Interpretation of TST & IGRA results

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Objectives

1. Be able to describe the strategies of
   a. Targeted testing for LTBI
   b. TB screening - active case finding
   c. Specific situations when LTBI testing is used for TB screening

2. Be able to describe the advantages and disadvantages of TST and IGRAs

3. Be able to apply epidemiologic data for interpreting test results in an patient
List targeted testing scenarios

- Evaluation of contacts to infectious TB
- Pre-departure testing of age 2-14 yr visa applicants
- Post-arrival evaluation of refugees or other immigrants from TB endemic countries
- Civil Surgeon exams for visa status change
- Evaluation of selected international students
- Baseline/repeat testing of health care workers
- Testing in congregate settings – shelters, corrections
- Testing patients with medical risk factors
- Others?

For which of the above is TB case-finding important?
Targeted testing scenarios: TB case-finding

- Evaluation of contacts to infectious TB
- Pre-departure testing of age 2-14 yr visa applicants*
- Post-arrival evaluation of refugees or other immigrants from TB endemic countries*
- Civil Surgeon exams for visa status change**
- Evaluation of selected international students**
- Baseline/repeat testing of health care workers*
- Testing in congregate settings – shelters, corrections**
- Testing patients with medical risk factors*
- Others?

*Minor focus or lower likelihood of TB
**Major focus and/or higher likelihood of TB

Targeted testing: A key component of active TB case finding in USA

At-risk person
  └─ Tuberculin test/IGRA + symptom review
      └─ Negative
          └─ LTBI treatment not indicated
          └─ Positive
              └─ Chest x-ray
                  └─ Normal
                      └─ Evaluate for active TB
                      └─ Abnormal
                          └─ Concerning symptoms?
                              └─ Potential candidate for LTBI treatment

TST and IGRA 3
Before Initiating Treatment for LTBI

- Rule out active TB
  - CXR on everyone
  - sputum collection if the CXR is abnormal or the person is symptomatic
- Determine prior history of treatment for LTBI or TB disease
- Assess risks of toxicity
- Determine current and previous drug therapy

If you collect sputum cultures, wait for the results before beginning LTBI therapy.

Example: Targeted testing of Asian-born Student in Her 20’s

PPD+ at College Clinic
- Erythromycin for mild pneumonia 6 mo. ago in Asia
- Asymptomatic now
- Chest X-ray: nodular infiltrate
- Sputum AFB smears negative, culture +

TST and IGRA
40 y.o. homeless woman with TST conversion but no symptoms

40 y.o. asymptomatic, TST+, Mexican applicant for permanent US residency
Tuberculosis in Nursing: Prevention, Treatment, and Infection Control
June 27-28, 2018
Curry International Tuberculosis Center

40 y.o. treated for drug-susceptible, AFB-smear+ cavitary TB

Primary Care Patient: Medical history

• 1997 first seen in primary care as 62 y.o. Mexican-born woman (in US 10 yrs) with prior CVA, hypertension & lung fibrosis
• Followed at a primary care, Pulmonary, Endocrine & Rheum. Clinics (RA) through 2010 (never by PH)

March 2006, earliest image
Further progression

Admit 12/10 wt loss 35 lb, 1 mo. cough: TST (-)*, AFB sm (-)  
Discharged to home hospice: 10 da. before death

*First recorded TST during 13 years of primary care and lung fibrosis.

Final follow-up

- AFB growth in sputum collected 17 days earlier during 8-day admission for progressive pulmonary fibrosis
- Patient in home hospice, expired that morning
- *M. tuberculosis*, susceptible to 1st-line drugs, smear-neg. sputum & tracheal aspirate
- CI: 4 of 8 adults with LTBI, 6 children negative
TST & Interferon Gamma Release Assays: Role in diagnosis of active TB

- NEVER allow a negative TST/IGRA exclude further evaluation for TB given compatible signs & symptoms – false (-) 10-25%

- but

- During targeted testing with TST or IGRA, active TB will be detected in < 0.1% up to 1-2.3% depending upon risk
  - Most will be asymptomatic
  - A minority will be AFB sputum smear +

TST for LTBI Diagnosis
Criteria for a Positive Reaction

<table>
<thead>
<tr>
<th>≥5 mm</th>
<th>≥10 mm</th>
<th>≥15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Recent immigrants</td>
<td>No risk</td>
</tr>
<tr>
<td>Contact to active TB case</td>
<td>Injection drug users</td>
<td>Children</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>High-risk medical conditions</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Residents and employees of jails/nursing homes, hospitals</td>
<td></td>
</tr>
</tbody>
</table>

Note: Skin test conversion is an increase of ≥10 mm within a 2-year period
Limitations of the TST

1. Subjective interpretation
2. Difficult to maintain proficiency
3. Requires 2 visits
4. Affected by prior BCG vaccination
5. Limited use by primary care providers
6. Despite > 100 years of use, there is no standard way to record and retrieve results
7. Shortages of PPD

IGRAs – Basic similarities

• Single blood draw
• Incubate blood cells with antigens from the region of difference 1 (RD1)
  • not contained in BCG but present in *M. bovis*
  • Antigens present in *M. marinum, kansasii, szulgai, and flavescens*
• Results available in 1 day
Interferon-gamma Release Assays (IGRAs)

1. Blood tests for detecting TB infection
2. Requires 1 visit
3. Results retrievable electronically
4. 2 FDA approved tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Components</th>
<th>Thresholds</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Spot</td>
<td>Plate ELISpot count:</td>
<td>Either Ag minus Nil:</td>
<td>Value of repeating borderline unclear</td>
</tr>
<tr>
<td></td>
<td>1. ESAT-6</td>
<td>Positive &gt; 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. CFP-10</td>
<td>Borderline 5-7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT-GIT</td>
<td>Tubes for ELISA:</td>
<td>Ag minus Nil:</td>
<td>Some experts call for a borderline zone up to 0.7</td>
</tr>
<tr>
<td></td>
<td>1. CFP-10+ESAT-6+TB7</td>
<td>Positive &gt; 0.35 IU/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Mitogen &amp; 3. Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT-Plus</td>
<td>Tubes:</td>
<td>TB 1 &amp;/or TB2 minus Nil:</td>
<td>Not yet clear if TB2 (&quot;CD8 response&quot;) is helpful.* Some suggest requiring both positive in low-risk patients</td>
</tr>
<tr>
<td></td>
<td>1. TB1 - ESAT-6+CFS-10</td>
<td>Positive &gt; 0.35 IU/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. TB2 – ESAT-6+CFS-10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity for Active TB

1. Meta-analysis
   – Data presented for the commercially available assays (QFT-GIT and T-SPOT)

2. Results:

<table>
<thead>
<tr>
<th></th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>70 (67-72)</td>
</tr>
<tr>
<td>QFT-GIT</td>
<td>84 (81-87)</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>90 (87-92)</td>
</tr>
</tbody>
</table>

Diel, Chest April 2010 137(4): 952

High Risk Populations – BCG-vaccinated
Better specificity of IGRAs

• Numerous studies and meta-analyses of the performance of QFT-GIT and T-SPOT

• (+) TSTs associated with prior BCG vaccination regardless of TB exposure

• No association with BCG and (+) IGRA

Diel Eur Resp J 2011; 37 (1): 88
Test characteristics

- **Sensitivity**: Positives/True Positives
- **Specificity**: Negatives/True Negatives (1-minus False-positive proportion)

- Positive predictive value (PPV)*: True positives/Test positives; “do you want to treat?”
- Negative predictive value (NPV)*: True negatives/Test negatives; “do you not treat?”

*Both PPV and NPV are influenced by prevalence of likely infection, not risk of progression.

Example: California TB Risk Assessment

TB risk factors
- **Exposure**:
  - Residence in countries with TB burden
- **Contact with TB**
- **Medical risk for progression**
Key questions for interpretation

• Why was the LTBI test done?
  1. Administrative: baseline health care, students
  2. Exposure risk: contact, residence in TB risk communities, countries, some congregate settings
  3. Medical progression risk
  4. Medical evaluation for active TB

• Who was tested?
  – For #’s 1 and 3 only, expect low PPV unless also #2
  – For #4, expect lower sensitivity & lower NPV


<table>
<thead>
<tr>
<th>Gender</th>
<th>Born in US</th>
<th>Foreign-born</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>1.8 M</td>
<td>0.4 M</td>
</tr>
<tr>
<td>Rate per 100K</td>
<td>2.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>7.0 M</td>
<td>1.1 M</td>
</tr>
<tr>
<td>Rate per 100K</td>
<td>1.6</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Overall HCW rate was 4.2 while national rates were 4.4 to 5.1

“Administrative” testing

- HCW now account for 3-4% of reported TB cases: 465/yr '95-'07, 366 in 2012
  - Occupational TB risk not apparent in TB rates
  - Infection rates extremely low without exposure
  - Majority of TB today likely due to exposure & infection prior to US-arrival among foreign-born HCW
  - Some cases due to travel, risk probably fairly low

- TB cases among foreign-born HCW
  - At least 7% likely imported – points to importance of screening new arrivals
  - Majority of cases, deaths (>10/year) & risk for transmission from HCW potentially preventable by targeted testing and treatment of LTBI

TB Epidemiologic Studies Consortium:
Performance of TST & Two IGRA in US HCW

- Longitudinal study baseline, 6, 12, 18 months
  - HCWs undergoing routine LTBI testing
  - TST- positive HCW recruited to participate
- 4 sites: Denver, Houston, Baltimore, NYC
- Study population 2418 (excl. 77 prior LTBI Tx)
- US-born 83%, FB 17% (n=428)
- Prior BCG history 9% (n=224)
- Prior TST in 96%, only 97 not previously tested
  - Positive TST in155
  - Negative in 2178 - usual population for annual testing
- Travel > 1 mo. outside US during 18 mo: only 52

S Dorman, Amer J Respir Crit Care Med 2014
### Baseline Positive Results (n) by Prior TST

<table>
<thead>
<tr>
<th>Test</th>
<th>Prior Pos. N=155</th>
<th>Prior Neg. N=2166</th>
<th>None N=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>55% (85)</td>
<td>1.3% (28)</td>
<td>12% (12)</td>
</tr>
<tr>
<td>QFT</td>
<td>21% (33)</td>
<td>3.5% (76)</td>
<td>9.3% (9)</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>20% (31)</td>
<td>4.9% (105)</td>
<td>8.2% (8)</td>
</tr>
</tbody>
</table>

- Knowing the risk of TB exposure improves the interpretation of results for TST and IGRAs.
- Exposure risk needs consideration even with elevated risk for progression to active TB – J Gray CID 2011

### . . and very different results in follow-up

- Triple-positive, likely true-positive, at baseline had stable repeat IGRAs: only 6.7 & 16.7% of positive QFT & T-SPOT reverted to neg.
- Isolated positive IGRAs likely to revert to neg.:
  - QFT - 67% (30/45)
  - T-SPOT - 58% (47/81)
- Isolated positive TST:
  - BCG-history in 58/80 for OR 33.4
  - 50 recruited into Impact of TST on IGRA boosting
Cumulative Conversions and Reversions after Repeats at 6, 12 & 18 months

<table>
<thead>
<tr>
<th>Test</th>
<th>Conversion</th>
<th>Reversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (2293)</td>
<td>21 (0.9)</td>
<td>11 / 12 (91.7)</td>
</tr>
<tr>
<td>QFT (2263)</td>
<td>138 (6.1)</td>
<td>81 / 106 (76.4)</td>
</tr>
<tr>
<td>T-SPOT (2137)</td>
<td>177 (8.3)</td>
<td>91 / 118 (77.1)</td>
</tr>
</tbody>
</table>

Conversion = (-) baseline (+) in f/u. . Reversion = (+) baseline (-) next test

Note: 15-18% of IGRA conversions occurred among those with initial values just below positive. Reversions > 50% up to QFT & T-SPOT of 3.0 IU/ml & 10 spots.

Conclusions:
It is time to stop routine annual testing for TB infection for all but selected higher-risk HCW in the US.

- NTCA working group plans MMWR update
- Greater emphasis on LTBI treatment of “true-positives”, e.g. prior exposure or new exposure
Why I think you should be interested in testing & treatment of LTBI in HCW

Your next HCW with active TB is most likely to result from

• LTBI acquired by worker who was born or lived in a higher TB incidence country & never treated – LPN from high-burden country

• Active TB missed by inadequate diagnostic evaluation during LTBI screening – RN student with chronic cough, prior study in South Africa

Performance of Screening Tests for Latent Tuberculosis in Young, Foreign-born Children Using Latent Class Analysis

IUATLD World Congress 2016
Jason Stout, Yanjue Wu, Smita Ghosh, Matthew Whipple, Matthew Johnson, April Pettit, Christine Ho for the Tuberculosis Epidemiologic Studies Consortium
Methods

• TBESC prospectively enrolled participants at high risk for LTBI from 10 sites in the United States
• All 3 tests for LTBI (TST, QFT, TSPOT) performed on all participants
• For this analysis, we included foreign-born children under 5 years of age who were HIV-seronegative (N=463)
• We used Bayesian Latent Class Analysis to estimate test characteristics (sensitivity, specificity) and LTBI prevalence in this cohort

Results

<table>
<thead>
<tr>
<th>Test Combination (TST/QFT/TSPOT)</th>
<th>N (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>328 (70.8%)</td>
</tr>
<tr>
<td>++</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>+</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>+</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>++</td>
<td>114 (24.6%)</td>
</tr>
<tr>
<td>+++</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>+++</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>+++</td>
<td>9 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>463</td>
</tr>
</tbody>
</table>
Results

- LTBI prevalence 4.2% (1.9-6.7)
- Sensitivity:
  - TST 68.8% (58.2-79.1)
  - QFT 70.4% (54.4-86.1)
  - TSPOT 58.9% (42.5-75.7)
- Specificity
  - TST 74.0% (69.7-78.0)
  - QFT 98.9% (97.7-99.9)
  - TSPOT 99.0% (98.1-99.9)
### Predictive Value of Tests Age < 5 yr

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Predictive Value (95% CrI)</th>
<th>Negative Predictive Value (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>10.2% (5.0-16.9)</td>
<td>98.3% (96.7-99.3)</td>
</tr>
<tr>
<td>QuantiFERON</td>
<td>73.8% (43.3-95.5)</td>
<td>98.7% (97.3-99.6)</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>71.9% (45.4-93.2)</td>
<td>98.2% (96.5-99.4)</td>
</tr>
</tbody>
</table>

### Predictive Value of Tests Ages ≥ 5 yrs

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Predictive Value (95% CrI)</th>
<th>Negative Predictive Value (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>60.0% (56-63)</td>
<td>81.8% (74-89)</td>
</tr>
<tr>
<td>QuantiFERON</td>
<td>97.6% (94-99.9)</td>
<td>85.0% (79-91)</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>98.6% (96-99.8)</td>
<td>84.5% (78-91.0)</td>
</tr>
</tbody>
</table>

Poster by Jason Stout et al, IUATD World Congress 2016
Conclusions of LCA

- Consistent with other observations, QFT and TSPOT were found to be more specific (and roughly comparable).
- Sensitivity of all available tests for LTBI is suboptimal in young children.
- Relatively low specificity and LTBI prevalence were associated with very poor positive predictive value for TST without any improvement in negative predictive value, especially < 5 yrs of age.
- Either QFT or TSPOT would be preferred over the TST for LTBI screening in foreign-born populations.

HIV-infected Patients Atlanta, GA

- Patient population: 336 HIV-infected patients at 2 clinics in Atlanta, Sept ’05 to July ’06

Results:
- TST (+) 7 (2.5%)
- QFT-GIT (+) 9 (2.7%)
- T-SPOT (+) 14 (4.2%)
- Any (+) 27 (8.0%)
- All 3 (+) 1 (0.3%)

Conclusion: Poor concordance among tests

TBESC Study: Talati, BMC Infect Dis 2009; 9:15
Screening for TB & LTBI in Two HIV Clinics in Denver, CO

- Denver Health & University of Colorado each care for about 1,000 HIV-positive patients
- Poor completion rate for TST readings
- TB in HIV-infected individuals infrequent
- TB CO in 2010: 71 cases, rate 1.4 per 100K
  - US-born rate 0.4 per 100K
  - Foreign-born rate 11.5 per 100K
  - HIV-positive TB cases 8.5%, 4% not tested

Screening for TB & LTBI in Two HIV Clinics in Denver, CO

- QFT implemented in 2009
  - Denver Health – DHMC laboratory
  - University of CO – National Jewish Health lab
- Initial observations
  - Higher screening completion – 50% with TST
  - False-positive QFT suspected
    - Most QFT+ patients US-born, no TB exposure risk
    - Many had prior negative TST(s)
High Risk Populations - HIV-infected

Methods:
– retrospective review of repeat QFT-GIT at 2 HIV clinics in Denver, July 2009-June 2010

Results:

<table>
<thead>
<tr>
<th></th>
<th>Overall N= 1364</th>
<th>Repeat Test – No TB Risk N = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>94 (7%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1243 (91%)</td>
<td>33 (80%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>27 (2%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Gray CID 2012; 54: e20

Outcome of tested HIV+ patients in two clinics in Denver

- Positive QFT2 11 - offered Tx, no TB
- Negative QF2 35 - not treated, no TB
  - Mean of 500 days follow-up
  - Total of 41.1 patient-years follow-up

- Limitations: small N, few with low CD4

J Gray, CID 2011
Screening for TB & LTBI in Two HIV Clinics – interpretation

- In well-characterized HIV Clinic populations at overall low-risk for exposure
  - Inadvertent repeat QFT in foreign-born indicates true-positives remain so - 6/8
  - Most positives in low-risk are false-positive, identified by retesting
  - Quantitative QFT1 poor predictor of QFT2
  - More complete LTBI screening with < 7% repeats makes QFT testing superior to TST

Screening for TB & LTBI in Two HIV Clinics: Policy change

Policy change due to perceived false-positive QFT in HIV-infected patients at low risk for TB exposure

- Routine repeat QFT (QFT2) implemented for asymptomatic, low-risk patients with “suspected false-positive” QFT
  - Repeat “soon” or next visit
  - No chest X-ray or treatment with negative QFT2
High Risk Populations – Other Immunosuppression

1. Rheumatoid Arthritis
   – QFT-G (+) similar in patients and healthy controls
     Inanc J Rheum 2009; 36:12

1. Hemodialysis
   – TST correlated with BCG vaccination
   – QFT-GIT and T-SPOT correlated with exposure risk
     Chung Clin Micro Infect 2009

Summary of TST and IGRA

- **IGRAs should be preferred overall**
  - Better in BCG-vaccinated
  - One visit and results are easily retrieved

- **Use TST when logistics call for it**

- **Confirm all (+) IGRAs in people at low risk for TB exposure**
  - Repeat the IGRA

- **Choice of IGRA should be based on local cost and logistics**
**CDC IGRA Guideline 2010**

- IGRA preferred for individuals
  - Unlikely to return for TST result
  - Likely prior BCG vaccination
- Screen HIV-positive patients for LTBI
  - Use TST, QFT or T-SPOT.TB
  - Treat for LTBI if any test is positive
- Approach to positive IGRA in low risk*
  - Repeat the same or a different test
  - Ignore the result as a false-positive

But what about HIV+ at low-risk for LTBI?
What about other medical risk only?

*both low exposure and low medical risk

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**Case 1 - 20 y/o student**

- Born in India
- Required to get TB testing for college enrollment
- TST = 11 mm  CXR = normal
  - “It’s due to my BCG”
- QFT positive (TB-nil = 1.15)
  - “It’s boosting from the TST”
Case 1 - 20 y/o student

- Born in India
- Required to get TB testing for college enrollment
- TST = 11 mm  CXR = normal
  “It’s due to my BCG”
- QFT positive (TB-nil = 1.15)
  “It’s boosting from the TST”
- Repeat QFT negative (TB-nil = 0.34)
  “Finally we agree”

Key questions for interpretation

- Why was the LTBI test done?
  1. Administrative only, no risks: low PPV, consider repeat testing
  2. Exposure risk: IGRA if possibly BCG vaccinated, high PPV
  3. Medical progression risk only: low PPV – options
     - Retest cautiously
     - Some experts recommend both tests to increase sensitivity
  4. Medical evaluation for active TB: negative is really inconclusive