Programmatic Experience with IGRA Testing: San Francisco

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Disclosures: None

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Overview

- San Francisco tuberculosis epidemiology
- Predictive value of IGRA for progression to disease in pediatric patients
- Predictive value for progression to disease in the foreign born

San Francisco Demographics

- Population: 805,235 (2010)[1]

- 286,085 foreign born (2010)[1]
  - 35.5% of the population
  - 23% with LTBI by QFT-GIT =65,800 persons

- 6,445 homeless: 1,479 in shelter (2011)[2]
  - 7% LTBI by QFT-GIT = 451 persons
  - 31% have a substance abuse problem (alcohol and/or other drugs)
  - 5% have HIV/AIDS
  - 51% are homeless >1 year, 29% >3 years

- 1,244 people living in DPH-subsidized supportive housing (2011)[3]

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Span of TB Control Activities San Francisco - 2012
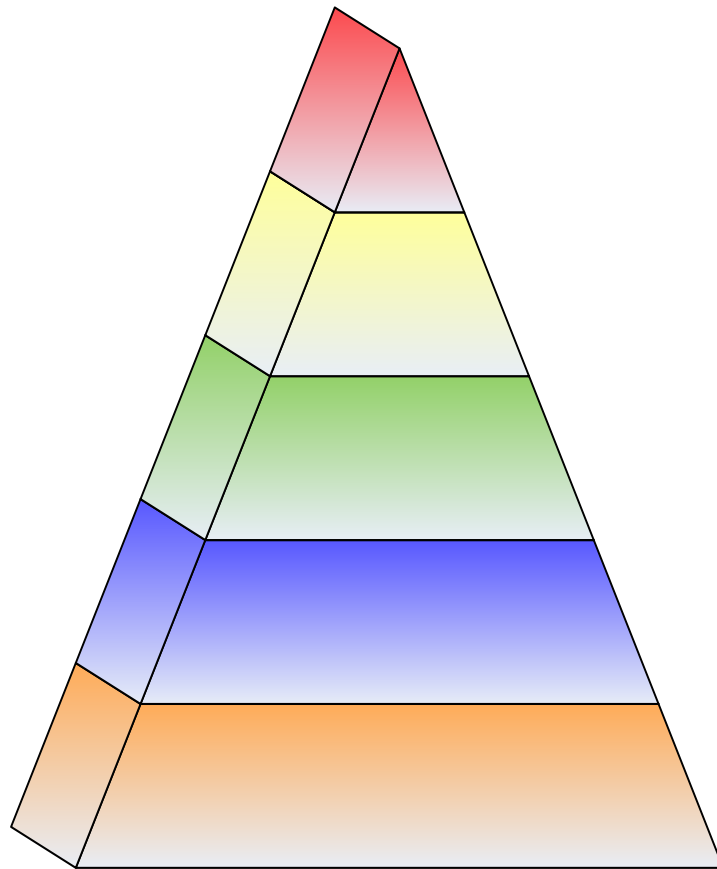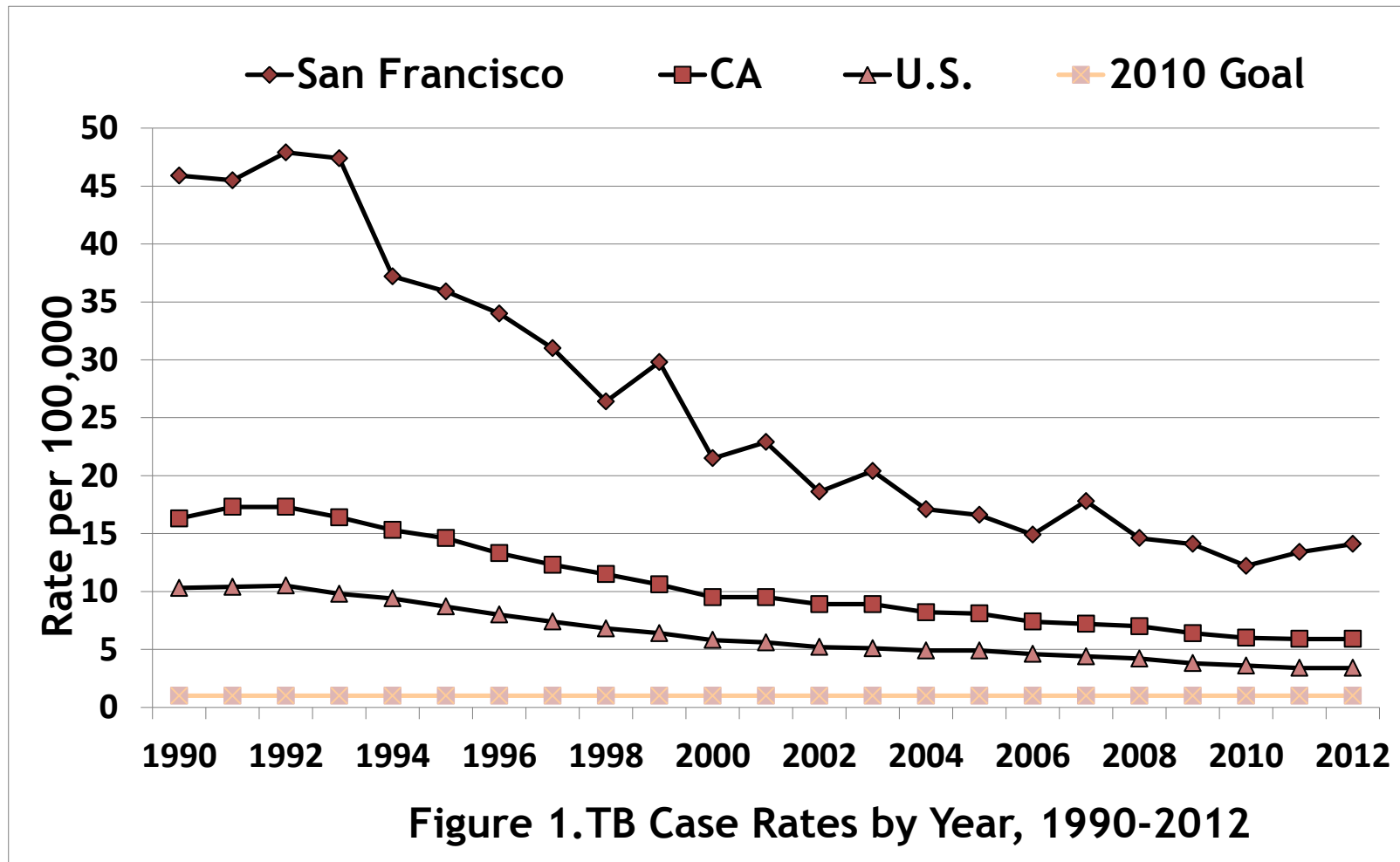
116 San Franciscans with TB

Over 500 TB Suspect Cases

950 Contacts to Cases

78,000 San Franciscans Infected

820,000 San Franciscans

San Francisco Tuberculosis Case Rate is Stable (for now)

Figure 1. TB Case Rates by Year, 1990-2012

IGRA Testing in San Francisco

- Initiated in 2005 and integrated into the homeless shelter screening at the same time
- Approximately 10,000 tests per year (QFT)
- San Francisco Public Health Laboratory runs QFT for:
  - City and County ambulatory care system in the neighborhoods
  - SFGH campus, including TB clinic
- Blood is collected on site and must be transported to public health lab by courier
  - A few sites have capability of incubating specimens (TB clinic) prior to courier pick up
- Supported by City and County general fund, TB control federal funding, State TB Branch funding
  - Reagents, Courier services (23$ per day)
  - FTE to run tests in public health laboratory
- T-spot available through participation in CDC research study (2012-present)

TB Infection Prevalence By Test and Clinic Type

	Homeless	TB Clinic	Methadone	Immigrant
TST (2001-2003)	26%	~50%	10%	37%
QFT-1 (11/03-2/05)	17 % n=1848	48 % n=292	18 % n=346	37 % n=344
QFT-G (3/05-11/08)	7 % n=9166	23 % n=4042	4 % n=1261	14 % n=2505
QFT-IT (4/08-2/09)	6 % n=1625	22 % n=1555	——	20% n=323
Decline in positive rate from TST	- 73%	- 54%	- 60%	- 62%

QFT Results by Clinic and Test Type March 2005 – February 2009

|	Homeless n=10135 (%)	TB Clinic n=4931 (%)	Methadone n=1463 (%)	Immigrant n= 2755 (%)	Refugee n=741 (%)	HIV n=826 (%)	Community n=6240 (%)
Positive							
QFT-G	730 (7)	942 (22)	50 (4)	392 (14)	111 (15)	24 (3)	379 (8)
QFT-IT	92 (6)	349 (22)	____	66 (20)	0	____	56 (9)
Negative							
QFT-G	8606 (89)	3177 (73)	1351 (92)	2235 (80)	574 (77)	798 (92)	4353 (88)
QFT-IT	1507 (93)	1166 (75)	____	252 (78)	4 (100)	____	582 (89)
Indeterm.							
QFT-G	352 (4)	218 (5)	62 (4)	157 (6)	57 (8)	40 (5)	198 (4)
QFT-IT	26 (1)	40 (3)	____	5 (2)	0	____	13 (2)

CDC guidelines: IGRA testing

- IGRA (Tspot or QFT) preferred test for BCG vaccinated or unlikely to return for TST reading
- TST preferred test in children < 5 yo
- No preference for HCW screening, contact investigations, other populations

IGRAs and Pediatric Public Health Screening: San Francisco 2005-2008

Study Population and final TB diagnosis by QFT
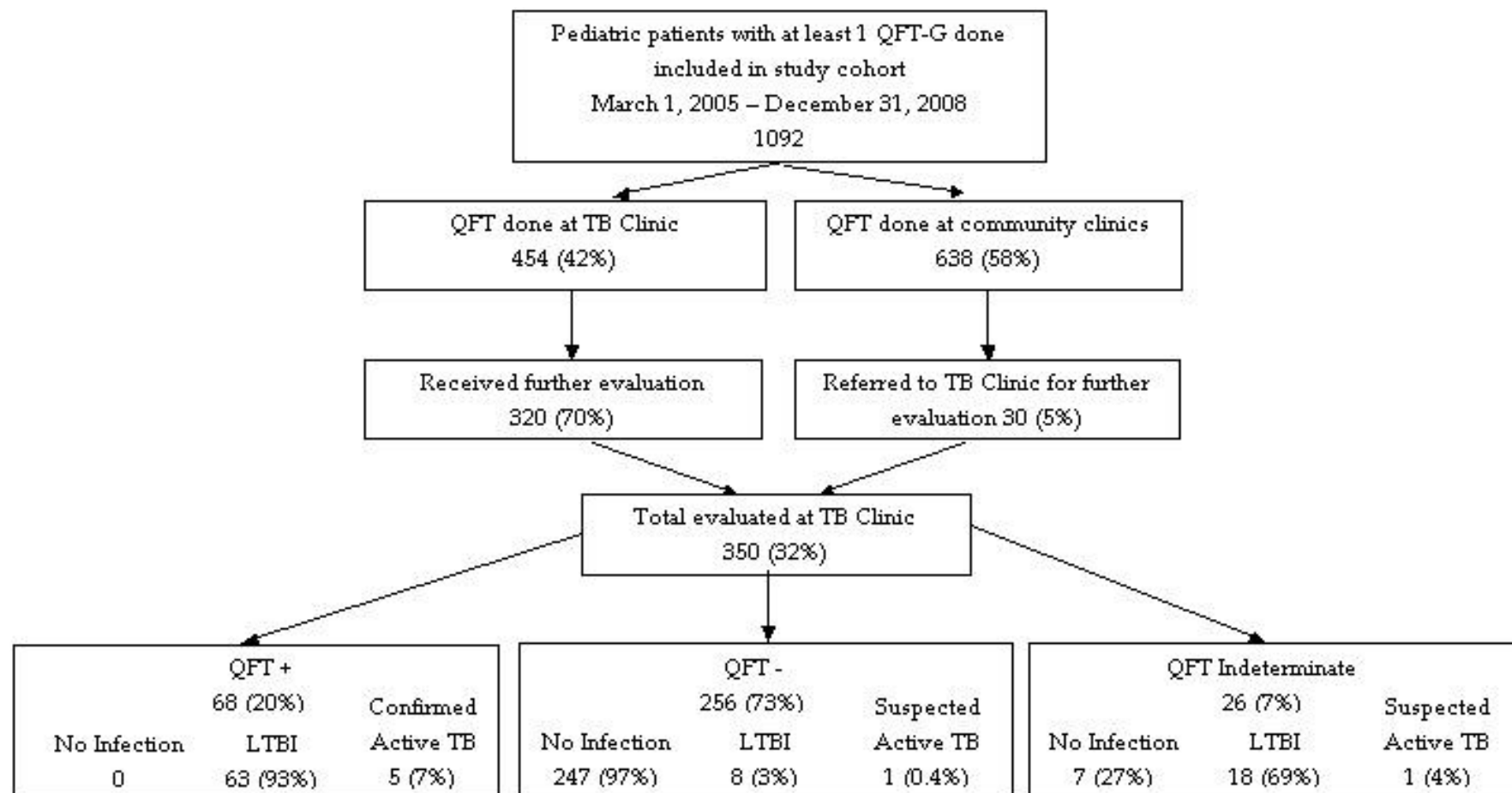
Demographics of children by age group (1)

	Age 0-4	Age 5-14	Total (%)
Number of Children	292	800	1092
Gender			
Male	149	396	547 (50)
Female	143	404	548 (50)
Race/Ethnicity			
Asian	169	566	748 (67)
Black	16	47	63 (6)
Hispanic	95	142	237 (237)
White	14	45	59 (59)

QFT results by age group

	Age 0-4 (%)	Age 5-14 (%)	Total (%)
Test Version			
Gold	200 (69)	622 (78)	822 (75)
In-Tube	92 (31)	178 (22)	270 (25)
QFT Result			
Positive	10 (3)	62 (8)	72 (7)
Negative	254 (87)	689 (86)	943 (86)
Indeterminate	28 (10)	49 (6)	77 (7)
Indeterminate Reason			
High Nil	4 (14)	24 (49)	28 (36)
Low Mitogen	24 (86)	25 (51)	49 (64)

Pediatric QFT-G Results Stratified by Age
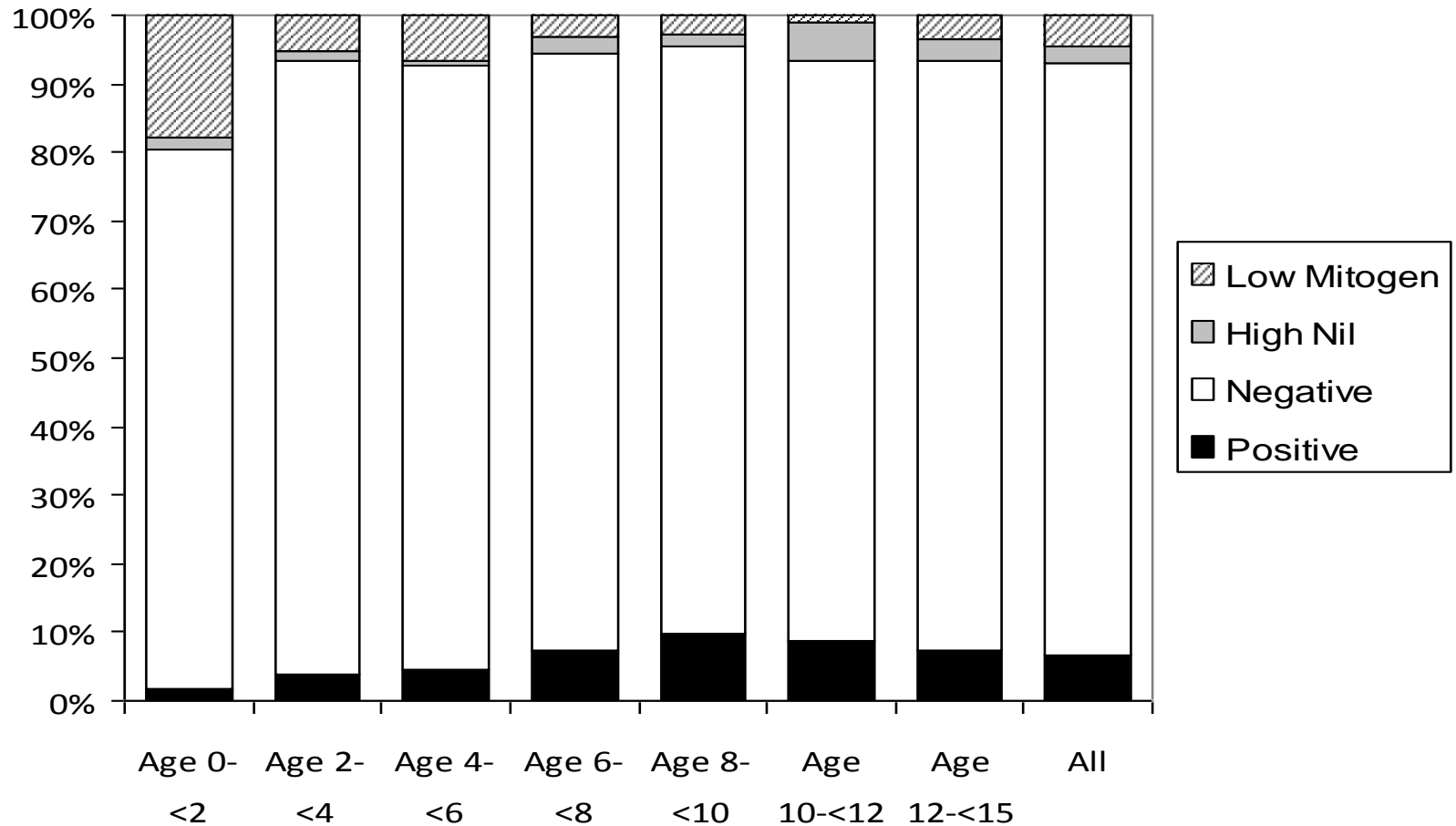
Observations

- Children < 5 were more likely to have an indeterminate QFT result

- The QFT-IT produced significantly fewer indeterminate results than the QFT-Gold test

- Limitation of QFT in young children is indeterminate result related to low mitogen response

- The likelihood of having a positive QFT result increased steadily from age 0-9

Demographics of children by age group (2)

	Age 0-4	Age 5-14	Total
Number of Children	292	800	1092
Country of Birth			
Foreign Born	199	645	853
U.S. Born	93	146	239
TB exposure			
Contact	39	97	136
Non-Contact	253	703	956

QFT/TST Discordance

	Age 0-4 (%)	Age 5-14 (%)	Total (78)
Number of Children	75	142	217
Concordant (TST+/QFT+)			
BCG	5 (9)	37 (28)	42 (22)
No BCG	12 (71)	5 (50)	17 (63)
Discordant TST+/QFT-			
BCG	53 (91)	95 (72)	148 (78)
No BCG	5 (29)	5 (50)	10 (37)

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<.003

<.0001

Observations

- BCG vaccinated children in general were more likely to have a discordant TST+/QFT- result than children who were not BCG vaccinated

- BCG vaccinated children < 5 were more likely to have a discordant TST+/QFT- results than BCG vaccinated children > 5

Evaluation Outcomes

- 1092 evaluations completed

- 109 diagnosed as LTBI (TST or QFT positive)

- 109 initiated LTBI and completed a median of 234 days of therapy

- 7 diagnosed with active TB disease

- 146 children < 5 were TST+/QFT- and did not start LTBI treatment

Local and State Registry Match

- Followed for median 5.6 years

- Records were matched with the California state TB registry and local SF DPH TB program

- Match confirmed 7 known cases

- No additional cases found for the remaining 979 children

Characteristics of Pediatric Active TB Disease Cases

- Country of Origin
  - U.S. born cases were Hispanic (3), Black (1), and Asian (1)
  - Foreign born cases were Asian

- Age
  - U.S. born cases all 5 or younger
  - Foreign born cases - 2 yo, 12 yo

- TB exposure
  - Five cases were contacts to an active TB case

- QFT result
  - Five QFT positives (all these were culture confirmed or clinical cases with clear improvement on CXR)
  - One indeterminate (< 1 yo, TST neg) (MD decision to treat)
  - One negative (1 yo, no TST) (MD decision to treat)

Discussion

- Study was limited by matching only to the California state TB registry. Children who moved out of California and developed TB disease would be missed

- Small subset of children in the study received both TST and IGRA for TB screening in this study

- In SF, excellent negative predictive value in children who are lower risk (e.g. noncontact, BCG vaccinated)

SF DPH approach to IGRA in pediatric population

- BCG vaccinated and greater than 1 yo without immunosuppression
  - If referral with positive TST, proceed with IGRA
  - TST+/IGRA-, presume BCG related TST response, do not offer LTBI
  - Payor source may not cover < 5yo
- Otherwise, for U.S. born, TST preferred unless difficulty with return for TST reading
- In tubersol shortage, SF TB program recommended IGRA as reasonable alternative in all children < 5 yo

TB Progression Rates in Foreign Born Persons Following Screening with IGRAs

2005-2012

Immigration Screening: Does IGRA Predict Progression to Disease?

- 1159 new immigrants screened with IGRA from 2005-2012
  - 2-15 y (n=155), >15 y (n=1004)
  - IGRA positive n=519, IGRA negative n=640
  - TST positive n= 229, TST negative n=71
  - Excluded – any TB disease identified within one year of immigration
- CXR
  - Normal cxr n=269 Abnormal cxr n=888
- US LTBI treatment n=436
  - IGRA negative – 32% treated for LTBI with 15% treated in the U.S.
  - IGRA positive – 87% treated for LTBI with 66% treated in the U.S.
- N=5 developed active TB disease in mean of 4.4 years of f/u
  - IGRA negative – two cases
  - IGRA positive – three cases

Immigration Screening: Does IGRA Predict Progression to Disease? The SF experience

Case	Sex	Age	Immigration Date	Country of origin	Evaluation Date	TB Diagnosis Date	TST	IGRA	Treatment Status	ESAT Ag-Nil	CFP Ag-Nil	CXR
1	M	39	May 2005	China	May 2005	June 2011	N/A	–	None	0.3	0.1	N-NC
2	M	54	Sept 2005	China	Sept 2005	Dec 2009	pos	+	None	0.8	0.1	AB N-NC
3	F	46	Dec 2005	Philippines	Jan 2006	Sept 2009	N/A	–	Prior to US	0.2	0.1	AB N-NC
4	M	52	Feb 2006	China	Mar 2006	Jan 2009	N/A	+	Prior to US	2.3	0.8	AB N-NC
5	F	51	April 2007	China	May 2007	Mar 2012	N/A	+	US LTBI	1.2	3	AB N-NC

IGRA alone is not sufficient to make LTBI diagnosis

Table 3. Incidence rate of active TB by IGRA result and treatment history

IGRA Status	n	Active TB in Follow-Up	Total Follow-Up (person-years)	Incidence Rate (95% CI) (person-years)
Overall Incidence Rates				
IGRA +	519	3	2,292	131 per 100,000 (42-406)
IGRA −	644	2	2,461	81 per 100,000 (20-325)
Past Treatment				
IGRA +	450	2	1,982	101 per 100,000 (25-404)
IGRA −	207	1	901	111 per 100,000 (16-788)
No Known Treatment				
IGRA +	69	1	310	322 per 100,000 (45-2,288)
IGRA −	433	1	1,560	64 per 100,000 (9-455)

Past treatment is defined by presence of reported treatment in patient's country of origin or documented LTBI treatment in the US as a consequence of screening. *Abbreviation definitions:* IGRA = interferon-gamma release assays; TB = active tuberculosis.

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Discussion

- All patients who developed TB were assessed with early version of QFT
- Two of the cases of active TB were culture negative, clinical cases
- None of the patients with normal chest x rays progressed to active TB disease

Take home messages

- Foreign born with:
  - Abnormal chest x ray (lung volume loss, extensive scarring)
  - Risk factor for progression (DM, active tobacco use, HIV, other immune suppression)
- Offer LTBI treatment even if IGRA is negative

TST vs. IGRA - What to do with Discordant Results

- Avoid using two tests for TB screening
- TST(+)/IGRA(-)
  - Foreign born with BCG and no severe immunocompromising condition - attribute to BCG
    - Caveat - abnormal CXR confirmed old TB and with risk factor for progression to disease, consider treatment
  - U.S. born - with no risk factors for exposure or risk factors for progression - may be NTM colonization
- TST(-)/IGRA(+), normal CXR
  - Foreign born with BCG and no severe immunocompromising condition - consider repeat IGRA if near cutoff point, e.g. TB Ag-Nil < 0.7, especially if normal CXR
  - U.S. born with no risk factors for exposure or progression - repeat IGRA
- If discordant TST/IGRA and severe immunocompromising condition, offer LTBI
- If severe immunocompromising condition and if TST-/IGRA- and abnormal CXR confirmed old TB, offer LTBI treatment

Acknowledgements

The real heroes!

- Jennifer Grinsdale MPH, TB epidemiology
- Masae Kawamura, MD, IGRA implementation
- Shamim Islam, MD Pediatric Study
- Payam Nahid, MD, IGRA foreign born study

Annual TB Program Cost: Homeless Screening

QFT-Gold In-tube Test: 1,729 x $32.86 =	**$56,827**
# needing chest x-ray and MD evaluation: 0.07 x 1,729 = 121	
Chest X-ray and MD evaluation: 121 x $82.50 =	**$9,987**
TB Clinic staff time: Clerical: 30.26 hours x $28.59 = $865 Health Worker: 14.12 hours x $27.69 = $392 Nurse: 18.23 min. x 10.09 hours = $665	**$1,922**
TOTAL ANNUAL COST	**$68,736**

Homeless Cases, 2005-2012

Year	Shelter		SRO	Street/Other
	City	Private		
2005 (n=17)	3 (18%)	0	7 (41%)	7 (41%)
2006 (n=22)	2 (9%)	1 (5%)	11 (50%)	8 (36%)
2007 (n=25)	3 (12%)	1 (4%)	12 (48%)	9 (36%)
2008 (n=15)	3 (20%)	0	5 (33%)	7 (47%)
2009 (n=15)	0	0	6 (40%)	9 (60%)
2010 (n=7)	1 (14%)	1 (14%)	2 (29%)	3 (43%)
2011 (n=11)	4 (36%)	0	5 (46%)	2 (18%)
2012 (n=12)	0	0	8 (67%)	4 (33%)
Total (n=124)	16 (13%)	3 (2%)	56 (45%)	49 (40%)

Characteristics SF City Shelter Cases, 2005-2012 (1)

	City Shelter	SRO
Pulm. Smear +	47%	45%
Pulm. Culture +	80%	73%
Pulm. Cavitary	0	36%
HIV +	36%	33%
Died	6%	14%

Characteristics SF HSA Shelter Cases, 2005-2012 (2)

	City Shelter	SRO
Converters	1	8
Clustered Cases[1]	0	9[2]

[1]*Clustered to another case in the same shelter or SRO at any time, 2005-2012.*

3 FDA approved highly specific IGRAs

QuantiFERON®-TB Gold (Cellestis Ltd., Carnegie,Australia)
- FDA cleared late 2004
- Uses ESAT-6 and CFP-10 as antigens

QuantiFERON®-TB Gold In-Tube
- FDA approved in Dec. 2007
- Uses 3 antigens affixed to inside of tube
  - Adds TB7.7 (RD4) antigen to ESAT-6 and CFP-10

T-Spot*TB*™ (Oxford Immunotec, Oxford, UK)
- FDA conditionally approved in Aug. 2008
- Use 2 antigens: ESAT-6 and CFP-10

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	Antigens	
	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	-	-

Diagnostic tools for tuberculosis infection

TB Skin Test (TST)

Interferon Gamma Release Assays (IGRAs)

# Interferon Gamma Release Assays vs. Tuberculin Skin Test

- *In vitro*
- Single antigens
- No boosting
- Not affected by BCG
- Result with one patient visit
- Minimal inter-reader variability
- Results in one day

- *In vivo*
- Multiple antigens
- Boosting
- BCG may affect results
- Two patient visits required for result
- Significant inter-reader variability
- Results in 2-3 days

QuantiFERON®-TB Gold In-Tube

Stage 1: Blood draw and Incubation

Blood drawn into three 1cc tubes

= nil antigens Mitogen
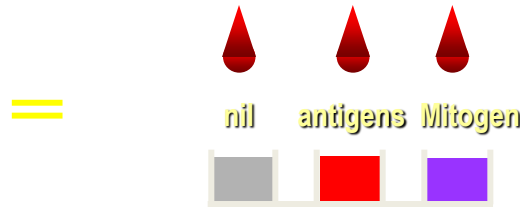
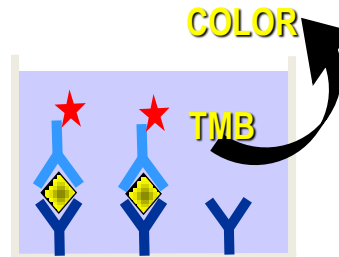**16 hour limit to get tubes Into incubator**
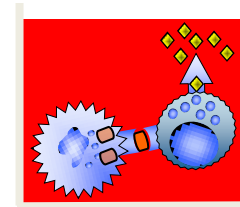
Incubate 16-24 hrs at 37°C at clinic or lab
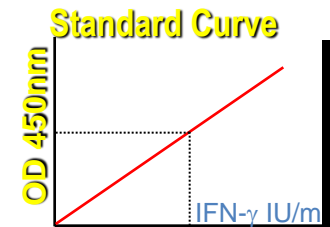
Remove and leave at room temp for up to 3 days

Stage 2: Laboratory processing and testing
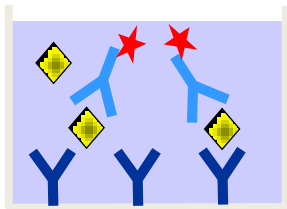
Harvest Plasma and add to antibody-coated QFT plate

COLOR

TMB

Wash, add Substrate, incubate 30 min then stop reaction

Standard Curve

OD 450nm

IFN-γ IU/m

Measure OD and determine IFN-γ levels

Report results Pos/ Neg/ Indeterminate

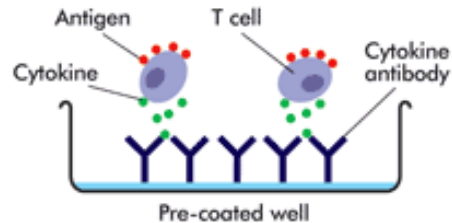# T-Spot.*TB*™

Step 1 — Collect the blood sample and centrifuge to separate Peripheral Blood Mononuclear Cells (PBMCs)

Step 2 — Wash and count the PBMCs

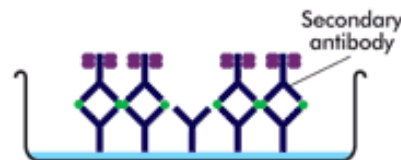**Step 3** — Add PBMCs to wells with antigens and incubate overnight (37°C, CO_2)

Antigen — T cell — Cytokine — Cytokine antibody — Pre-coated well

Step 4 — Wash and add secondary antibody

Secondary antibody

Step 5 — Add substrate and count any resulting spots. One spot = one T cell

Nil Control

Infection

Infection

Positive Control

Oxford Immunotec

TITLE

Bullet 1: Point 1

Bullet 2: Point 2