IGRA Use in HIV-Infected Patients: Efficacy and Operational/Cost Considerations

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Problems with TST…

Poor inter-reader reliability

9 mm (negative) vs. 10mm (positive)?

False-positives/specificity

- NTM infection
- Prior BCG

Poor positive-predictive value in low prevalence populations (like U.S.)

Cost/time of patient visits

- Unread tests

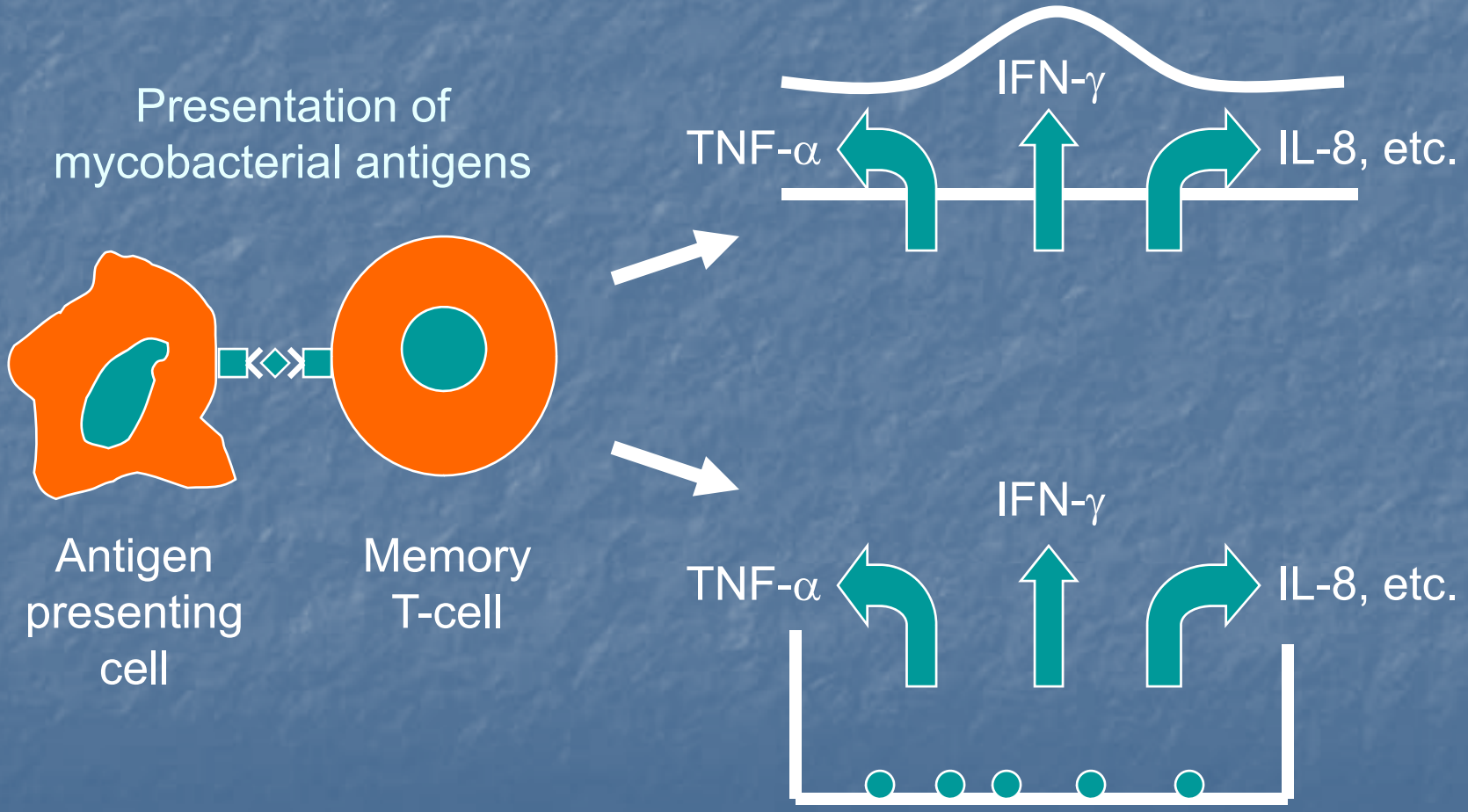
Sensitivity?

- Reaction wanes over time
- Lack of gold standard

Program Implications of a More Specific Blood Based TB test

- ↓ Societal costs and ↑public safety: Elimination of unnecessary CXRs, evaluation and treatment
- ↑ Program efficiency: More results means targeting efforts on “positives” instead of on retesting individuals who fail to show up for TST readings (homeless, jails, employee testing)
- ↑ Public confidence : Reliable and specific results
- New surveillance capabilities: laboratory based targeted testing

In Vivo and In Vitro Diagnostic Tests



Andersen P, et al. Lancet 2000;356:1099

Interferon Gamma Release Assays vs. Tuberculin Skin Test

IGRA	TST
In vitro	*In vivo*
Single antigens	Multiple antigens
No boosting	Boosting
Not affected by BCG or most NTM	May be affected
One patient visit	Two patient visits
Minimal inter-reader variability	Significant inter-reader variability
Results in one day	Results in 2-3 days

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	-	-

FDA approved IGRAs (2)

- QuantiFERON®-TB 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*™
  - FDA conditionally approved in Aug. 2008
  - Use 2 antigens: ESAT-6 and CFP-10

QuantiFERON®-TB In-Tube

Stage 1: Blood draw and Incubation

Blood drawn into three 1cc tubes

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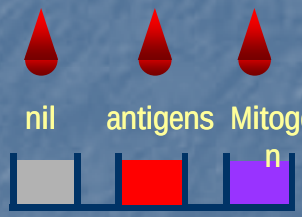


16 hour limit to get tubes Into incubator

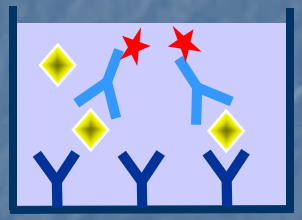
→

Incubate 16-24 hrs at 37°C at clinic or lab

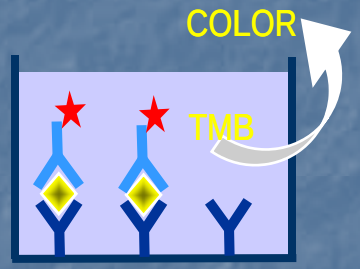
→

Remove and leave at room temp for up to 3 days

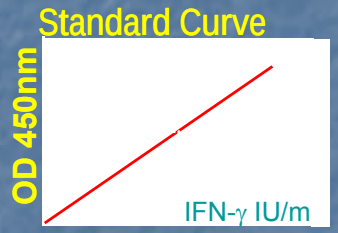
Stage 2: Laboratory processing and testing



Harvest Plasma and add to antibody-coated QFT plate



Wash, add Substrate, incubate 30 min then stop reaction



Measure OD and determine IFN-γ levels

Report results
Pos/ Neg/ Indeterminate

*graphics source – Cellestis, Australia

QuantiFERON®-TB Gold

Principle of the Test:

Compare IFN-γ levels of the antigen well to the 2 controls wells.

TB Antigen – Nil	Mitogen – Nil	Result
≥ 0.35 IU and > 25% of Nil	Any	Positive
Nil ≤ 8.0 and (<0.35 or	≥ 0.5	Negative
≥0.35 IU and < 25% of Nil result)	<0.5	Indeterminate
Nil >8.0 but peptide less than 50% above Nil	Any	

Operational Issues

	QFT-G	QFT-GIT	Tspot
12 hour limit to get blood to lab	YES	NO	YES
Human resources	MOD	LEAST	MOST
Methodology	FAMILIAR	FAMILIAR	NEW
Automation	PARTIAL	FULL	MANUAL
Effects of altitude and temperature	T°=YES Alt=no	T°=YES Alt=yes	T°=YES Alt=no
Detection of test failure	YES	YES	YES

2004 QFT-G CDC Guidelines

***MMWR*. December 16, 2004 / Vol. 54 / No. 49**

- QFT-G can be used in all situations where the skin test is currently being used

  -includes contact investigation, immigrant evaluation and serial testing of HCWs

- Use with caution when interpreting negative QFT results in children, immunocompromised, and HIV-infected adults because of limited data

NOTE: Over 200 published articles since 2004. New guidelines are currently being developed for IGRAs by CDC. Completion expected by end of 2008

Table 1. **Summary of Sensitivity from Pooled Estimates from All Studies***

Variable	Studies, *n*	Sensitivity (95% CI)†	Chi-Square Test for Heterogeneity
Tuberculin skin testing			
All studies	14	0.71 (0.65–0.74)	61.4 (0.001)
Size of reaction, *mm*			
5	9	0.74 (0.66–0.82)	23.5 (0.001)
10	4	0.72 (0.50–0.95)	18.0 (0.01)
15	1	0.40 (0.25–0.56)	–
Sample			
Pediatric	4	0.55 (0.43–0.67)	17.4 (0.01)
Adult	10	0.73 (0.68–0.78)	35.7 (0.001)
QuantiFERON			
All studies	13	0.76 (0.7–0.83)	38 (0.001)
Antigens			
ESAT-6 only	1	0.58 (0.34–0.80)	–
ESAT-6/CFP-10	9	0.80 (0.73–0.87)	20.9 (0.001)
ESAT-6/CFP-10 and TB7.7	3	0.67 (0.56–0.78)	6.8 (0.05)
Sample			
Pediatric	4	0.66 (0.5–0.83)	11.0 (0.01)
Adult	10	0.76 (0.7–0.83)	32.5 (0.001)
Elispot or T-SPOT.TB			
All studies	12	0.88 (0.81–0.95)	57.3 (0.001)
Antigens			
ESAT-6	3	0.93 (0.91–0.96)	0.8 (NS)
ESAT-6/CFP-10	9	0.87 (0.78–0.95)	51.7 (0.001)
Sample			
Pediatric	2	0.62 (0.43–0.81)	3.0 (0.08)
Adult	10	0.92 (0.88–0.95)	17.1 (0.001)

* Patients with active tuberculosis were used as surrogates for latent tuberculosis. NS = not significant.
† All 95% CIs are corrected for overdispersion.

Table 2. Summary of Specificity from Pooled Estimates from Studies of Persons at Very Low Risk for Tuberculosis Infection*

Grouping	Studies, *n*	Specificity (95% CI)	Chi-Square Test for Heterogeneity	*P* Value
Tuberculin skin testing				
All studies	8	0.66 (0.46–0.86)	251	0.001
BCG vaccination				
Not vaccinated	3	0.98 (0.96–1.0)	4.0	NS
Vaccinated	5	0.56 (0.34–0.78)	122	0.001
Criteria				
Positive ≥10 mm	6†	0.58 (0.37–0.79)	155	0.001
Positive ≥15 mm	3†	0.87 (0.7–1.0)	31.4	0.001
QuantiFERON				
All studies	9‡	0.97 (0.95–0.99)	25.4	0.01
ESAT-6	2	1.0 (0.94–1.0)	0	
ESAT-6 and CFP-10	7	0.96 (0.94–0.99)	17.6	0.01
BCG vaccination				
Not vaccinated	3	1.0 (0.94–1.0)	0	
Vaccinated	6	0.96 (0.93–0.99)	14.3	0.02
Elispot or T-SPOT.TB				
All studies	4	0.92 (0.88–0.95)	21.3	0.01

* BCG = bacille Calmette–Guérin; NS = not significant.

† In 1 study (30), data for 2 tuberculin skin test cut-points are given.

‡ In each of 2 studies (68, 69), 2 different very-low-risk populations were tested. These were counted as separate studies.

Performance of QFT-GIT in HIV-infected Adults, San Francisco

- 294 HIV-infected adults
- Methods: TST and QFT-GIT
- Results:
  - 70% returned for evaluable TST
  - 85% concordance for -/-, 4.1% for +/+
  - Indeterminate QFT results in 5.1%, indeterminate and negative results generally increased when CD4 decreased; RR of indeterminates w/ CD4 <100 was 4.24. Indeterminates all due to low IG levels in mitogen control. See Table 2.

Luetkemeyer AF, et. Al. Am J Respir Crit Care Med 2007; 175 (7): 737-742.

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 (4/08-11/08)	7 % n=483	23 % n=613	-	-
Decline in positive rate from TST	↓ 73%	↓ >54%	↓ 60%	↓ 62%

Updated

San Francisco TB Control