# Tuberculosis Screening and Testing

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# Who Should be Tested for TB Infection?

## Targeted Testing for TB Infection

The simplified version:

- Persons who are at increased risk for *M. tuberculosis* infection
- Persons at increased risk for progression to active disease if infected with *M. tuberculosis* (even if not at increased exposure risk)

And those who tend to be tested in addition:

- Persons tested for administrative reasons (e.g., mandatory employment testing)
- Persons with symptoms of active TB disease (fever, night sweats, cough, and weight loss)

# Who Should be Tested for TB Infection?

## Targeted Testing for TB Infection

- Contacts of persons with active TB
- HIV positive individuals
- Immigants from high prevalence countries
- Injection Drug Users
- Residents and Employees of high risk congregate settings:
  - Correctional facilities and Homeless Shelters
  - Hospitals, Clinics, Nursing Homes, Substance Abuse Facilities
- Newest Category:
  - Patients considering treatment with TNF-α Antagonists
- Children exposed to high-risk adults or environments

# Contacts of Individuals with Active TB

- Among close contacts to a TB Case:
  - 30% have TB Infection
  - 1-3% have active TB disease
- Without TB Infection treatment:
  - 10% with TB Infection with develop Active TB
    - Approximately 5% of contacts with newly acquired TB Infection progress to TB disease within 2 years
    - The other 5% activate > 2 years after acquisition
- Examination of contacts is one of the most effective strategies for TB Infection diagnosis and TB control!

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# Percent Risk of Disease by Age

| Age at Infection | Risk of Active TB |
|---|---|
| Birth – 1 year* | 43% |
| 1 – 5 years* | 24% |
| 6 – 10 years* | 2% |
| 11 – 15 years* | 16% |
| Healthy Adults | 5-10% lifetime risk |
| HIV Infected Adults+ | 30-50% lifetime |

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

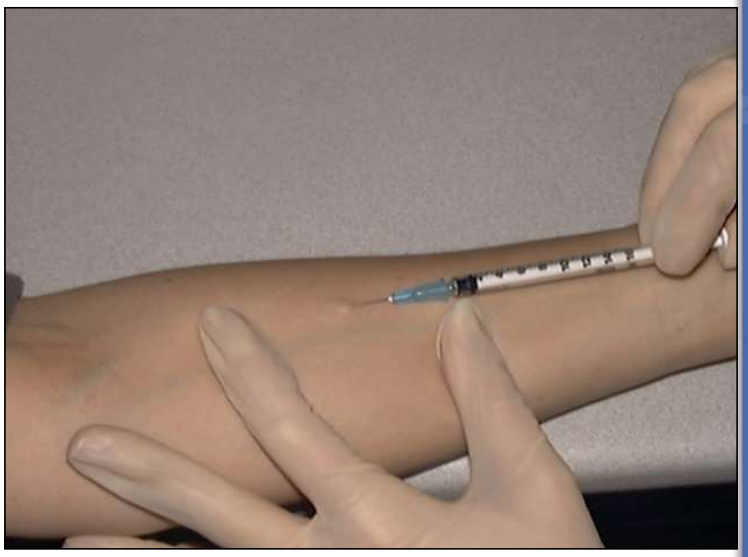
+WHO, 2004

# TB Infection Diagnostics

- TB Skin Test (TST)
- Interferon Gamma Release Assays (IGRA)

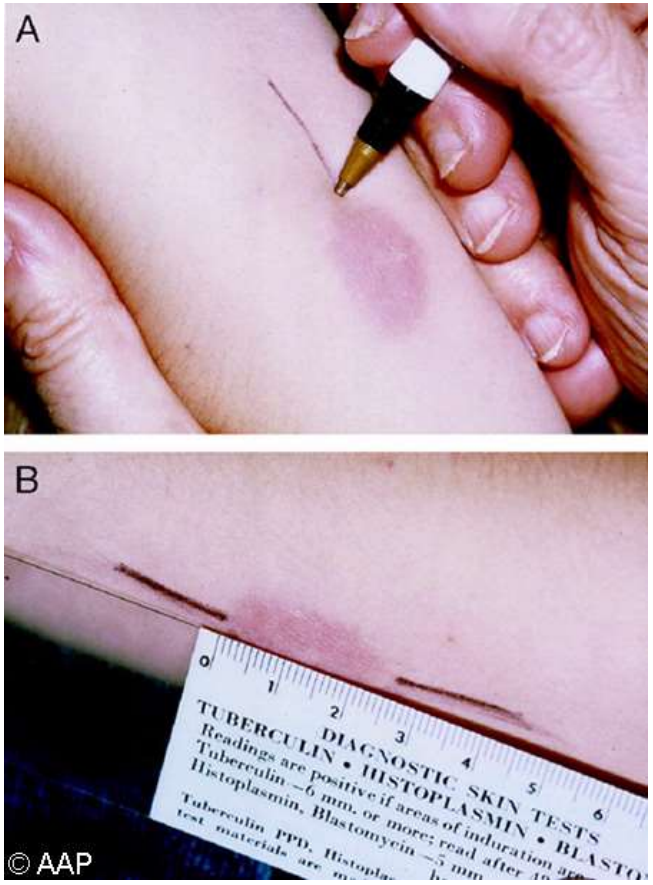
# The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- **Induration** in millimeters read 48-72 hours after injection



# Reading the TB Skin Test

Measure **induration**,
not erythema!!!



# TB Skin Test (TST)

- Pros:
  - Inexpensive
  - Simple to perform
    (if you know what you are doing….
    and know how to herd cats…… )

- Cons:
  - Must return in 48-72 hrs
  - Interpretation is somewhat subjective
  - False Negatives:
    - Elderly
    - Immunosuppressed
  - False Positives:
    - Low risk populations
    - Non-tuberculous mycobacteria
    - BCG vaccination

# Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

# Classifying the Tuberculin Reaction

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

# Classifying the Tuberculin Reaction

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups

# Let’s talk about IGRAs

# Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)
- Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)
- *M. tuberculosis*-specific antigens
  - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
  - ESAT-6, CFP-10, TB 7.7 (actually simulated using overlapping peptides)

# Antigens for Gamma-Release Assays

| Tuberculosis complex | Antigens ESAT | CFP | Environmental strains | Antigens ESAT | CFP |
|---|---|---|---|---|---|
| M tuberculosis | + | + | M abcessus | - | - |
| M africanum | + | + | M avium | - | - |
| M bovis | + | + | M branderi | - | - |
| BCG substrain | | | M celatum | - | - |
| gothenburg | - | - | M chelonae | - | - |
| moreau | - | - | M fortuitum | - | - |
| tice | - | - | M gordonii | - | - |
| tokyo | - | - | M intracellulare | - | - |
| danish | - | - | M kansasii | + | + |
| glaxo | - | - | M malmoense | - | - |
| montreal | - | - | M marinum | + | + |
| pasteur | - | - | M oenavense | - | - |
| | | | M scrofulaceum | - | - |
| | | | M smegmatis | - | - |
| | | | M szulgai | + | + |
| | | | M terrae | - | - |
| | | | M xenopi | - | - |

# FDA Approved IGRAs

- QuantiFERON®-TB Gold Plus (QFT-Plus)
  - FDA approved 2017
- T-Spot®.*TB* (T-Spot)
  - FDA approved July 2008

# QuantiFERON®-TB Gold Plus

**Mitogen – Positive Control**
Low response may indicate inability to generate IFN-γ

**Nil – Negative Control**
Adjusts for background IFN-γ

**TB1 – Primarily detects CD4 T cell response**

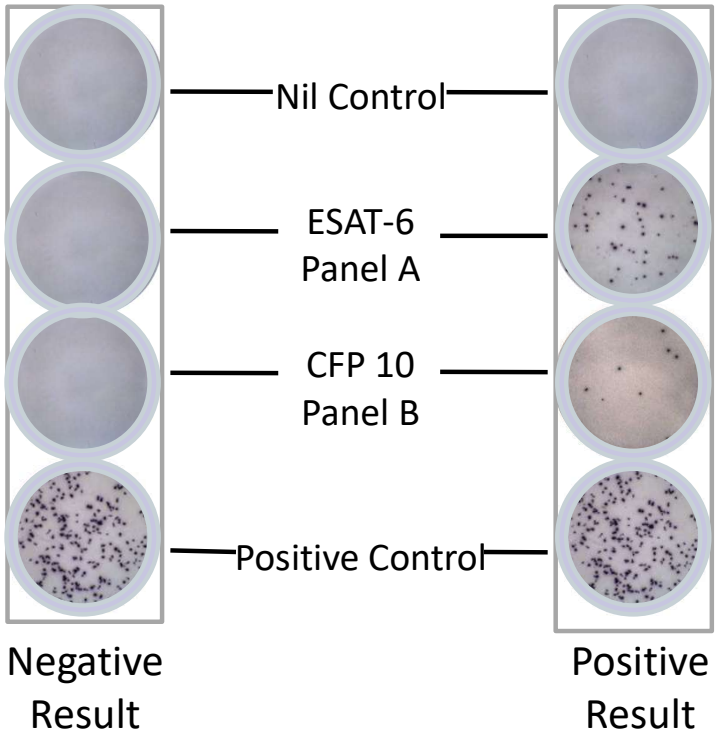
**TB2 – Optimized for detection of CD4 and CD8 T cell responses**


- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value

# Interpretation Criteria for the QFT-GIT Test

| Nil (IU/mL) | TB Antigen minus Nil (IU/mL) | QFT-GIT (IU/mL) | Mitogen | Interpretation |
|---|---|---|---|---|
| ≤ 8.0 | ≤ 0.35 or < 25% of Nil value | Negative | ≥ 5.0 | *M. tuberculosis* infection unlikely |
| ≤ 8.0 | ≥ 0.35 and ≥ 25% of Nil value | Positive | ANY | *M. tuberculosis* infection likely |
| ≥ 8.0 | ANY | Indeterminate | ANY | Indeterminate |
| ≤ 8.0 | ≤ 0.35 and or < 25% of Nil value | Indeterminate | < 5.0 | Indeterminate |

# Interpretation of Results



# Interpretation Criteria for the T-Spot.TB

| Result | Nil* | TB Response# # | Mitogen++ | Interpretation+ |
|---|---|---|---|---|
| Positive | ≤ 10 spots | ≥ 8 spots | Any | *M.tuberculosis* infection likely |
| Borderline | ≤ 10 spots | 5, 6, or 7 spots | Any | Uncertain likelihood of *M. tuberculosis* infection |
| Negative | ≤ 10spots | ≤ 4 spots | | M Tb infection unlikely |
| Indeterminate | > 10<br>≤ 10 | Any<br>< 5 spots | Any<br>< 20 spots | Uncertain likelihood of *M. tuberculosis* infection |

# Indeterminate and Borderline Results

- Indeterminate
  - Negative control result is too high
    - High background production of IFN-γ
  - Positive control result is too low
    - Immunocompromised patients may not respond to mitogen
- Borderline (T-Spot only)
  - Falls within borderline zone close to negative/positive cut point

# (New) ATS/CDC/IDSA Guidelines

*Clinical Infectious Diseases*

IDSA GUIDELINE

# Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

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Lewinsohn et al. CID. 2016

| Groups with Increased Likelihood of Infection with Mtb | Benefit of Therapy | LTBI Testing Strategy | |
|---|---|---|---|
| Household contact or recent exposure of an active case | Yes | Likely to be Infected<br>Low to Intermediate Risk of Progression<br>(TST ≥ 10mM) | Likely to be Infected<br>High Risk of Progression<br>(TST ≥ 5mM) |
| Mycobacteriology laboratory personnel | Not demonstrated | | |
| Immigrants from high burden countries (>20 / 100,000) | Not demonstrated | | |
| Residents and employees of high risk congregate settings | Yes | | |
| None | Not demonstrated | Unlikely to be Infected<br>(TST > 15mM) | |

Risk of Infection

Risk of Developing Tuberculosis if Infected

| Low | Intermediate (RR 1.3 -3) | High (RR 3-10) |
|---|---|---|
| No risk factors | Clinical predisposition<br>Diabetes<br>Chronic renal failure<br>Intravenous drug use | Children age less than 5<br>HIV infection<br>Immunosuppressive therapy<br>Abnormal CXR consistent with prior TB<br>Silicosis |

| Benefit of Therapy | |
|---|---|
| Not demonstrated | Yes |

In developing a diagnostic approach for the evaluation of those with suspected LTBI, we recommend the clinician weigh the likelihood of infection, the likelihood of progression to TB if infected, and the benefit of therapy (Horsburgh, C.R., Jr., and E.J. Rubin. 2011. Clinical practice. Latent tuberculosis infection in the United States. The New England journal of medicine 364:1441-1448). Recommendations were formulated for each of the three groups illustrated above. These groups are concordant with current recommendations for the interpretation of the TST ( 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 49:1-51).

# New in the Diagnosis Guidelines

- Decisions to test or treat are based on likelihood of infection and likelihood of progression
- IGRAs are recommended for testing for TB infection in individuals ≥ 5 years old with low or moderate risk if infection or progression
  - Note: IGRAs are a 'better' choice
    - When TST administration is questionable
    - In BCG vaccinated populations (increased specificity)
    - In populations with a poor rate of return
- Testing in low-risk populations is still not recommended. When it is necessary, such as required HCW screenings, use an IGRA
- In populations at high risk for infection or progression, either a TST or IGRA is appropriate

# Pearls for TST vs. IGRAs

- Discordance between the TST and IGRAs has been measured up to 20% in patients known to be infected with Mtb. Don't order both tests, pick the right test to start with!
- The tests are not perfect. They provide one piece of your whole picture when assessing a patient, not the 'answer'.
- No test (TST or IGRA) overrides clinical, epidemiologic or historical data

37 y.o. male from Eritrea. Entered U.S. 10/15/2016
05/13/2019 Tspot (+)

32-year-old wife/mother

No prior TB test

05/02/2019
TSpot (+)

17 mo. old Male

No prior TB test (U.S. Born)

05/04/19
TST (+) 14 mm

3 –year- old Male

06/11/2018
Tspot (-)

05/04/2019
TST (+)15 mm

4 –year- old Female

06/11/2018
Tspot (-)

05/04/2019
TST (+) 18mm

13 –year- old Female

05/08/2018
TSpot (-)

05/02/2019
TSpot (+)

15 –year- old Male

05/02/2018
Tspot (+)

No current testing