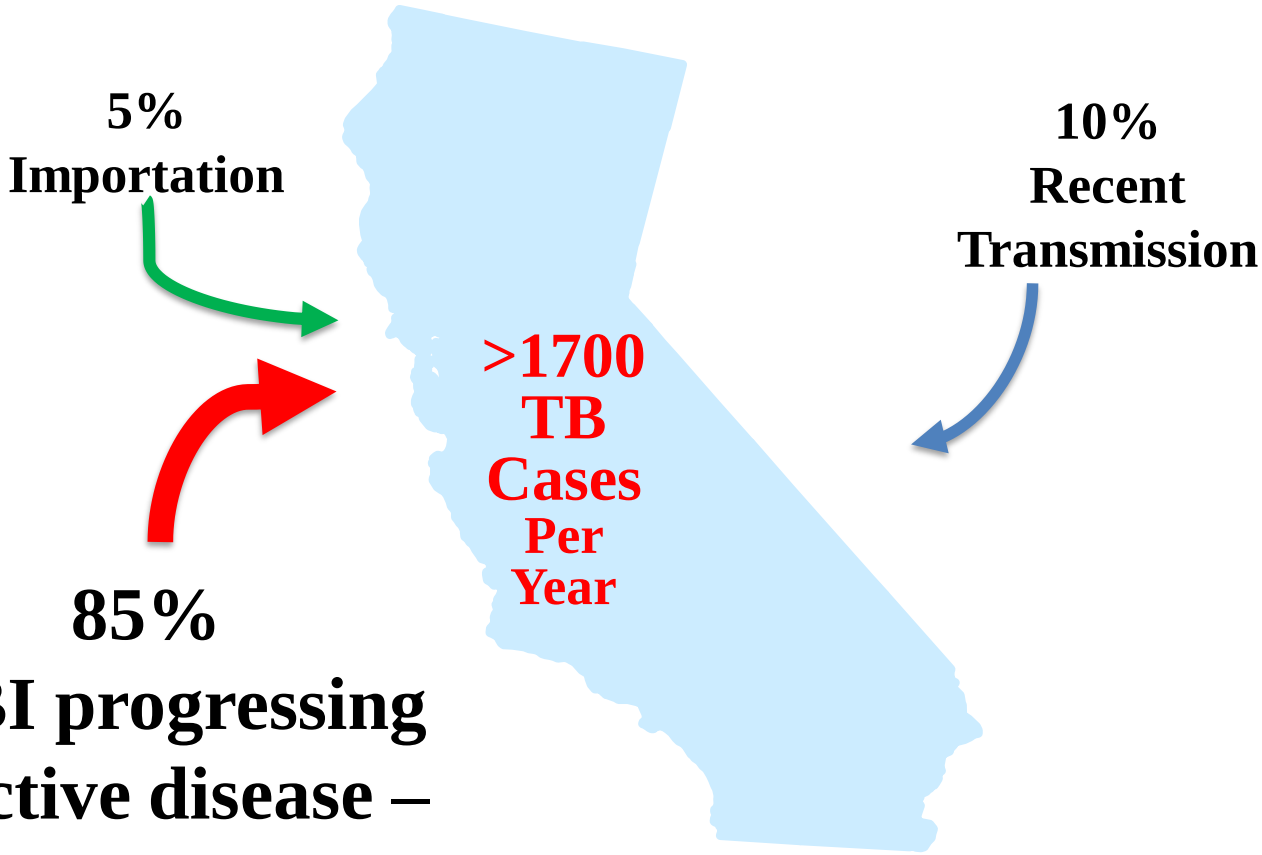
Why are we unsatisfied?

- TB is diagnosed every 4 hours
- Every other day a Californian dies with TB
- Each week at least one child found to have TB disease

TB is preventable!

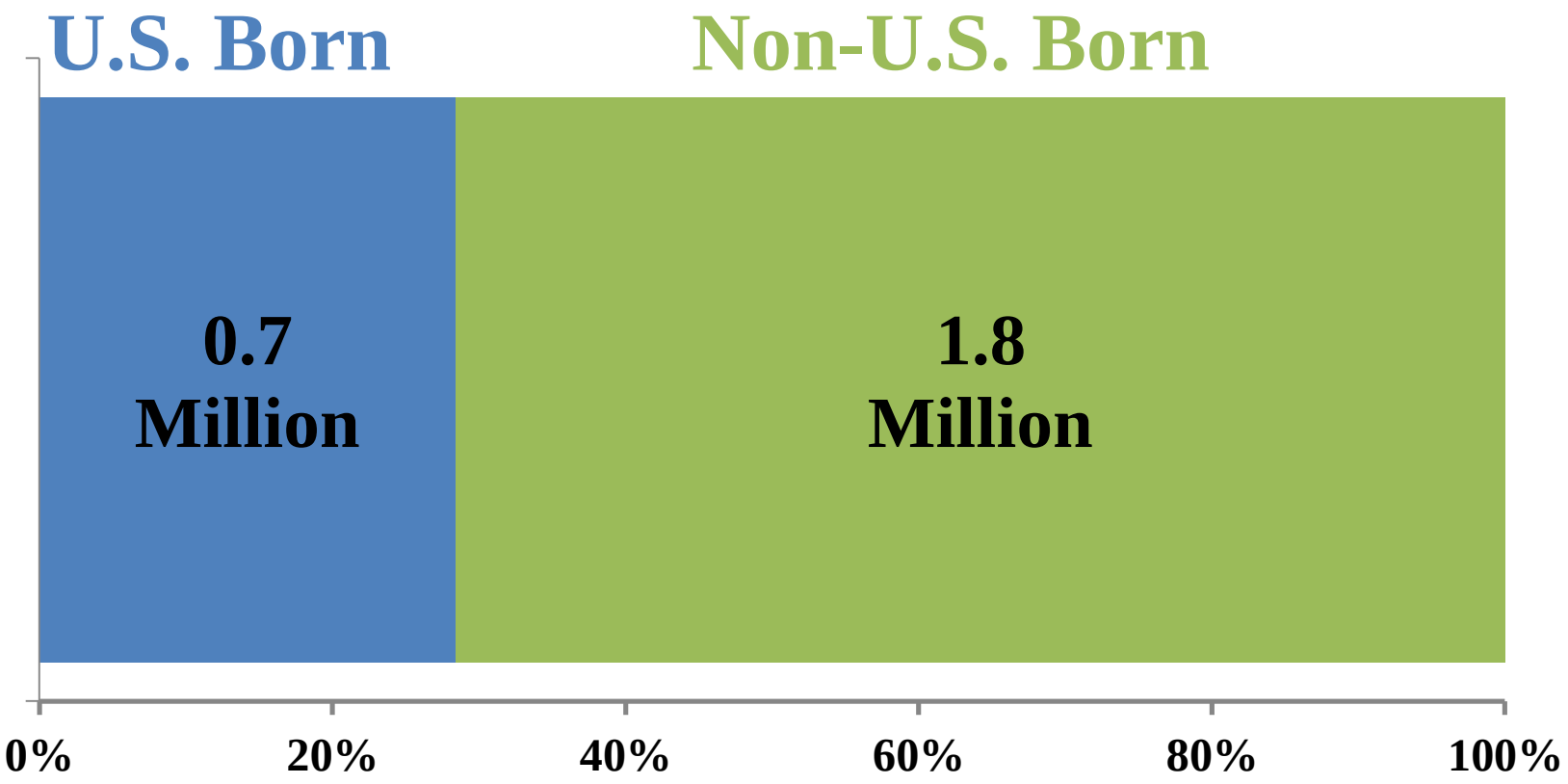


Relevance of LTBI in California



Tuberculosis Control Branch. California Department of Public Health, Feb 2021.

>2 Million with Latent TB Infection
Most Unaware and Untreated



TB is a health disparity in California

In 2020 in California:

- **More than half (52%)** of all TB cases occurred in Asians
- The rates of TB in **Asians born outside the U.S. were 50x 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, Feb 2021.
https://cchealth.org/tb/pdf/TB-In-California.pdf

PART 2: WHO TO TEST? WHAT TEST TO USE?

What is targeted testing?

Only test patients who have “TB risk factors”

Most persons with a positive test for LTBI should be treated

CDC, MMWR, 2000

TB Risk Factors

Exposure/Infection	Progression
• Non-U.S.-born*	• HIV/AIDS
• Known contact to infectious case	• 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

*From a country with elevated TB rate

CDC, MMWR, 2000

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 age?

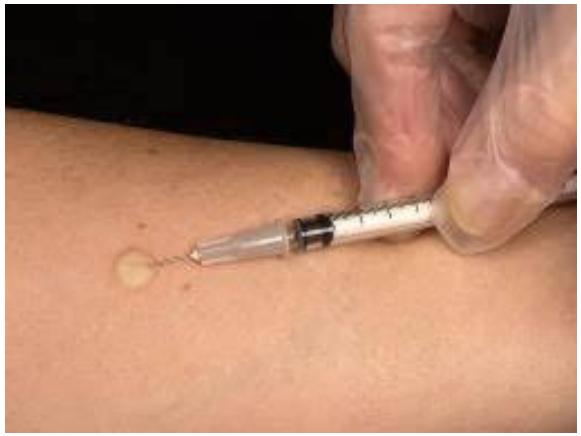
- No upper limit of age has been set for TB screening
  - Consider individual TB risks, comorbidities, and life expectancy
  - Older age is a risk factor for death if active TB develops
- Screen and treat for LTBI as with any other USPSTF recommended screening
- Younger persons have longer expected life during which TB progression from LTBI to active TB could occur

CDC Annual Report, 2015 | Miramontes, PLOS One, 2015 | Pascopella OFID 2015

How do you test for TB infection?

TB free CALIFORNIA

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



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

Part 2: Key Points

- Use a risk-based approach to testing
- Patients should be evaluated for TB risk factors regardless of age or time since entry into the U.S.
- IGRAs preferred over TST for most persons (especially if born outside the U.S.)
- Most persons with risk factors and a positive test (IGRA or TST) should be treated
- Medi-Cal Plans cover TST; majority also cover IGRA testing but may require prior authorization

Rule Out Active Disease Before LTBI Treatment

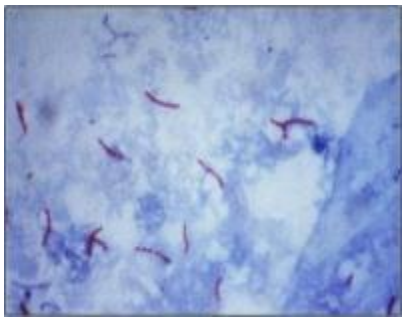
TB free CALIFORNIA

1. Symptom screen

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

2. Chest x-ray

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

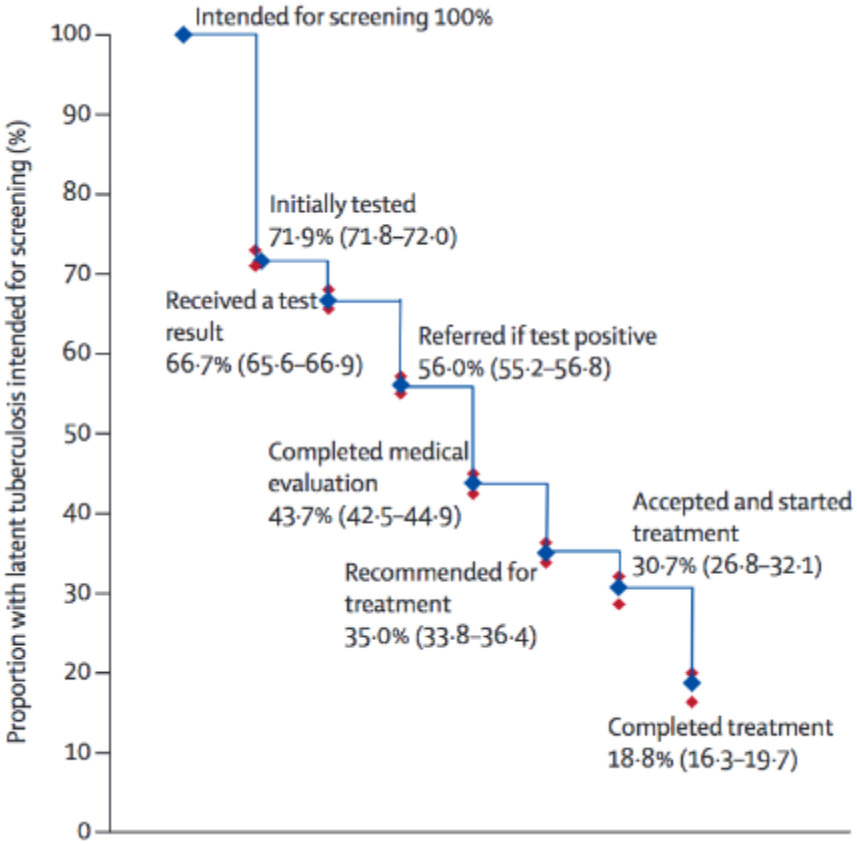


3. Sputum collection if chest x-ray and/or symptoms screen abnormal

- AFB smear & culture
- MTB PCR

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

Less than 25% of patients with LTBI complete treatment



- Systematic review & meta-analysis of 58 studies
  - >740,000 people
  - >80% from high income countries
- Identified % completing each cascade step
- Less than one-quarter of at-risk people with LTBI complete treatment

Alsdurf H et al. Lancet ID, 2016

PART 3: WHAT TO USE FOR LTBI TREATMENT

Treatment Regimens for Latent TB Infection

TB free CALIFORNIA

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

Timothy R. Sterling, MD[1]; Gibril Njie, MPH[2]; Dominik Zenner, MD[3]; David L. Cohn, MD[4]; Randall Reves, MD[4]; Amina Ahmed, MD[5]; Dick Menzies, MD[6]; C. Robert Horsburgh Jr., MD[7]; Charles M. Crane, MD[8]; Marcos Burgos, MD[8,9]; Philip LoBue, MD[2]; Carla A. Winston, PhD[2]; Robert Belknap, MD[4,8] (View author affiliations)

LTBI 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

Strongly preferred regimen

- Suitable for most patients
  - Adults and kids (all ages)
  - Avoid in most PLHIV
- Clinical considerations include:
  - **Drug interactions** (rifampin lowers plasma levels of drugs including dabigatran, oral contraceptives, methadone, most HIV medications and cancer chemotherapy)
  - Adverse drug reactions
    - Pruritis, rash, hepatotoxicity (<INH), orange body fluids

Rifampin Drug Interactions

Drug	Interaction	Monitoring and dosage considerations
Antiretroviral drugs (most)	Various mechanisms with concern for reduced ART efficacy and virologic failure	- Majority of data for LTBI + ART is 9H - Avoid rifampin if on protease inhibitors elvitegravir (EVG), etravirine (ETR), rilpivirine (RPV), or TAF
Oral contraceptives	Decrease blood levels of OCPs	- Use back-up non-hormonal birth control
Direct oral anticoagulants (dabigatran, apixaban, rivaroxaban)	Decreased serum concentration of DOACs	- Concurrent use with rifamycins not recommended - Consider alternate anticoagulant
Statins (NOT rosuvastatin and pravastatin)	Can decrease effectiveness of statin	- Concurrent use with rifamycins not recommended
Angiotensin II receptor blockers (losartan, valsartan	Various	- Monitor blood pressure carefully - Dose adjustment may be necessary
Anti-depressants (citalopram, escitalopram, sertraline, venlafaxine)	Decreased levels and effects of many SSRIs and SNRIs	- Dose adjustment may be necessary - Escitalopram may be less affected than other SSRIs
Beta-blockers (NOT atenolol)	Decrease levels of beta-blockers	- Monitor blood pressure and heart rate - Dose increase may be required
Levothyroxine	Decrease levothyroxine efficacy	- Monitor patients for reduced levothyroxine efficacy - Dose increase may be necessary
Methadone	Decrease the level or effect of methadone	- May need to adjust dose until steady state (approximately within 2 weeks)
Oral hypoglycemics (glitazones, metformin)	Various	- Monitor glucose closely during the first 2 weeks - Dose increase may be necessary
Warfarin	Decrease levels of warfarin	- Dose increase needed to maintain anticoagulation

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

Strongly preferred regimen

- Suitable for many patients:
  - Motivated to finish treatment in the shortest time possible
  - Can use in adults, kids ≥ 2, HIV-infected*

- Clinical considerations include:
  - Ability to remember **weekly** (rather than daily) dose
  - High **pill burden** and **higher dose of drugs**
  - Drug interactions (rifapentine interactions generally ↓ than rifampin)
  - Hypersensitivity or **flu-like reaction**, rash, hepatotoxicity (↓ risk than 9 month INH)

*if no significant drug interactions or not on ART

3HR = Rifampin 600 mg + Isoniazid 300 mg Daily x 3 months

Conditionally preferred regimen

- Suitable for some patients:
  - Adults, kids of all ages, HIV-infected*
- Considerations include:
  - **Rifampin** drug interactions
  - Lower quality evidence than 4R or 3HP regimens
  - Hepatotoxicity risk might be greater with INH+RIF than with either drug given alone

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

1.Hong Kong Chest Service Am Rev Respir Dis 1992 2.. Spyridis CID 2007 3. Ena J. CID 2005 4. Geijo MP Enferm Infec Microbio Clin 2007

Image: The Guardian, 2017. Accessed at: https://www.theguardian.com/lifeandstyle/2017/may/22/knew-they-were-sugar-pills-felt-fantastic-rise-open-label-placebos

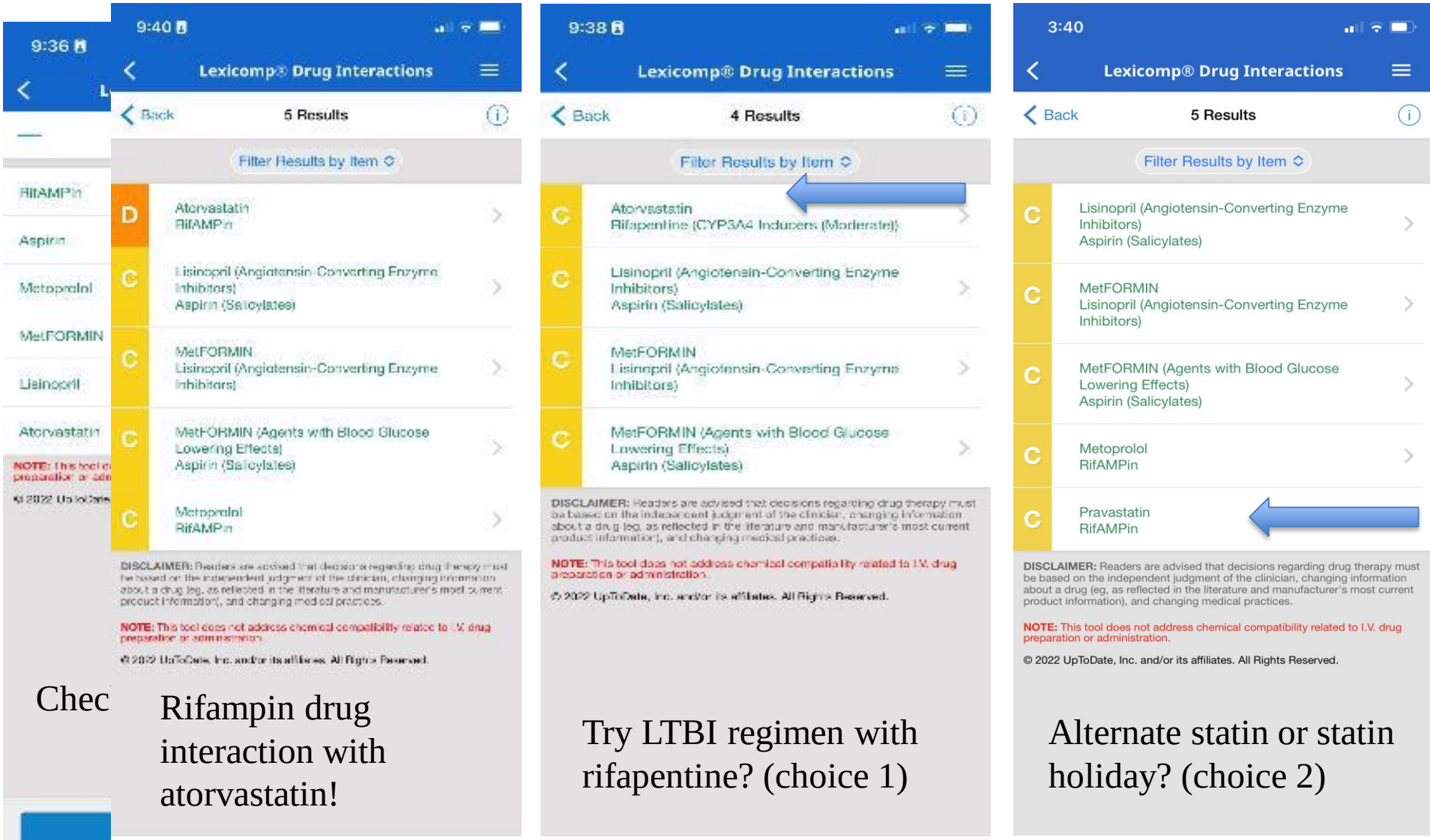
Rifampin/Rifapentine drug interactions

- Many rifampin and rifapentine (both in *rifamycin class)* drug interactions can be **managed with clinical monitoring and/or dose adjustment**!
- Find your favorite resource:
  - Lexicomp
  - Micromedex
  - Heartland: Tuberculosis Medication Drug and Food Interactions
  - TB Free CA: Common Drug Interactions Related to 12-Dose (3HP) Regimen
  - DHHS AIDS-info (HIV specific)

Table 2: Rifapentine drug interactions

Class of interaction	Drug	Interaction	Monitoring and dosage considerations
Major	Antiretroviral therapy (ART) drugs, including protease inhibitors, darunavir, etravirine, tenofovir alafenamide (TAF)	Various mechanisms occur that can result in reduced ART efficacy and virologic failure; review comprehensive list here: https://aidsinfo.	- In persons on ART, the majority of data and clinical experience for LTBI treatment is with use of INH x 9 months - Current Department of Health and Human Services (DHHS) guidelines suggest that efavirenz or raltegravir-based regimens (in combination with either abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) can be used with 3HP. Consider use of these regimens and 3HP with close viral load monitoring - Insufficient data characterizing interactions between other antiretrovirals and rifapentine
Major	Cancer treatment drugs	Various mechanisms	- Consult oncologist and/or clinical pharmacist - Co-administration with rifamycins generally not recommended
Major	Hepatitis C virus drugs (HCV)	Various; decrease	- Co-administration with rifamycins not recommended
Major	Oral contraceptives	Decrease blood	- Ask patient to use a back-up non-hormonal form of birth control while on rifamycins
Major	Statins (EXCEPT rosuvastatin)	Increase blood levels of statins	- Concurrent use with rifamycins not recommended - Consider use of non-interacting statin (rosuvastatin), or alternate anti-lipid agent
Moderate	Anti-arrhythmic drugs including amiodarone, and digoxin	May decrease effectiveness of anti-arrhythmic or digoxin	- Monitor serum digoxin concentrations during and after rifapentine therapy - May require increase in the anti-arrhythmic or digoxin dose - Consider possibility of antiarrhythmic toxicity after withdrawing concomitant rifapentine
Moderate	Beta-blockers (EXCEPT atenolol)	May decrease concentrati	- Monitor blood pressure and heart rate carefully - Beta-blocker dosage increase may be required
Moderate	Ciprofloxacin	May result in decreased ciprofloxacin	- Dose increases of ciprofloxacin may be required - Consider completing a course of therapy prior to prescribing rifapentine, or using alternate
Moderate	Clopidogrel	May increase antiplatelet activity of	- Evidence on this interaction is limited - Consider indication for clopidogrel - Consider involving cardiologist and/or clinical pharmacist
Moderate	Levothyroxine	May result in decreased levothyroxine	- Monitor patients for reduced levothyroxine efficacy - Levothyroxine doses may need to be increased when rifapentine is given concomitantly

In many cases, rifamycin drug interactions can be managed by dose adjustments, substitutions, or clinical monitoring



Chec

Rifampin drug interaction with atorvastatin!

Try LTBI regimen with rifapentine? (choice 1)

Alternate statin or statin holiday? (choice 2)

9H (6H)= 9 (or 6) Months of Isoniazid 300 mg Daily
Alternative Regimens

- **Second line regimen**, suitable for some patients:
  - People living with HIV on antiretroviral therapy, or patients with major drug interactions limiting use of rifamycins
  - Pregnant women
  - Okay in kids/infants, although usually not 1st choice
- Clinical considerations include:
  - **Lower completion rate** than first line regimens
  - Adverse drug events including **hepatotoxicity** (incidence ↑ with age), peripheral neuropathy
  - Clinical f/u time for 6-9 months
  - **Fewer drug interactions**

1. Nolan, JAMA, 1999, 2. Smieja, Cochrane Database Syst Rev, 2000, 3. Menzies, Ann Int Med, 2008

How do I counsel my patients?

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 BCG vaccine when I was a child, how can I get TB?"

How do I counsel my patients?

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?"

Talking points

- You are infected with TB germs. **TB germs can hide in the body for years.** People with hidden ("latent") TB do not feel sick, however, TB germs can eventually "wake up", make you ill, and spread to loved ones…
- TB is a **slow-growing germ**, so treatment of TB infection takes longer than antibiotics you take for other infections…
- The TB vaccine (called BCG) is not completely effective, and it **doesn't protect you for your whole life**…

Monitoring for LTBI patients

Evaluate all patients monthly* for:

***Does not have to be in-person visit – can be done by nursing**

- 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

Who needs baseline labs?

Not everyone needs baseline labs

Check baseline LFTs for these patients:

- People living with HIV
- Pregnancy / Early postpartum (<3mo)
- Liver disease (hepatitis B or C, alcoholic hepatitis or cirrhosis)
- Regular EtOH use
- Consider for:
  - Statin/other hepatotoxic meds
  - Age >50

Treatment Switches

- No guidelines or data
- Approaches: start over vs partial credit
- Okay to ask a “TB expert” for input

- Partial credit example:
  - Pt completes 3 doses of 3HP (25% of planned regimen)
  - Needs 75% of RIF regimen (i.e. 3 months if using 4R regimen) to complete LTBI therapy

LTBI in Pregnant Women

- Make sure you **exclude TB disease**
  - Symptom screen, CXR with abdominal shielding, +/- sputum
- Unless immune-compromised or a contact, can ***defer treatment*** until 3 months postpartum
  - <20% of women complete LTBI therapy after delivery
- Don't suspend LTBI therapy if patient gets pregnant
- 4R, 3HR, or 9H are acceptable treatments
  - B6 supplementation recommended with INH
  - Breastfeeding not contraindication

1. Cruz CA. Am J Obstet Gynecol, 2005 2. https://www.cdc.gov/tb/topic/treatment/pregnancy.htm 3. Am Academy Pediatrics & Am College of Obstetricians and Gyn. Guidelines for Perinatal Care, 2017.

Medi-Cal LTBI Treatment Coverage

Medi-Cal Rx Contract Drugs List

Effective 04/01/2022

Drug Name	Dosage	Strength/ Package Size	Billing Unit	UM Type	Code 1
Isoniazid	Injection	100 mg/ml 50 mg	ml ea		
	Tablets +	100 mg 300 mg	ea ea		
	Liquid	50 mg/5 ml	ml		
Pyrazinamide	Tablets or capsules	500 mg	ea		
Rifabutin	Capsules	150 mg	ea		
Rifampin	Capsules	150 mg 300 mg	ea ea		
	Vial	600 mg	ea		
Rifampin and Isoniazid	Capsules	300 mg/150 mg	ea		
Rifampin, Isoniazid and Pyrazinamide	Tablets	120 mg/50 mg/ 300 mg	ea		
Rifapentine	Tablets	150 mg	ea		

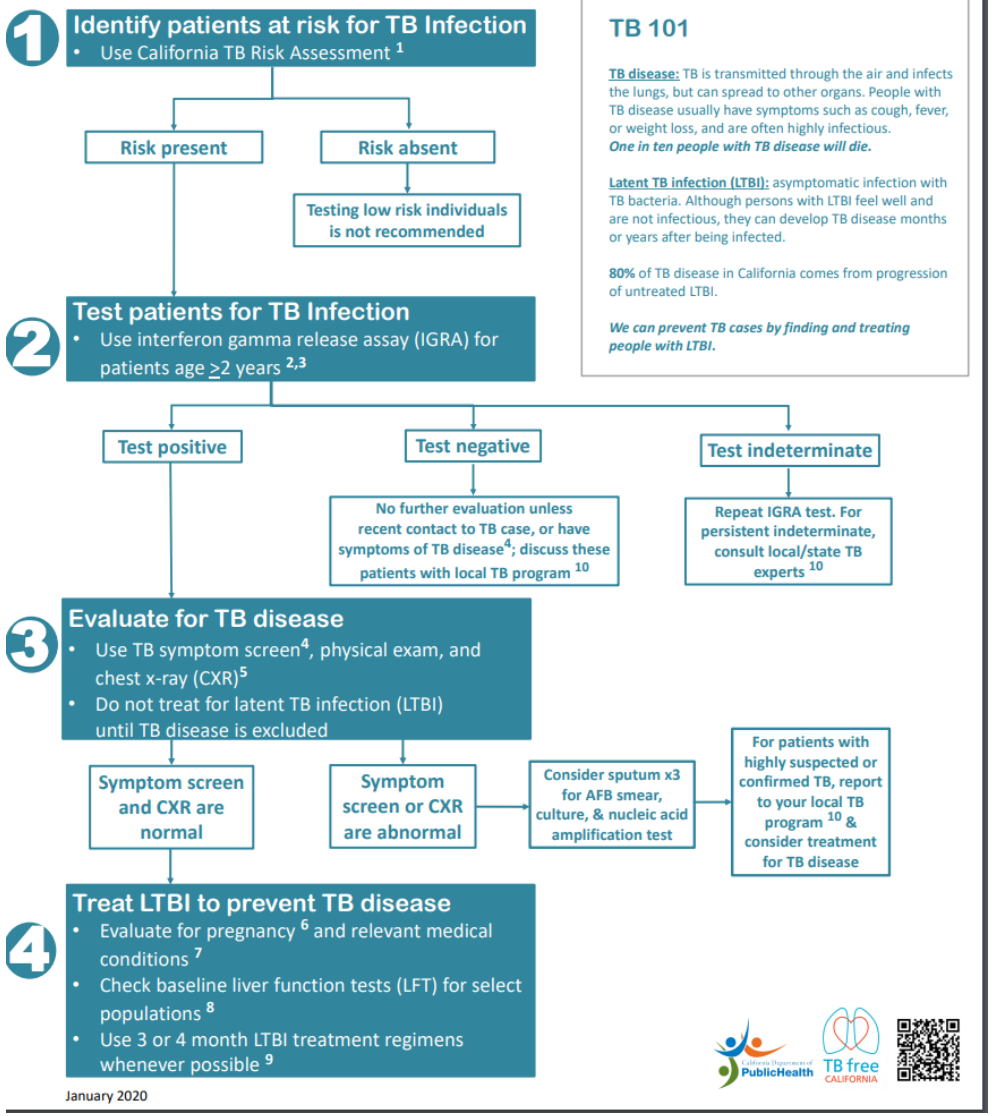
Source: https://medi-calrx.dhcs.ca.gov/home/cdl/

Summary

1. Treating patients for LTBI is an opportunity to prevent TB disease
2. Rule out TB disease before treating LTBI
3. Shorter regimens such as 4R and 3HP improve LTBI completion rates (preferred in adults AND children)

Image: Getty Images

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



January 2020

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/PreventTBin4%20Steps_%20AGuideforMedicalProviders.pdf

Preventing Tuberculosis in Your Clinical Setting:

A PRACTICAL GUIDEBOOK

California Department of Public Health
Tuberculosis Control Branch

TB and LTBI resources

Local TB Program:
https://ctca.org/directory/

California Department of Public Health, Tuberculosis Control Branch
tbcb@cdph.ca.gov
Phone: (510) 620-3000

Curry International Tuberculosis Center
https://www.currytbcenter.ucsf.edu/

Clinical support for LTBI, including:

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

Thank you!

Case 1

67 M, with positive QFT+. Born in China, in U.S. since 1980s. QFT 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 –evaluation is complete
- Additional workup is needed
- Offer treatment for LTBI
- Encourage treatment for LTBI
- Other

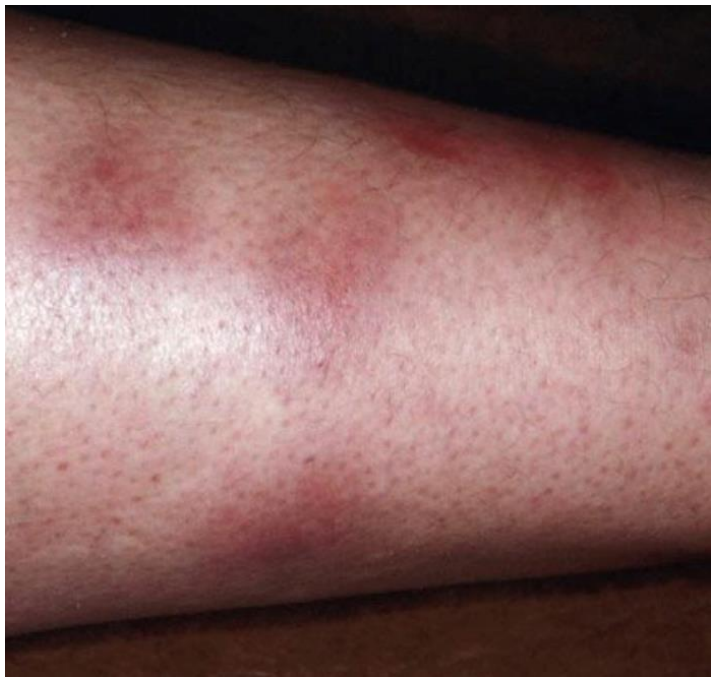


Photo: Uptodate, “Erythema nodosum”

Case 1 continued

67 M, born in China, with positive QFT+. 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 atorvastatin

What do you do?

- Encourage treatment with 9 months of INH
- Encourage treatment with 4 months of Rifampin
- Encourage treatment with 3 months of 3HP
- Other

Encourage treatment with 4R or 3HP

Consider obtaining baseline LFTs d/t age, statin use