IGRAs in Public Health
Practice: San Francisco TB Control

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Regarding QFT-G......

This has been the single biggest advance in delivering healthcare to people who are homeless in my 20 years of doing healthcare.

Barry Zevin
San Francisco homeless healthcare provider
May 5, 2008

San Francisco Demographics

- Population: 814,225 (2009)^1
- 35.7% foreign born^2
- 27,000 living with AIDS (2007)^3
- 6,514 homeless (1,500 in shelter)^4
  (10.5% HIV+, 7% LTBI by QFT-G)
- 18,000+ injection drug users
  (22% HIV+)
- ~55,000 jail bookings each year^6

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^2 U.S. Census Bureau, 2005-2007 American Community Survey.
^6 http://www.sfsheriff.com/jails.htm
SF 2009 TB Case Rates

- 116 new cases reported
- Incidence rate = 14.2
- Highest rate of TB in California
  >2x California rate of 6.4
  >3x U.S. rate of 3.8
- Rates remain high in Chinatown and the TL/SOMA
  >100/100,000

Case Finding Methods

**Passive**
- Hospital and MD referrals

**Active**
- Immigration screening
- Contact Investigation (CI)
- Community screening: Targeted testing
  - 2005-2009: 30% of cases found through active TB screening (2009: 37 of 116 active cases)
  - Targeted testing yields 3x more cases than CI and immigration screening combined (2009: 27 of 37 cases from TT)

Number of QFT Tests Performed By Month, November 2003 – April 2010
2002: Why switch to QFT?

- Better test (more specific)
  - TST performance highly variable
  - Reduce the number of false positives
  - No quality control of >10,000 TSTs/yr

- Operational advantages
  - Less staff time
  - Results for every patient
  - Improved documentation, surveillance & communication

- Low confidence in the TST by providers caring foreign-born because of BCG vaccination
- ‘Use it or lose it’

Clinical OBSTACLES: The big unknowns

- No gold standard for LTBI: belief IGRA may be less sensitive
- Sensitivity in case finding?
- Cases may be missed: sensitivity in highly vulnerable populations: young children under <5 yrs and immunocompromised
- Risk of progression of a positive IGRA?

Reality check:

- <50% rate of TST return from SF homeless and HIV clinics
- Contacts <5yrs old are put on window prophylaxis

TST case finding reality: Sensitivity by rate of return for test reading

<table>
<thead>
<tr>
<th>TST rate of return</th>
<th>Theoretical Ideal sensitivity</th>
<th>Sensitivity per 2007 meta-analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>95</td>
<td>74</td>
</tr>
<tr>
<td>90%</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>80%</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>70%</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>60%</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>50%</td>
<td>47</td>
<td>37</td>
</tr>
</tbody>
</table>

2003-2010: SF Journey to QFT-GIT

- 2003-2008 Seed funding using roll-over grant dollars and City new technology grant
- Demand created and IGRAs are now the standard of care for homeless and foreign-born patients in SF community clinics
- Sustainability: State and federal government insurance reimbursement and health system savings from unnecessary CXRs, medical visits
- 2009: Health Department funds now covering costs of kits

Perceived public benefit and reimbursement was the deciding factor in the end

Key to economic obstacle: Reimbursement for IGRAs

California state reimbursement
Reimbursement amount $69
(excludes pediatric and HIV patients)

Federal reimbursement
Reimbursement amount $86.58

Private reimbursement
Reimbursement amount $70

2009 Cost of running QFT in San Francisco Public Health Laboratory: $36.42

IGRAs (QFT) in San Francisco: Highlights
Site Implementation begins: standard process developed

1. Discuss QFT with site management
2. Provider guidelines and frequently asked questions document
3. In-service to staff (medical and nursing)
4. Clinic site adapts protocols
5. Clinic site responsible for lab courier – blood to lab by 4 pm

Provider Guidelines

Communication of QFT Results Back to Ordering Providers

QFT Surveillance Results by Clinic and Test Type
March 2005 – April 2010

<table>
<thead>
<tr>
<th></th>
<th>Homeless</th>
<th>TB Clinic</th>
<th>Methadone</th>
<th>Immigrant</th>
<th>Refuges</th>
<th>HIV</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=13,880</td>
<td>n=9130</td>
<td>n=2359</td>
<td>n=4230</td>
<td>n=880</td>
<td>n=943</td>
<td>n=6353</td>
</tr>
<tr>
<td>Positive QFT-G</td>
<td>734 (7)</td>
<td>940 (20)</td>
<td>51 (7)</td>
<td>302 (14)</td>
<td>111 (13)</td>
<td>34 (3)</td>
<td>349 (10)</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>258 (6)</td>
<td>306 (16)</td>
<td>23 (7)</td>
<td>235 (17)</td>
<td>11 (1)</td>
<td>288 (10)</td>
<td></td>
</tr>
<tr>
<td>Negative QFT-G</td>
<td>8646 (89)</td>
<td>3777 (77)</td>
<td>1374 (80)</td>
<td>3225 (82)</td>
<td>866 (53)</td>
<td>2059 (98)</td>
<td></td>
</tr>
<tr>
<td>QFT-IT</td>
<td>3010 (90)</td>
<td>3688 (79)</td>
<td>1115 (73)</td>
<td>1133 (62)</td>
<td>75 (52)</td>
<td>1200 (90)</td>
<td></td>
</tr>
<tr>
<td>Indeterm. QFT-G</td>
<td>352 (4)</td>
<td>218 (2)</td>
<td>63 (1)</td>
<td>127 (6)</td>
<td>57 (6)</td>
<td>40 (5)</td>
<td>139 (2)</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>69 (3)</td>
<td>151 (2)</td>
<td>31 (3)</td>
<td>18 (1)</td>
<td>9 (1)</td>
<td>3 (1)</td>
<td>63 (2)</td>
</tr>
</tbody>
</table>
### TB Infection Prevalence By Test and Clinic Type

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>26%</td>
<td>~50%</td>
<td>10%</td>
<td>37%</td>
</tr>
<tr>
<td>QFT-T</td>
<td>17%</td>
<td>48%</td>
<td>18%</td>
<td>37%</td>
</tr>
<tr>
<td>QFT-G</td>
<td>7%</td>
<td>22%</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>6%</td>
<td>20%</td>
<td>7%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Decline in positive rate from TST: ↓77% ↓>60% ↓30% ↓56%

### Quantiferon Results by Age Group and Test Type

- **March 2005 – April 2010**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SF TB Control Updated 05/04/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% - 9%</td>
<td>Positive: 80% Negative: 20% Indeterminate: 0%</td>
</tr>
<tr>
<td>9% - 19%</td>
<td>Positive: 70% Negative: 30% Indeterminate: 0%</td>
</tr>
<tr>
<td>19% - 29%</td>
<td>Positive: 60% Negative: 40% Indeterminate: 0%</td>
</tr>
<tr>
<td>29% - 39%</td>
<td>Positive: 50% Negative: 50% Indeterminate: 0%</td>
</tr>
<tr>
<td>39% - 49%</td>
<td>Positive: 40% Negative: 60% Indeterminate: 0%</td>
</tr>
<tr>
<td>49% - 59%</td>
<td>Positive: 30% Negative: 70% Indeterminate: 0%</td>
</tr>
<tr>
<td>59% - 69%</td>
<td>Positive: 20% Negative: 80% Indeterminate: 0%</td>
</tr>
<tr>
<td>69% - 79%</td>
<td>Positive: 10% Negative: 90% Indeterminate: 0%</td>
</tr>
<tr>
<td>79% - 89%</td>
<td>Positive: 0% Negative: 100% Indeterminate: 0%</td>
</tr>
<tr>
<td>89% - 99%</td>
<td>Positive: 0% Negative: 100% Indeterminate: 0%</td>
</tr>
<tr>
<td>99% - 100%</td>
<td>Positive: 0% Negative: 100% Indeterminate: 0%</td>
</tr>
</tbody>
</table>

### Active TB: TST and QFT Sensitivity (culture proven cases)


<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (n=321)</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>83.6% (112/134)</td>
<td>-</td>
</tr>
<tr>
<td>QFT-G</td>
<td>73.3% (137/187)</td>
<td>-</td>
</tr>
<tr>
<td>QFT-G and TST</td>
<td>91.1% (92/101)</td>
<td>69%</td>
</tr>
</tbody>
</table>

- **1/2009 – 2/2010**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (n=85)</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>77.3% (34/44)</td>
<td>-</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>75.4% (43/57)</td>
<td>-</td>
</tr>
<tr>
<td>QFT-IT and TST</td>
<td>89% (33/37)</td>
<td>62%</td>
</tr>
</tbody>
</table>
Contact Investigation and IGRAs: QFT-G
March 1, 2005 – December 31, 2007

<table>
<thead>
<tr>
<th>N=1365</th>
<th>Contacts tested</th>
<th>650</th>
<th>715</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fully evaluated</td>
<td>361 (56%)</td>
<td>331 (66%)</td>
</tr>
<tr>
<td></td>
<td>Cases found</td>
<td>5 (1.4%)</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>Infection prevalence</td>
<td>140 (38.8%)</td>
<td>131 (27.9%)</td>
</tr>
<tr>
<td></td>
<td>Initiation of LTBI treatment</td>
<td>101 (72%)</td>
<td>117 (89%)</td>
</tr>
<tr>
<td></td>
<td>Completion of Treatment among those who started</td>
<td>73/101 (72%)</td>
<td>94/117 (80%)</td>
</tr>
<tr>
<td></td>
<td>Completion of treatment among those infected</td>
<td>73/140 (52%)</td>
<td>94/131 (72%)</td>
</tr>
</tbody>
</table>

CI Infection rates by Smear and Culture Status

<table>
<thead>
<tr>
<th>Micro status</th>
<th>All Contacts</th>
<th>Smear + Smear- Culture + Culture-</th>
<th>QFT-G*</th>
<th>TST</th>
<th>QFT-G*</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear +</td>
<td>95/451 (21%)</td>
<td>133/439 (30.7%)</td>
<td>75/227 (33.4%)</td>
<td>92/104 (50.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear- Culture+</td>
<td>37/265 (14%)</td>
<td>47/211 (22.3%)</td>
<td>25/129 (19.4%)</td>
<td>42/88 (47.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conversion rates by Smear and Culture Status

<table>
<thead>
<tr>
<th>Micro status</th>
<th>All Contacts</th>
<th>Smear + Smear- Culture + Culture-</th>
<th>QFT-G*</th>
<th>TST</th>
<th>QFT-G*</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear +</td>
<td>12/234 (5.4%)</td>
<td>3/260 (1.2%)</td>
<td>6/139 (4.3%)</td>
<td>2/69 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear- Culture+</td>
<td>3/201 (1.5%)</td>
<td>2/150 (1.3%)</td>
<td>3/89 (3.4%)</td>
<td>1/44 (2.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

San Francisco: Pediatric IGRA Outcomes
March 2005 and December 2007

n=792

- None of the 749 QFT-G negative or indeterminate children progressed to active disease. Includes:
  - 190 untreated children <5 yrs
  - 41/45 untreated discordant TST+/QFT- <5 yrs
  - 38 children tested during contact investigations
- QFT-G identified all 4 active pediatric cases
  - 2 <5yrs, 2 >5yrs
- Trend toward discordance was associated with BCG status and younger age
IGRA (QFT): Test of choice
SF TB Control programmatic perspective

IGRAs surpass TST in performance because of single step to get results, higher specificity and reliability of results.

SURVEILLANCE
- IGRA superior to TST

ACTIVE CASE FINDING
- Contact investigation:
  - IGRA preferred by investigators
  - Better evaluation and treatment outcomes
  - Results correlate to intensity of exposure
- Shelters/homeless programs: IGRA superior and preferred by providers

SF Pediatric QFT-G Results by Age Group
March 2005 and December 2007
n=792

TST/QFT-G Discordance by Age and BCG Vaccination or FB status

SF TB Control programmatic perspective
IGRA (QFT): Test of choice
SF TB Control programmatic perspective

TARGETED TESTING
- Screening BCG vaccinated populations: IGRA has significantly decreased the number of referrals to the TB Clinic and LTBI treatment
- Pediatric
  - No known cases missed
  - Negative predictive value excellent at >24 months follow up
  - Screening asymptomatic TST+ BCG vaccinated children <5 yrs old: Phlebotomy is more difficult but parents continue to demand IGRA
- Methadone Clinics:
  - Referrals and LTBI DOT dramatically reduced by IGRA
- Jail TST conversion verification: IGRA verifies suspected poor reading of TSTs

SF Clinical Experience using IGRAs
Negatives: IGRAs are tools and not a panacea!
- Provider and patient misconception on what IGRA can and cannot do
- Discordant TST+/QFT- results are problematic in TB suspects and immunocompromised: misinterpreted as "TB ruled-out!"
- Indeterminate results cause disappointment and confusion on next steps
- New test = new problems
- Switching test = different results

Impact on clinical decision making:
- Active cases: No different than TST
- LTBI: marked impact on decreasing further work up and treatment

Conclusions
- IGRAs in SF 2003-2010: excellent track record
- IGRAs are a significant advance because of its high specificity and operational advantages to the TST
- Sustainability: QFT pays for itself in SF and public demand comes from its convenience and specificity
- IGRAs are the TB test of choice in SF
- "Once you use them, you can't go back"
Acknowledgments: Thanks for taking the IGRA plunge!

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SF community clinics