Why IGRA?

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TB - Current Situation

Global TB Picture

2009 Data
- 9.4 million new cases
- 1.7 million deaths
  - 4700/day
- TB is among 3 leading causes of death among women aged 15-44 worldwide

- 9.4 million new cases
- 1.7 million deaths
- TB is among 3 leading causes of death among women aged 15-44 worldwide
WHO Fact Sheet on Tuberculosis

- Someone in the world is newly infected with TB every second.
- ~1% of the world’s population is newly infected with TB each year.
- 1/3 of the world’s population is currently infected with the TB.

The Global TB Picture
WHO estimates (2008)

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>9.4 million (139 per 100,000)</td>
<td>1.8 million (27 per 100,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB (MDR-TB)</td>
<td>511,000</td>
<td>~150,000</td>
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<tr>
<td>Extensively drug-resistant TB (XDR-TB)</td>
<td>~50,000</td>
<td>~30,000</td>
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<tr>
<td>HIV-associated TB</td>
<td>1.4 million (15%)</td>
<td>456,000</td>
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</tbody>
</table>

WHO 2009

TB in Canada

- New TB case in Canada every 6 hours
Proportion of TB cases by age group and origin in Canada: 2007

<table>
<thead>
<tr>
<th>Age group</th>
<th>Proportion</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>Canadian-born Aboriginal: 3.0%</td>
</tr>
<tr>
<td>1-4</td>
<td>Foreign-Born: 14.1%</td>
</tr>
<tr>
<td>5-14</td>
<td>Non-Aboriginal: 68.5%</td>
</tr>
<tr>
<td>15-24</td>
<td>- Rate: 34.1/100,000</td>
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<tr>
<td>25-34</td>
<td>- Rate: 28.1/100,000</td>
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<tr>
<td>35-44</td>
<td>- Rate: 18.1/100,000</td>
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<tr>
<td>45-54</td>
<td>- Rate: 1.4/100,000</td>
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<tr>
<td>55-64</td>
<td>- Rate: 0.1/100,000</td>
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<tr>
<td>65-74</td>
<td>- Rate: 0.0/100,000</td>
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<tr>
<td>75+</td>
<td>- Rate: 0.0/100,000</td>
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</tbody>
</table>

TB Rates BC - 2008

- 305 cases
- 14.1% Aboriginal - Rate: 34.1/100,000
- 68.5% Foreign-Born - Rate: 18.1/100,000
- 14.1% CB Non-Aboriginal - Rate: 1.4/100,000

TB Control

- Detect and treat persons with Active TB Disease
- Detect asymptomatic persons with Latent TB Infection (LTBI) and prevent the development to active TB disease
IGRAs for diagnosis of latent tuberculosis infection

Is this a magic bullet?

TST

- The standard for immunologic diagnosis of M. tuberculosis infection has been TST

- Concerns - lack of sensitivity and specificity resulting in false positive and false negative results

Purified protein derivative PPD

- Tuberculin, purified protein derivative (PPD) is indicated as a diagnostic aid in the detection of Mycobacterium tuberculosis infection.

- Tuberculin PPD is a sterile isotonic solution of tuberculin. It is obtained from a human strain of Mycobacterium tuberculosis grown on a protein-free synthetic medium and buffered with potassium and sodium phosphates.
Bacille Calmette-Guérin - BCG

- a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus, *Mycobacterium bovis*, that has lost its virulence in humans by being specially cultured in an artificial medium.

TST: False negatives / False positives

<table>
<thead>
<tr>
<th>False negatives</th>
<th>False positives</th>
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</thead>
<tbody>
<tr>
<td><strong>Technical factors</strong></td>
<td>- Infection with nontuberculous mycobacteria</td>
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<tr>
<td>- Application</td>
<td>- BCG vaccination</td>
</tr>
<tr>
<td>- Reading</td>
<td></td>
</tr>
<tr>
<td>- Improper storage of PPD</td>
<td></td>
</tr>
<tr>
<td><strong>Biological factors</strong></td>
<td></td>
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<tr>
<td>- Poor nutrition</td>
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<tr>
<td>- Infection</td>
<td></td>
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<tr>
<td>- Immunosuppressive drugs</td>
<td></td>
</tr>
<tr>
<td>- Malignancy</td>
<td></td>
</tr>
<tr>
<td>- Age</td>
<td></td>
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<tr>
<td>- Stress</td>
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Interferon Gamma Release Assays (IGRAs)

- 2007, IGRAs new diagnostic tests
- in-vitro blood tests that measure cell-mediated immune response after stimulation by M.TB-specific antigens (ESAT-6 and CFP10, both of which are not present in the BCG vaccine)
Interferon Gamma Release Assays (IGRAs)

- IGRA test has a reported specificity range from 93%-99% while the skin test specificity with prior BCG vaccination is approximately ~60%

- TST specificity NO BCG- 97%

- It should be noted, however, that neither IGRAs nor skin tests can distinguish between active TB and latent TB infection.

- IGRAs are significantly more expensive than skin tests, special equipment is needed, and are time sensitive.

- Currently, these tests are only processed at the BCCDC, suggesting potential barriers for province-wide use with shipping the time-sensitive samples.

IGRA and TST

- **IGRA**
  - *in vitro* test
  - Specific antigens
  - No boosting
  - 1 patient visit
  - Lab variability
  - Results possible in 1 day
  - Requires phlebotomy

- **TST**
  - *in vivo* test
  - Less specific PPD
  - Boosting
  - 2 patient visits
  - Inter-reader variability
  - Results in 2-3 days
  - No phlebotomy required
## Assay antigens

MTB specific antigens include early secreted antigenic target (ESAT-6) and culture filtrate protein 10 (CFP-10). These are encoded by genes located within the region of difference segment of MTB genome.

More specific for MTB than PPD as do not share with any BCG vaccine.

## Types of assays

- **QuantiFERON-TB Gold In-Tube -QFT-GIT**
  
  is an ELISA based whole blood test that uses peptides from 3 TB antigens (ESAT-6, CFP-10, and TB7.7) in an in-tube format.

- **T-SPOT.TB**
  
  is an enzyme-linked immunospot (ELISPOT) assay performed on separated and counted peripheral blood mononuclear cells.

## Sensitivity and Specificity

- Specificity IGRA > 95%
- Sensitivity for T-SPOT appears higher than QFT-GIT or TST. (~90%, 80%, and 80%)
- T-SPOT useful for immunosuppressive conditions
- TST specificity NO BCG- 97% - with BCG ~60%
- IGRA and TST sensitivity is diminished by HIV infection, lower CD4 counts
- IGRAs and TST should not be used for diagnosis active TB
Results and Interpretation

- **RESULT**
  - Positive
  - Negative
  - Intermediate

- **INTERPRETATION**
  - ESAT-6 and/or CFP-10 Responsiveness detected: M. tuberculosis infection likely
  - No ESAT-6 or CFP-10 Responsiveness detected: M. tuberculosis infection unlikely
  - MTB infection status cannot be determined as a result of impaired immunity and/or incorrect performance of the test

Prediction of active disease

- IGRA and TST appear to have only modest predictive value for identifying those at highest risk of progression to active TB disease

BCCDC Guidelines

- tst positive + foreign born OR tst positive and BCG OR tst negative and immune compromised (t-spot for immune compromised)

- for communities and field operations: physician at TB Control will recommend IGRA in physician narrative. HCP contact TB Control nurse to coordinated location (Vancouver, Prince George, Kelowna and Victoria)
Limitations IGRA

data lacking on how to interpret repeated (serial) IGRA testing results

IGRA Research

Among 24 cross-sectional studies in low TB incidence settings, the pooled prevalence of positive IGRA using either test was significantly lower than for a positive TST.

No data suggesting that IGRAs are better at identifying the incidence of new TB infection than the TST.

What does this mean

The use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer persons require LTBI treatment.
Take home message

- Testing implies treatment: why are we testing: what diagnostic tools available
- Risk factors
- Contact history
- Symptoms
- HCP

QUESTIONS?