Diagnosis of Latent Tuberculosis Infection

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Disclosures

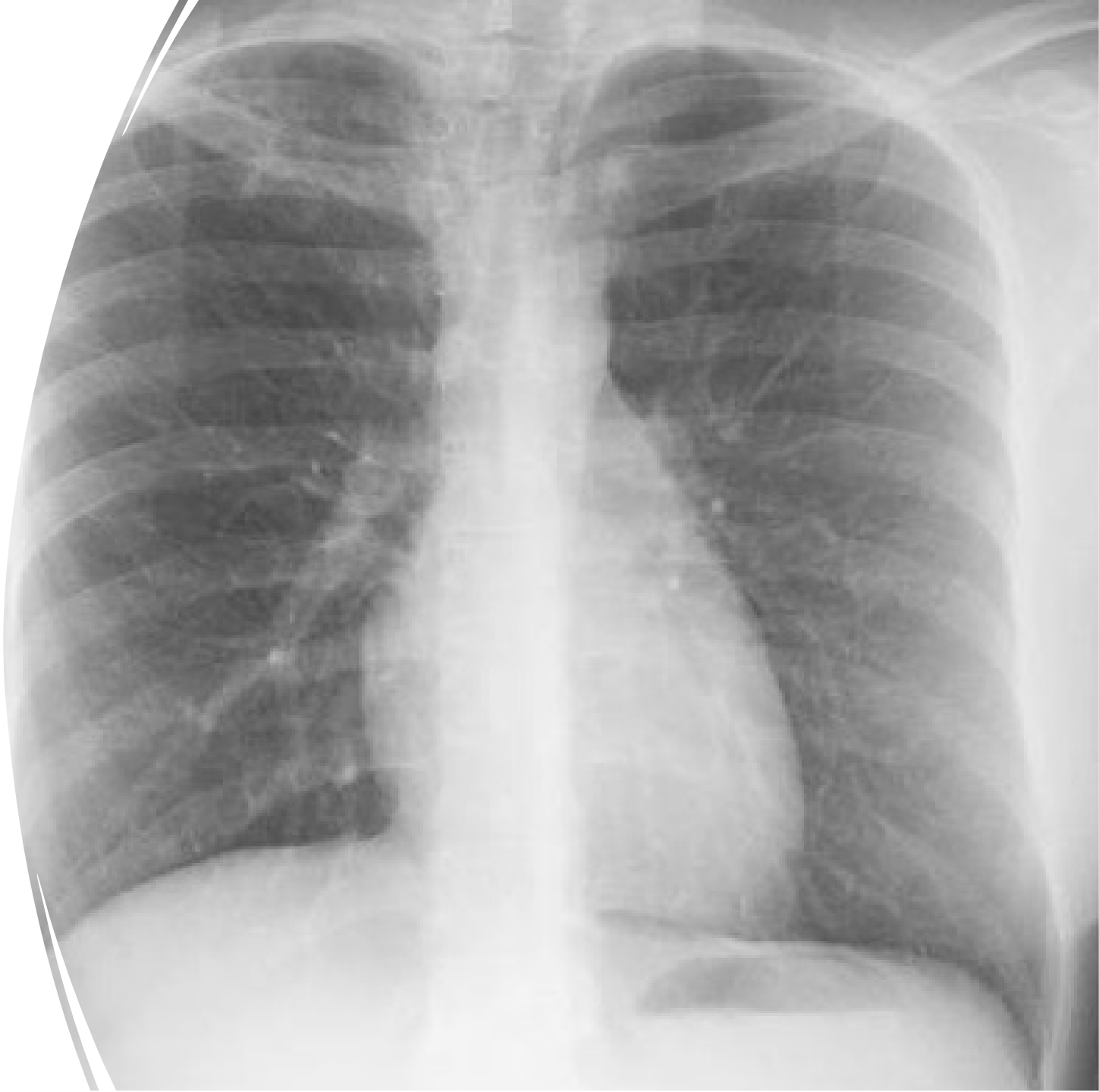
- I have nothing to disclose

Objectives

- Be able to define latent TB and differentiate this from active TB
- Understand identify risk factors for TB infection, and who should be offered testing for TB infection
- Be able to select testing for TB infection and how to interpret results
- Understand the pros and cons of the current tests for diagnosing LTBI

Clinical Scenario #1

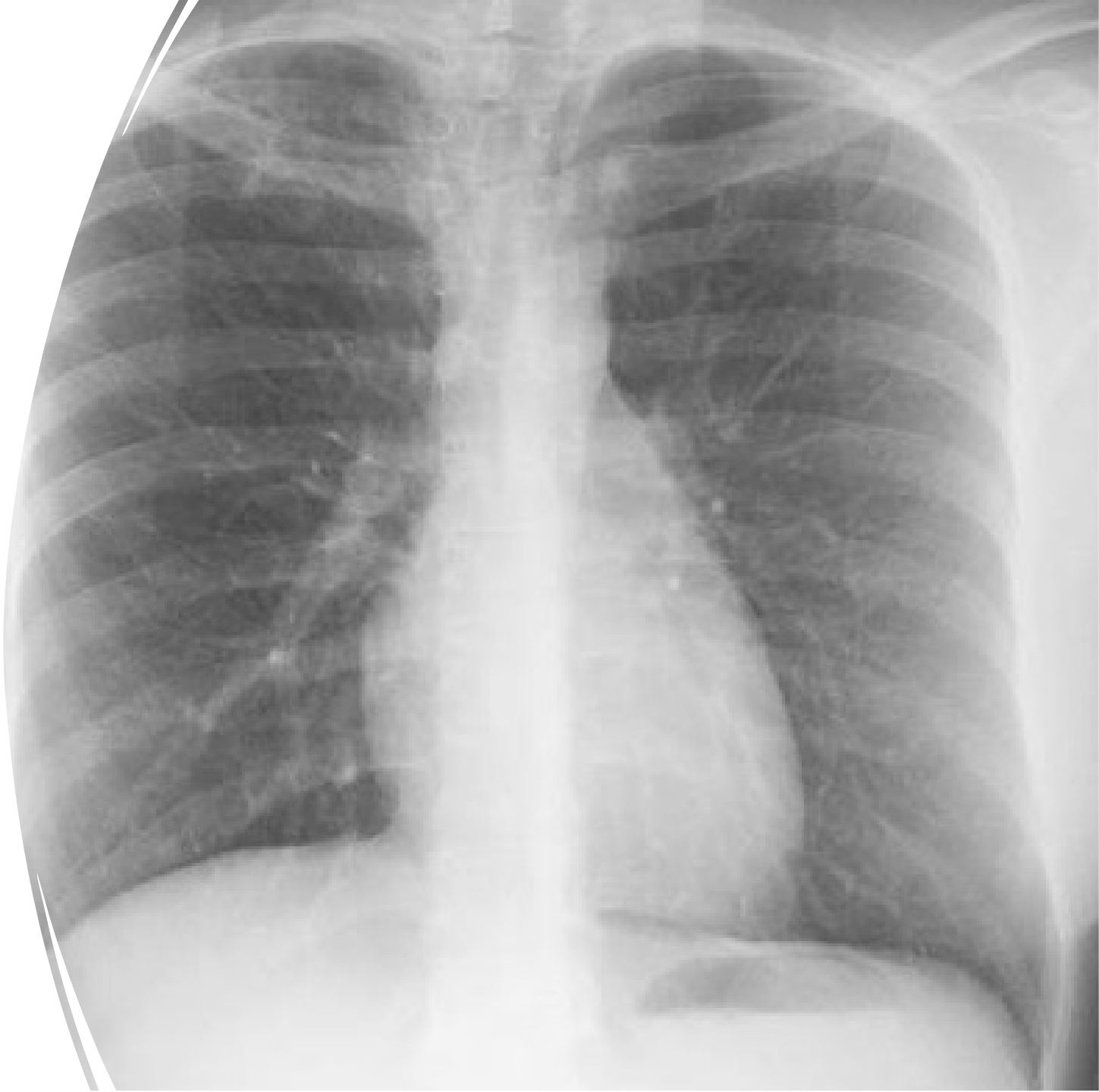
- 24 y/o from Botswana
- QFT (+); HIV (-)
- Asymptomatic
- CXR – right upper lobe fibrosis
- Is this LTBI?



Slide content courtesy of Robert Belknap

Clinical Scenario #1: Follow-up

- Asymptomatic
- QFT (+); HIV (-)
- CXR – right upper lobe fibrosis
- Sputum AFB x 3 negative by smear and culture
- Diagnosis: LTBI, not treated



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2 years later…seen for a cough

Chest X-ray

Impression: Dense right upper lobe consolidation, suspected pneumonia. Follow-up x-rays recommended after antibiotic treatment

Prescribed azithromycin for pneumonia

3 weeks later … seen at an urgent care

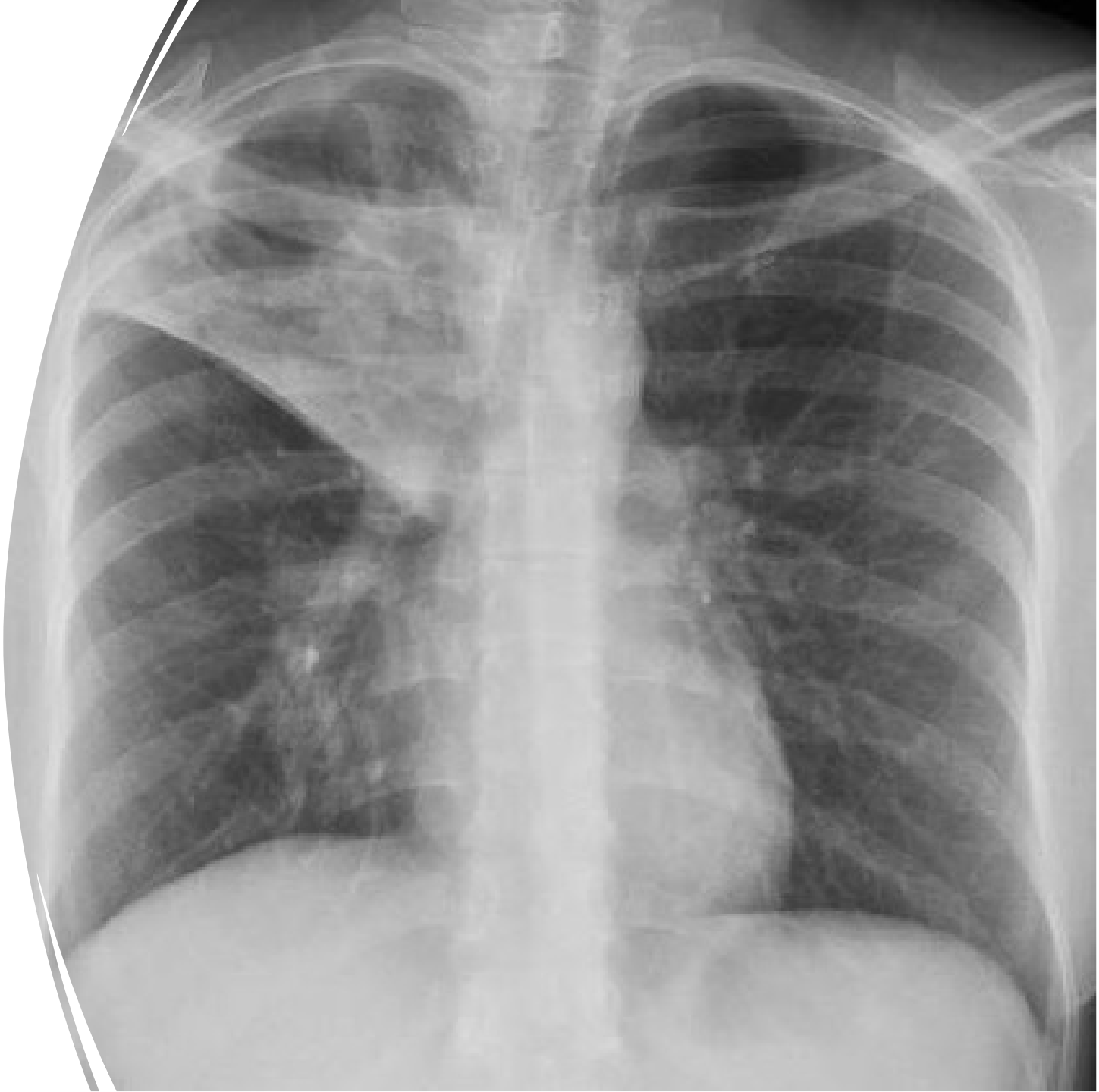
SARS-COV 2 negative

Diagnosed with pneumonia (no X-ray)

Prescribed doxycycline

Hospitalized 6 weeks after initial CXR

- Impression: Dense right upper lobe consolidation, suspected pneumonia. Follow-up x-rays recommended after antibiotic treatment
- Findings: Dense consolidation with 3.5 cm cavity without fluid level
- Eventually diagnosed with drug-susceptible cavitary pulmonary TB



Slide content courtesy of Robert Belknap

Clinical Definition of Latent TB Infection (LTBI)

Laboratory criteria

- A positive tuberculin skin test (TST)

OR

- A positive interferon-gamma release assay (IGRA)-QuantiFERON (QFT)

Clinical criteria

- No signs or symptoms of active TB

AND

- Chest imaging without abnormalities OR abnormal imaging with negative microbiologic testing

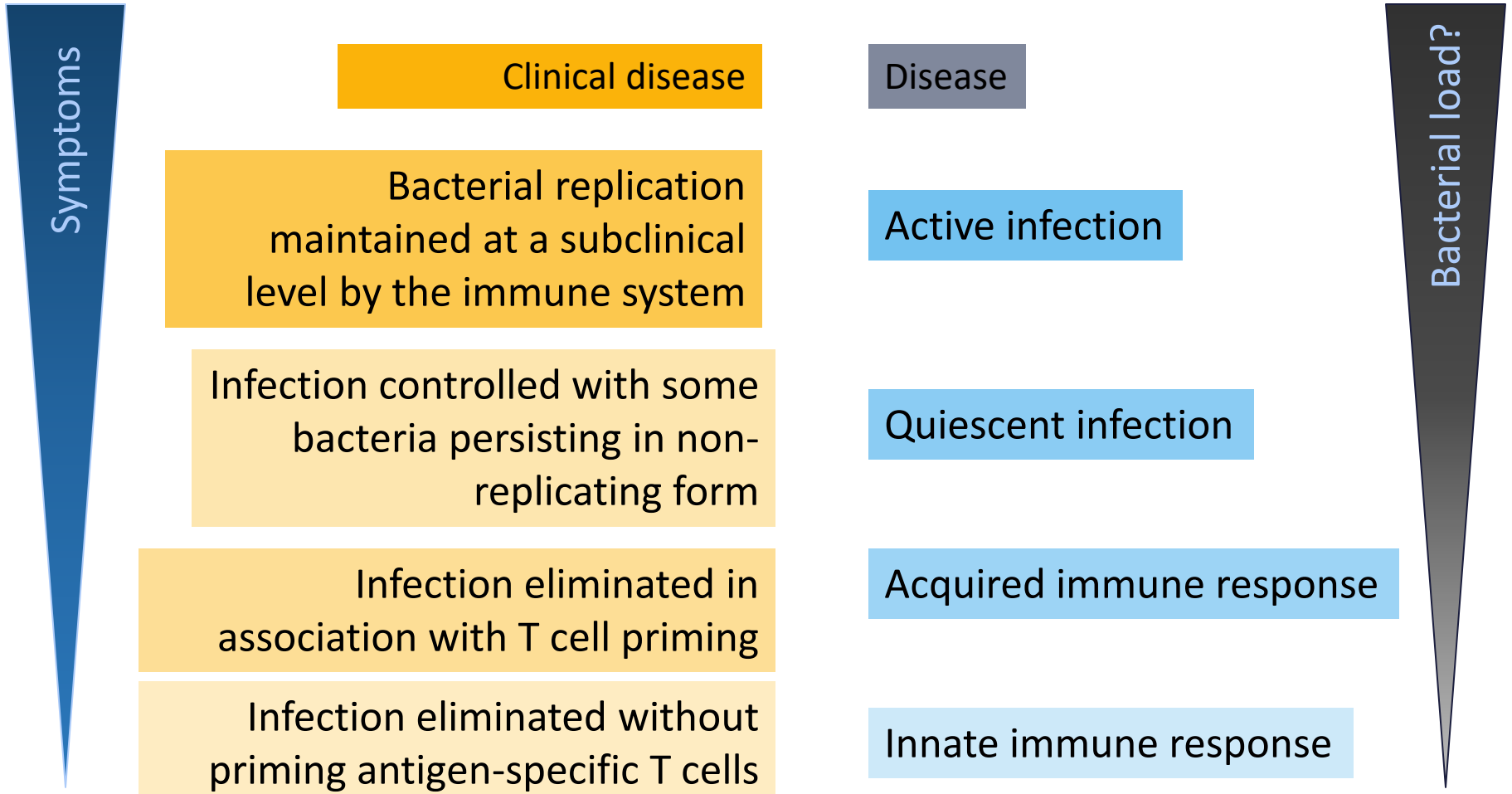
Compare LTBI vs Active TB

	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)

Risk Factors for Tuberculosis and lifetime risk of disease after TB infection

Risk Factors

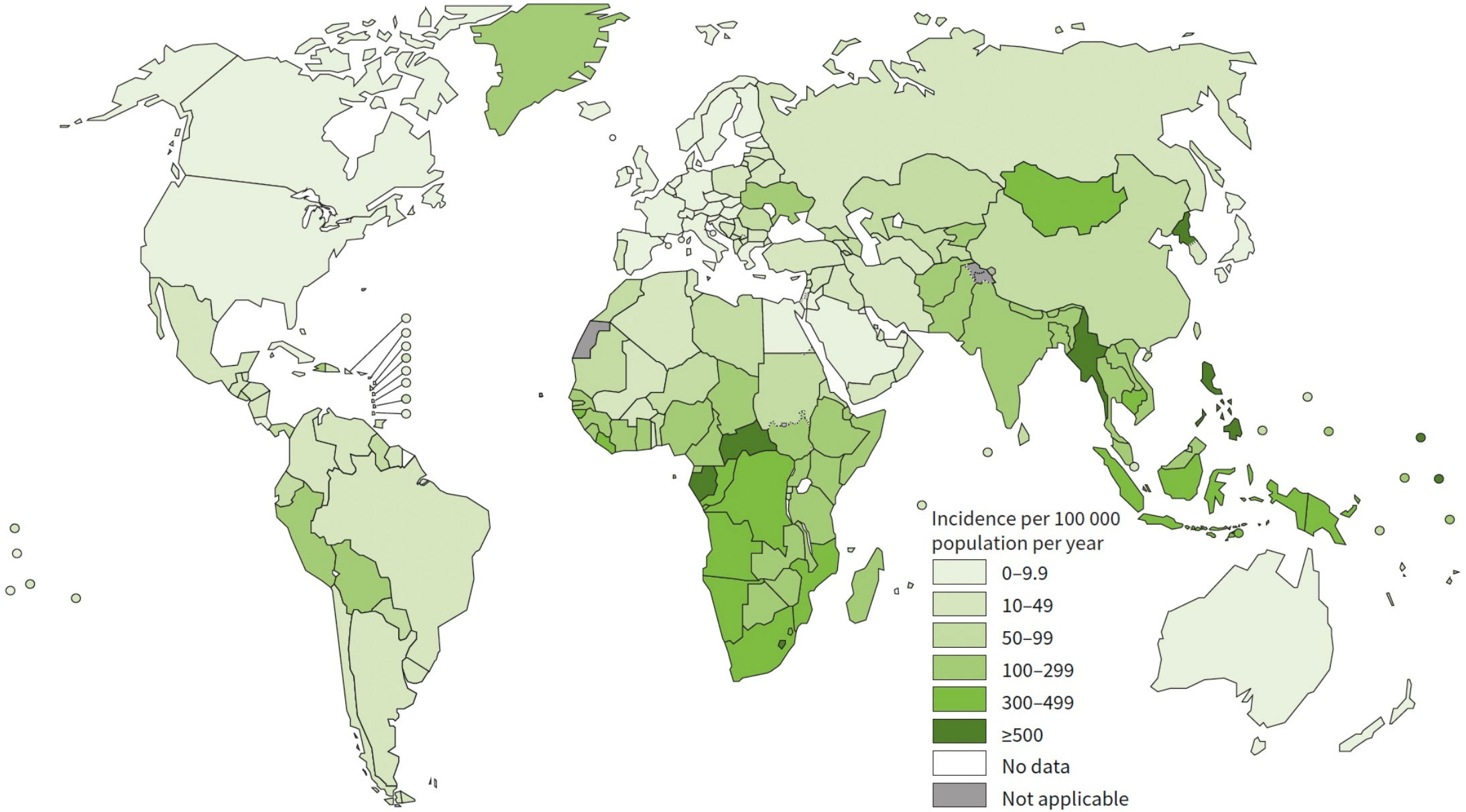
- Birth or travel to a high prevalence country
- Contact with an adult with active pulmonary TB

Lifetime Risk of TB disease after infection

- highest in initial 6 months but remains high for at least 2 years
- Adults 5-10% (50% in first three years)
  - Annual risk is 0.1% without other comorbid conditions
- Adolescents 15%
- Children (1 - 5 yr) 25%
- Children (< 1 yr) 40%

Red Book, 2018

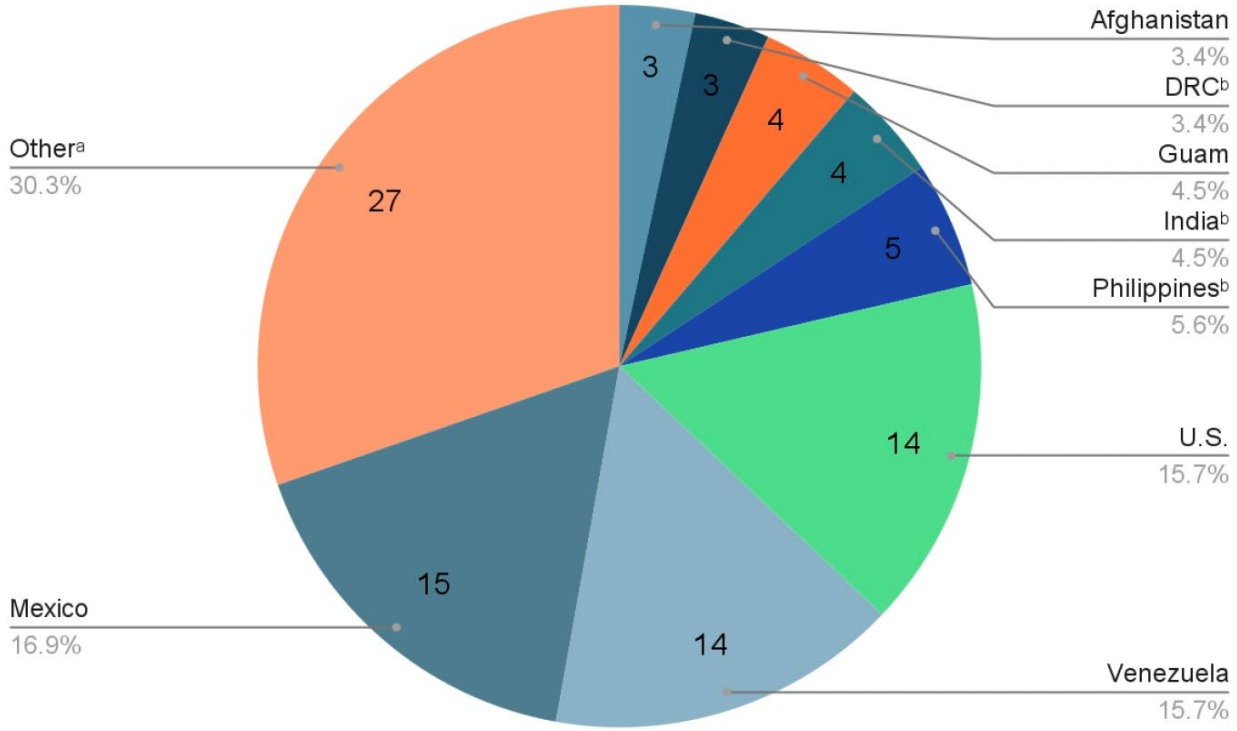
Estimated TB incidence rates, 2023



WHO Global TB Report 2024

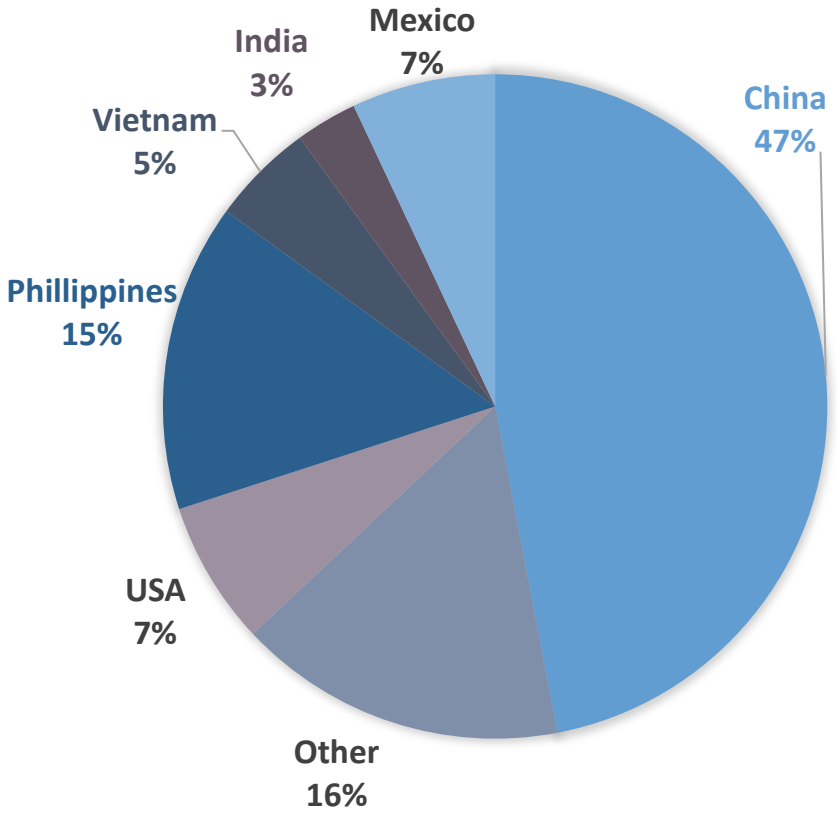
But look at what's happening in your own area……

Figure 6. TB patients by country of birth: Colorado 2023



[a]Other countries: 1- Cambodia, 1- Central African Rep[b]., 2- China[b], 1- Columbia, 1- El Salvador, 2- Ethiopia[b], 1- Guatemala, 2- Honduras, 2- Indonesia[b], 2- Rep of Korea, 1- Mali, 1- Myanmar[b], 2- Nepal, 2- Nicaragua, 1- Romania, 1- Rwanda, 1- Senegal, 1- Somalia, 2- Vietnam[b].

….compared to
2021 San Francisco, CA



South Africa: prevention priority populations: PWHIV, children <5 years

SW Denver: prevention priority populations- contacts, people who have lived in a TB endemic area, diabetes or immunocompromised

- Goals of TB testing:
  - identify people with TB infection and TB disease
  - Prioritize people most at risk for testing (targeted universalism approach that preserves resources and equity)
  - Balance of harm of missing TB against harm of treatment

Priority groups for testing for TB infection

Close contact to infectious (pulmonary) TB

Lived (born or traveled > 1 month) to a country where TB is common

- Anywhere but United States, Canada, Australia, New Zealand, or Western and North Europe

Current or planned immunosuppression

- HIV, TNF-alpha blocker, transplant

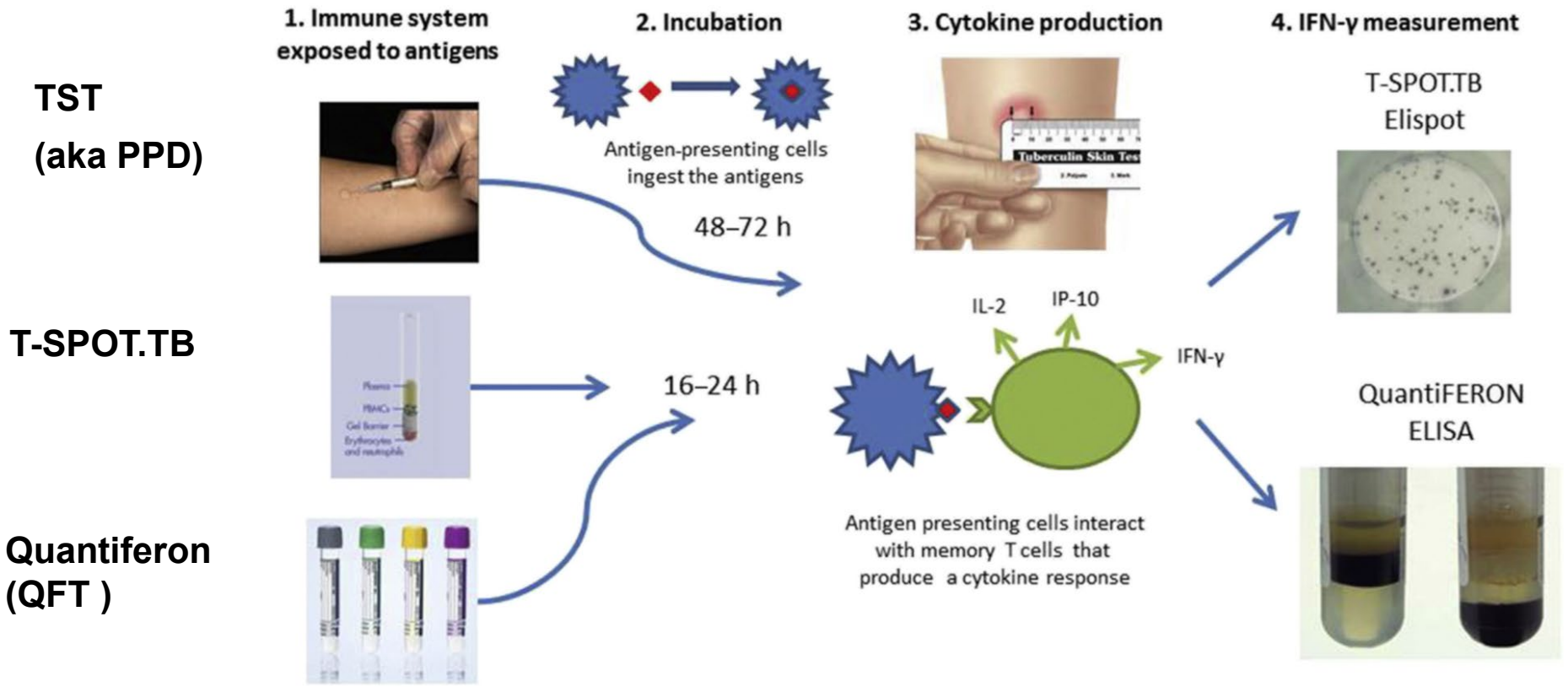
Talking to patients about TB Screening

← **Scary**

← **Still pretty 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”

Tests for TB infection

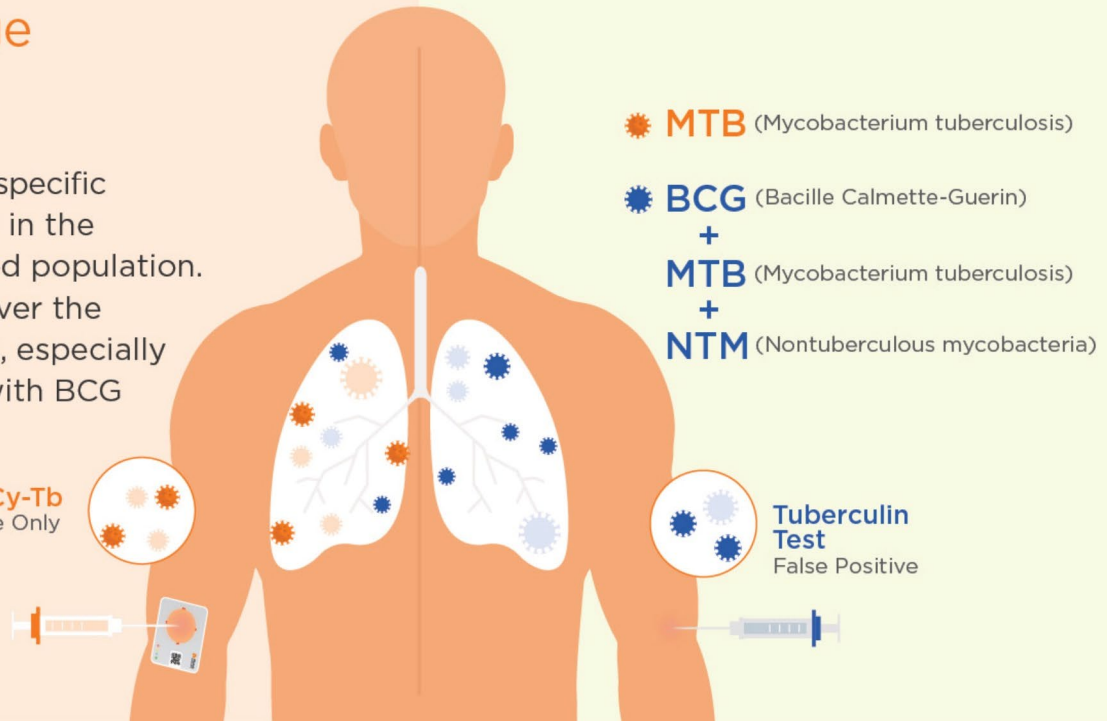


Haas Clin Chest Med 2019; 40(4): 829

There is a new test for TB infection! (but we don't have it in the US)

Cy-Tb Advantage

Cy-Tb selectively detects
• rdESAT-6 and
• rCFP-10 which are MTB specific
Eliminates false positivity in the previously BCG vaccinated population. This is a key advantage over the first-generation TST tests, especially in developing countries with BCG vaccination programs.



Method of Administration

Intradermal injection using mantoux technique

Interpretation

Induration of ≥ 5 mm indicates latent infection

Unaffected by BCG Vaccination Status

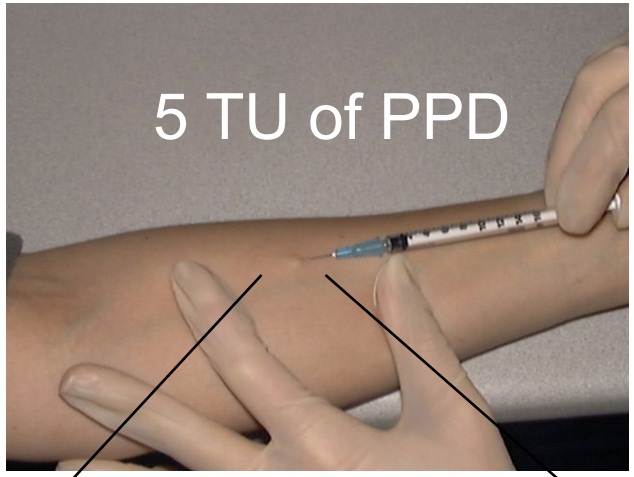
Cy-Tb overcomes the problem of false positive in the previously BCG vaccinated Individuals

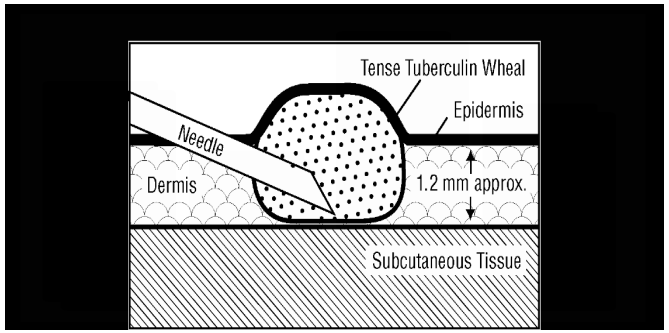
No Sample Handling

Unlike IGRA, no need for sample collection, transportation and testing in a controlled lab environment

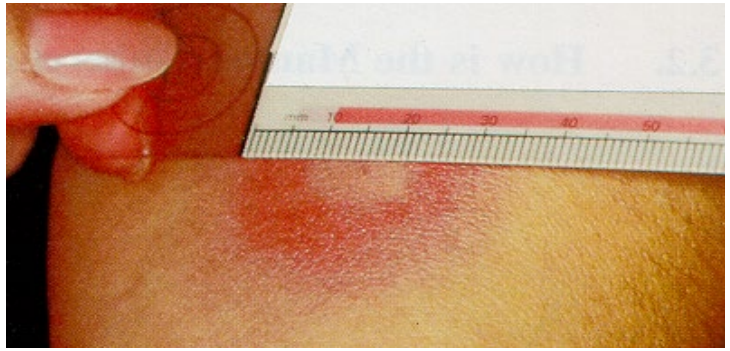
https://mylabglobal.com/cy-tb/#:~:text=Cy%2DTb™,effective%20a%20cross%20population%20groups.

Tuberculin Skin Testing
Mantoux Method





48 to 72 hours



Interpretation depends on person's risk factors

Purified Protein Derivative (PPD)

- Generated by autoclaving in vitro grown *M. tuberculosis* at 100° C for two hours
- Chemical composition:
  - 93% proteins
  - 1% nucleic acid
  - 6% carbohydrate

- Proteomic analysis has shown significant overlap between *M. avium* and *M. tuberculosis* PPD

Braz J Infect Di 2006;10:427

Criteria for a Positive TST Reaction

≥ 5mm	≥ 10mm	≥ 15mm
HIV infection	Recent immigrants	
Close Contacts	Children	No risk
Fibrotic CXR	Residents or employees in congregate settings	
Immunosuppression	Injection drug use	

Sensitivity  Specificity

Stability of Reactions and Inter-reader Variability

1. Biologic variation from test to test in the same patient is very small, approximately 1mm.
    - Chaparas et al. ARRD 1985;132:175.

2. Same reader - Standard deviations of 1.3-1.9 mm
    - Perez-Stable, et al. AJPH 1985;75:1341.
    - Erdtmann, et al. JAMA 1974;228:479.

3. Different readers - Standard deviations of 2.3-2.5 mm
    - Furcolow et al. ARRD 1967;96:1009.

Tuberculin Skin Test

False negative tests

- Quality and stability of reagents
- Poor technique
- Anergy (eg.HIV positive, very young or old)
- Recent or remote TB infection

False positive tests

- Reader error
- Presence of cross-reacting antigens
  - Nontuberculous mycobacteria
  - BCG vaccination

Interferon-gamma Release Assays (IGRAs)

T-SPOT.TB **QuantiFERON-TB Gold Plus**

- Single blood draw
- Incubate blood cells with antigens from the region of difference 1 (RD1)
- Results can be available in 1 day

Species Specificity of ESAT-6 and CFP-10

Tuberculosis complex	Antigens	
	ESAT	CFP
M tuberculosis	**+**	**+**
M africanum	**+**	**+**
M bovis	**+**	**+**
BCG substrain		
gothenburg	-	-
moreau	-	-
tice	-	-
tokyo	-	-
danish	-	-
glaxo	-	-
montreal	-	-
pasteur	-	-

Environmental strains	ESAT	CFP
M abcessus	-	-
M avium	-	-
M branderi	-	-
M celatum	-	-
M chelonae	-	-
M fortuitum	-	-
M gordonii	-	-
M intracellulare	-	-
M kansasii	**+**	**+**
M malmoense	-	-
M marinum	**+**	**+**
M oenavense	-	-
M scrofulaceum	-	-
M smegmatis	-	-
M szulgai	**+**	**+**
M terrae	-	-
M vaccae	-	-
M xenopi	-	-

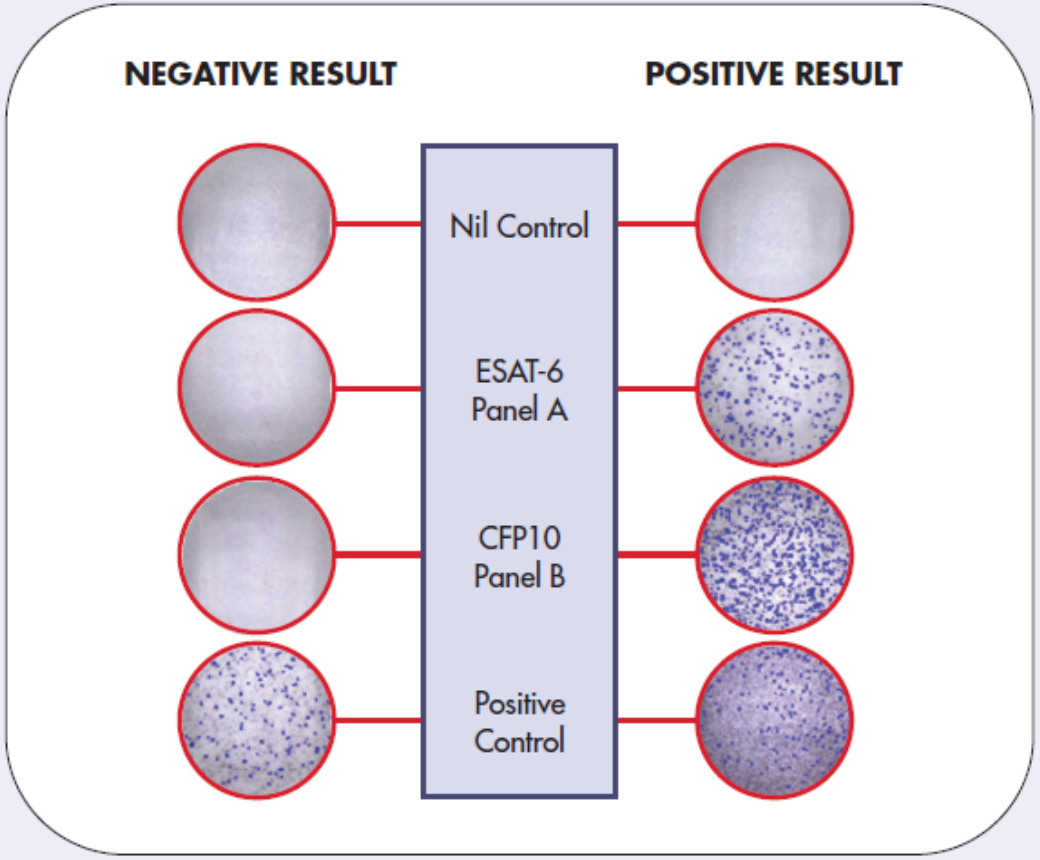
T-SPOT.TB

Interpretation of results

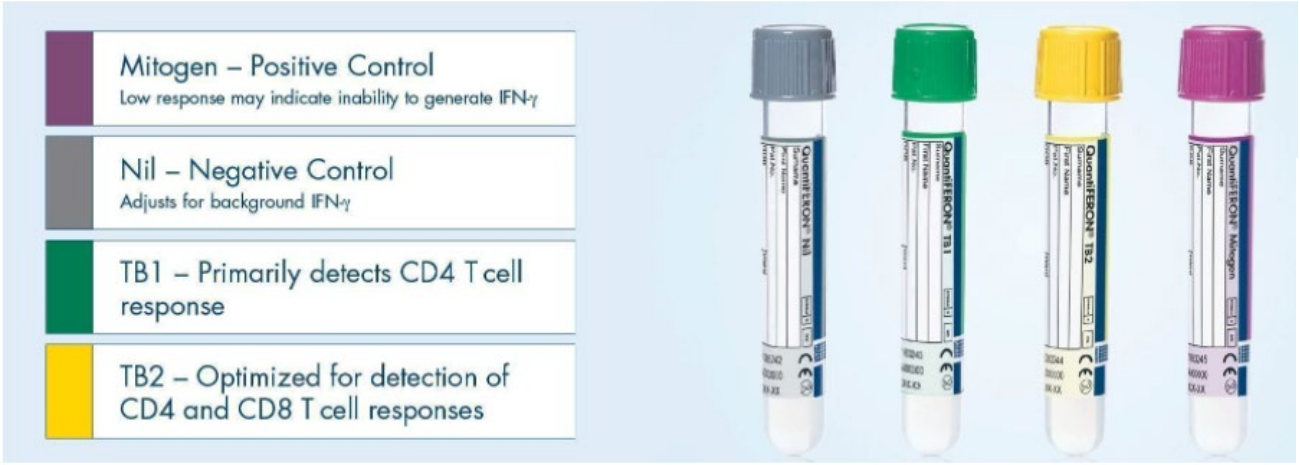
- Interferon-gamma is captured and presented as spots from T cells sensitized to TB infection
- Results are interpreted by subtracting the spot count in the negative (NIL) control from the spot count in Panels A and B
  - Positive ≥ 8 spots
  - Negative ≤ 4 spots
  - Borderline 5, 6 or 7 spots
  - Invalid
- The inclusion of a borderline category is intended to reduce the likelihood of false-positive or false-negative results around the test cut-off

Note: It is recommended that borderline and invalid results be retested with a new specimen

T-SPOT.TB



QuantiFERON-Gold Plus



	Ref Range & Units	3 d ago
Nil		0.040
TB1-Nil	>=-0.35	-0.01
TB2-Nil	>=-0.35	0.00
Mitogen		>10
Result	Negative, Indeterminate	Negative

Comment: M. tuberculosis infection NOT likely.

	Ref Range & Units	3 d ago
Nil		0.190
TB1-Nil	>=-0.35	0.85
TB2-Nil	>=-0.35	0.92
Mitogen		>10
Result	Negative, Indeterminate	Positive !

Comment: M. tuberculosis infection likely

QFT and T-SPOT Results

QFT

- Positive (≥ 0.35 IU/mL)
- Negative (< 0.35 IU/mL)
- Indeterminate
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

T-SPOT

- Positive (≥ 8 spots)
- Borderline (5-7 spots)
- Negative (≤ 4 spots)
- Invalid
  - Low mitogen
  - High nil
- Failed

TST and IGRAs in U.S. Healthcare Workers

	TST n(%)	QFT n(%)	T-SPOT n(%)
Baseline (+)	126 (5.2)	118 (4.9)	144 (6.0)
Conversion	**21 (0.9)**	**138 (6.1)**	**177 (8.3)**
Reversion*	11/12 (92)	81/106 (76)	91/118 (77)

* Not all converters had a repeat test

- 11 TST-positive HCWs treated for LTBI
- No cases of active TB

Dorman AJRCCM 2014;189(1): 77

Clinical Scenario #2

- 14-year-old boy was identified as a classroom contact to a patient with smear+/cavitary pulmonary TB. Had BCG as a child, lived previously in Nepal
- Approximately 300 contacts identified in this investigation

Programmatic decisions

- Offer TST to all students?
  - Pro: fast, inexpensive, easy to offer at the middle school
  - Con: false positives among BCG vaccinated students
    - ? Confirm these with QFT?
- Offer IGRAs to all students?
  - Lab capacity is 80 per day; difficulties with off-site phlebotomy and specimen transportation, slightly higher risk of adverse effects such as syncope
- Offer a mixture of TST and IGRAs
  - All the problems with #2 but also stigmatizing those who have had BCG as they will take longer to move through the queue, potentially compromising confidentiality.

Clinical Scenario #2

- 14-year-old boy was identified as a classroom contact to a patient with smear+/cavitary pulmonary TB. Had BCG as a child, lived previously in Nepal.
  - Initial TST negative
  - Follow up 8-week TST was 7 mm

- Mom isn't sure about treatment for LTBI. She requests another test to "confirm" the TST results

Interpretation and Management

- 1- interpret as positive and as a conversion. As an adolescent contact, higher risk of progression to active TB.
- 2- interpret as a positive result from “boosting” from remote TB infection and offer LTBI treatment, counsel against a QFT
- 3- interpret as a false positive result from “boosting” of BCG and agree to do a QFT and if negative, discharge from public health follow-up
- 4- same as #1 but offer QFT because you just know it will be positive and that will help mom get on board with treatment

Clinical Scenario #2

- 14-year-old boy was identified as a classroom contact to a patient with smear+/cavitary pulmonary TB. Had BCG as a child, lived previously in Nepal.
  - Initial TST negative
  - Follow up 8-week TST was 7 mm
  - QFT was done and this was negative

	Results
QFT - Nil	0.05
QFT - MITOGEN	>10
QFT - RESULT	Negative
QFT - TB1 Ag	0.06
QFT - TB2 Ag	0.06

- Mom believes the QFT and declines LTBI therapy for her son

IGRA vs. TST

Advantages over TST

- Not affected by BCG vaccination
- Not affected by most non-tuberculous mycobacteria
- Interpretation is more objective
- No return visit needed for interpretation of test
- Patients and providers may lack confidence in TST results

Disadvantages over TST

- Blood draw
- Cost
- Limitations on lab capacity for large contact investigations

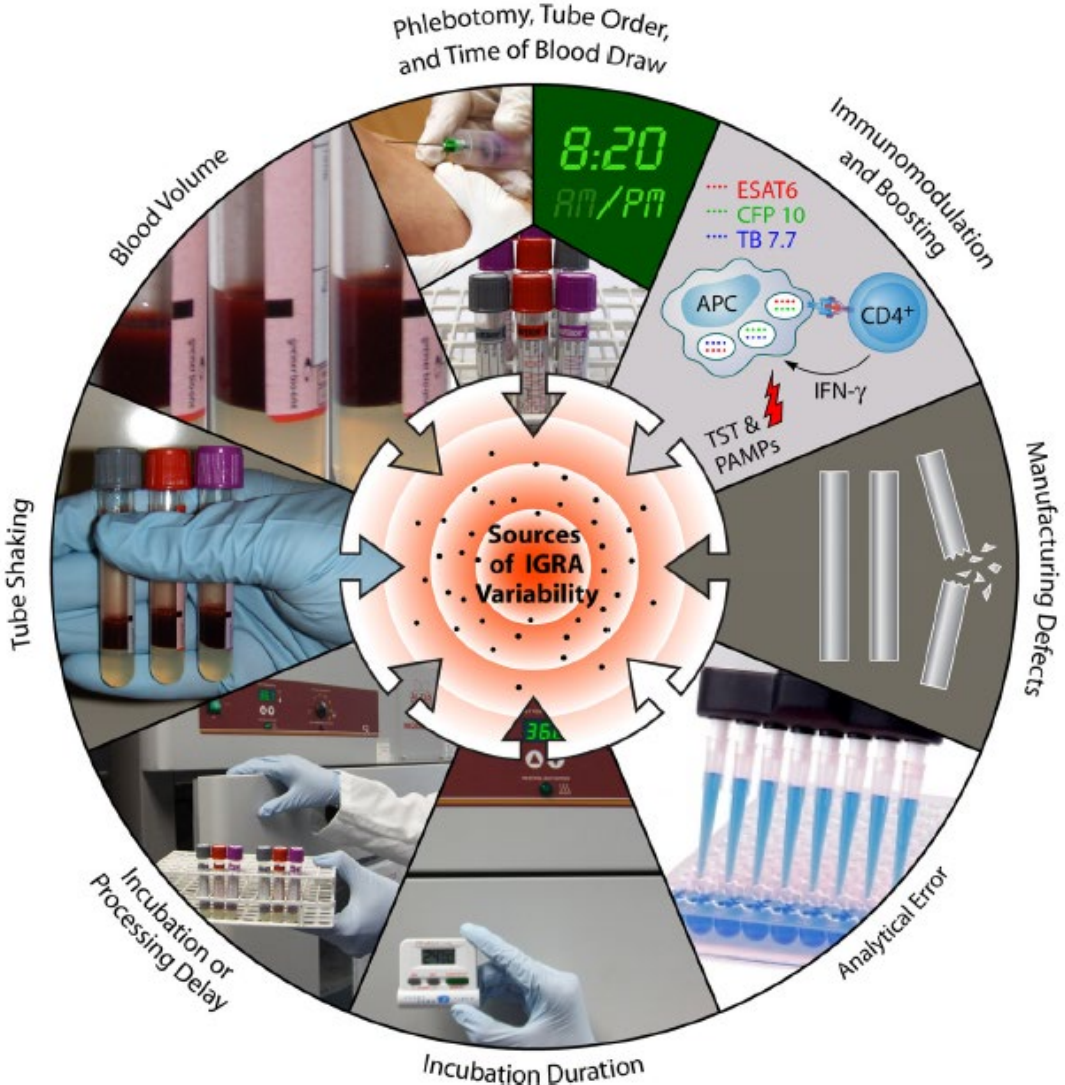
CDC, MMWR, 2010 | Pai, Clin Micro Rev, 2014

TST vs IGRA – shared challenges

- Low ability to predict short-term progression to active TB
  - Abubaker, Lancet ID 2018 18: 1077
  - Rangaka, Lancet ID 2012 12: 45
  - Diel, Chest July 2012 142: 63
- Reduced sensitivity in immunosuppressed
- Inability to differentiate a resolved infection from a new or ongoing infection

Sources of variability and indeterminate results

- IFN-γ may vary by +0.24 IU/ml when the result is between 0.25-0.80 (Metcalfe *AJRCCM* 2013)
- S. Africa study of serial QFTs – "converters" who had levels < 0.7 IU/ml had same TB risk as those with levels <0.2 IU/ml(Nemes *AJRCCM* 2017)



Pai, Clin Micro Rev, 2014

Indeterminate/borderline results

- Cannot determine whether someone has TB infection
  - Low lymphocyte count
  - Low lymphocyte activation potential
  - Specimen collection errors

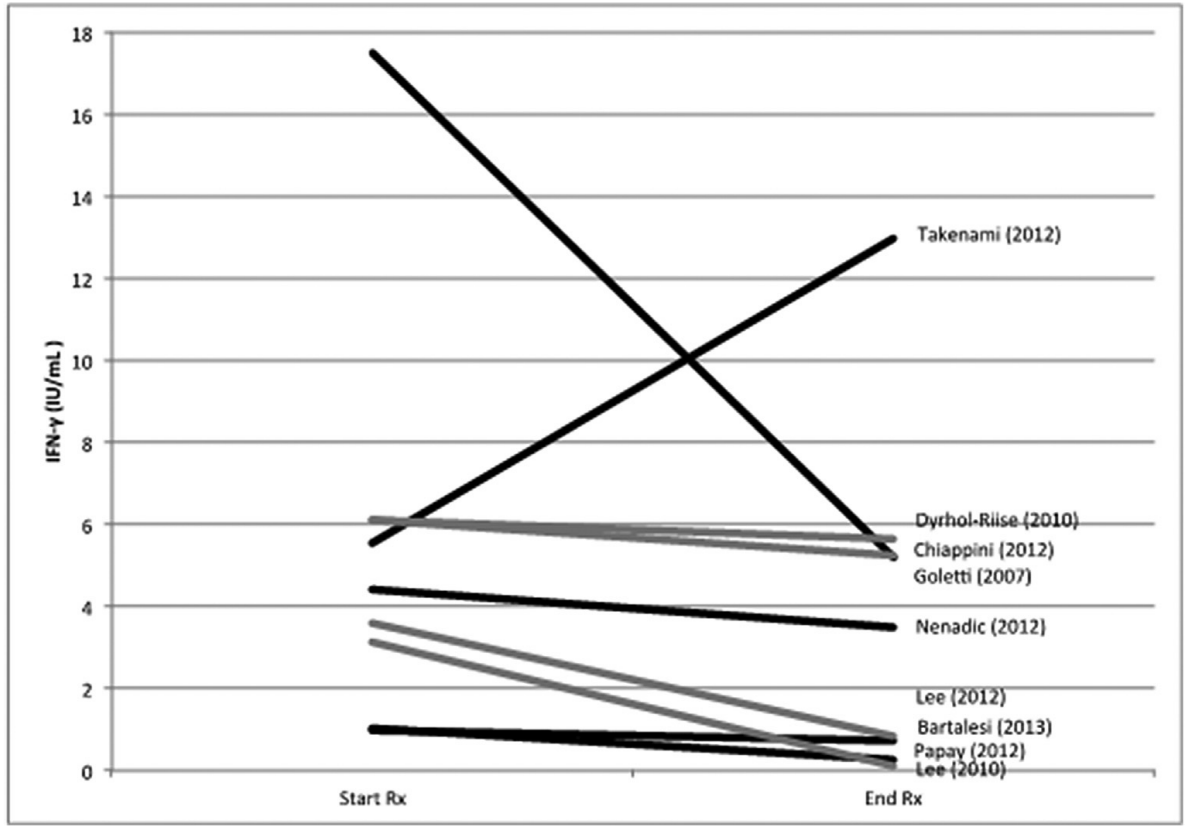
- Repeat test with valid result (pos/neg) in 68% (Banach IJTLD 2011)
  - Repeating the test is often the next step

Why do we repeat tests for TB infection?

- You don't like the first test result so you repeat it to get the one you like 
- First result was indeterminate
- Positive result in low risk individual (healthcare worker who is required to undergo testing)
- High risk individual who has a negative result
  - Repeating in person with HIV whose CD4 has risen above 200
  - 8 week testing in the context of a contact investigation
- Monitor treatment response 

IGRAs **cannot** be used to monitor treatment response

- 15 studies that evaluated LTBI responses
- No consistent pattern using reversions or quantitative IFN-gamma levels



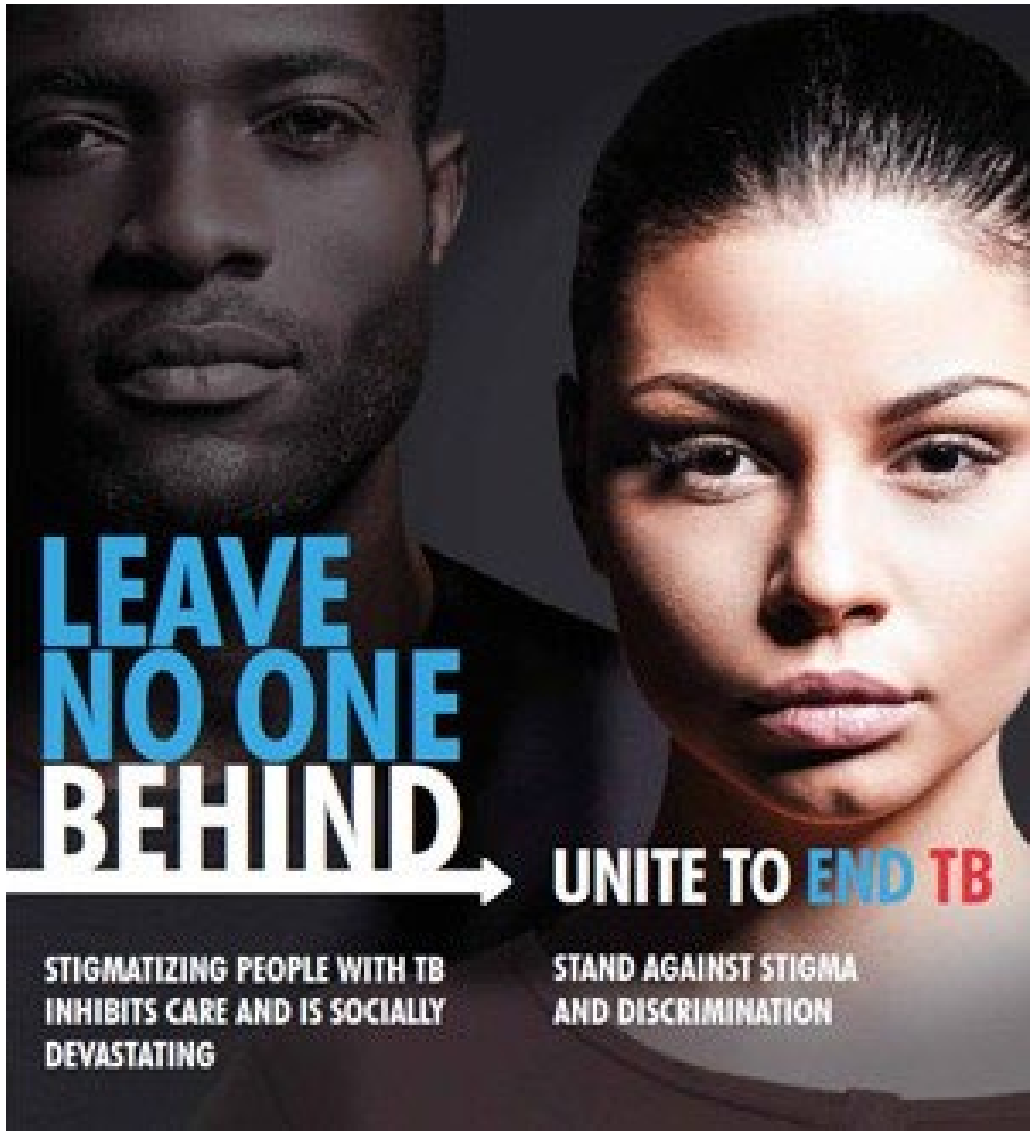
Slide courtesy of Dr. David Horne

Clifford, Tuberculosis 2015

Summary

- **Test people at risk for infection**
  - 1^{o} people born or lived in a TB endemic area
  - Prioritize those with risk for exposure AND progression **(**HIV, DM, ESRD etc.) on a programmatic level or clinic level
- **Choice of test and interpretation of results must be made based on the clinical situation, risk of the individual(s) being tested, and cost/logistics of testing**
- **Prefer IGRAs if available and feasible**
  - Better in BCG-vaccinated people
  - Results are easily retrieved
- **Repeat all (+) IGRAs in lower risk people**
  - healthcare workers, those at low risk for progression and no risk for exposure
- **Resist the temptation to continue to repeat tests in the context of discordant results**
  - Use your pre-test probability to interpret the results

Questions?


LEAVE NO ONE BEHIND
UNITE TO END TB
STIGMATIZING PEOPLE WITH TB INHIBITS CARE AND IS SOCIALLY DEVASTATING
STAND AGAINST STIGMA AND DISCRIMINATION