

Testing for Latent TB Infection:

Recent Advances and Implications for Occupational Health

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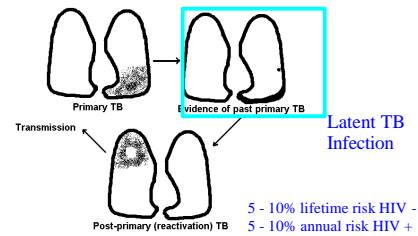


Figure 1. Stages of tuberculosis: (1) primary TB in the lower left lung, resulting from the inhalation of infectious droplet nuclei, (2) primary TB usually resolves with or without treatment, but sometimes leaves scars, as evidenced in the left lower lung, (3) months to years later, reactivation of infectious foci, often in the upper lung, leads to the chronic form of the disease, with lung cavitation. It is the cavitory form of the disease that is most likely to be infectious to others.

5 - 10% lifetime risk HIV -
 5 - 10% annual risk HIV +

TB Screening with Tuberculin Skin Testing (TST)

Problems:

- Placement errors
- Boosting
- False positives:
 - BCG
 - Nontuberculous mycobacteria
 - Reading error



Current US Risk Groups for TB

What is a positive PPD? (CDC, 1989)

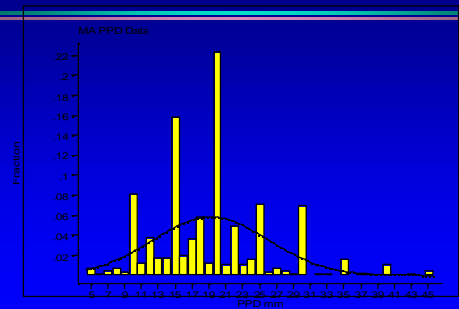
- **Highest risk groups (5 mm cut-off)**
 - Contacts*
 - HIV-infected (or high risk for HIV, untested)
 - Abnormal CXR: "old TB"
- **Moderate risk groups (10 mm)**
 - (next slide)
- **Low risk groups (15 mm)**
 - No recognized risk factors

Test Only High and Moderate risk groups

- **Low risk persons should NOT be tested**
 - PPD is a sensitive, but not very specific test
 - 10 mm reaction increasingly likely to represent cross-reactivity with environmental mycobacteria, BCG
 - raises unnecessary concern, x-rays, treatment
 - leads to more testing
 - diverts and dilutes efforts toward high-risk groups
- Most school and other mandatory testing is not warranted in the US today

Tuberculin Reaction Size

544 Culture + MA TB cases



PPD - Terminal digit preference

- Under low prevalence conditions, results in some misclassification into the “positive” range.
- 10 mm reactions may not always represent true infection

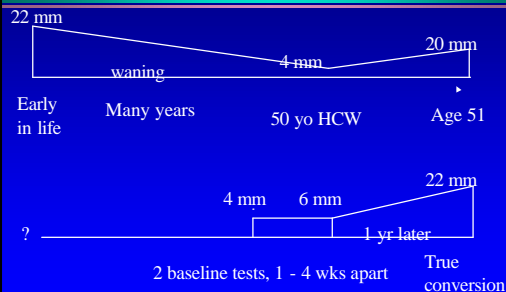
PPD Testing - technical issues

- 5 TU *Aplisol** or *Tubersol*
 - some large red reactions with *Aplisol*
- read 48 to 72 hrs, but late reactions occur
 - elderly and first time tested
- read induration only, across the arm only, and record in mm, including “0” mm
- “pos” or “neg” is not acceptable

PPD boosting

- PPD reactivity due to TB infection, BCG vaccination, and environmental mycobacteria all wane over many years
 - first PPD after many years may be neg, but itself serves to recall waned hypersensitivity
 - subsequent PPD (1 week to years later) may react fully, giving the appearance of “conversion”

Boosting and 2-Step testing



TB Screening with Tuberculin Skin Testing (TST)

Problems:

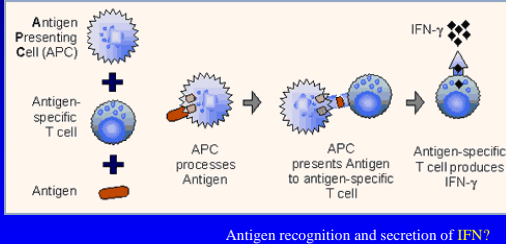
- False negatives
 - Host factors (drugs, illness)
 - Anergy
- Patients don't return
- Confusing cut-offs
- Time consuming



New test for TB Screening: QuantiFERON™ (QFT)

- Whole blood IFN- γ release assay
- Measures immune reactivity to *tuberculin*
- FDA approved (2001)
- Commercially available (Cellestis, Australia)

QFT Principles

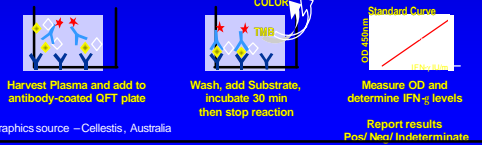


How QFT Works

Stage 1: Whole Blood-Antigen Incubation



Stage 2: IFN-gamma ELISA



*graphics source –Cellestis, Australia

Skin Test vs. CLINISPT-TB by Oxford Immunotec, UK



- **False Positives**
People who have received the BCG vaccine may show up positive
- **False Negatives**
Skin reaction is a very crude measure. Small responses not picked up (real problem in immunosuppressed patients) commonly negative in active disease (only 75-80% sensitivity. Worse in immunosuppressed).
- **CLINISPT-TB is very specific:**
CLINISPT-TB does not give false positive in people with prior BCG vaccination
CLINISPT-TB does not cross-react with common non-tuberculous (atypical) mycobacteria
- **CLINISPT-TB is very sensitive:**
picks up infected people missed by the skin test works even in immunosuppressed populations picks up new infection earlier than the skin test works well in children and infants maintains sensitivity even in active TB, including all types of extrapulmonary TB

QFT Clinical Trial

- 1,226 patients at 5 sites
 - 98 low risk
 - 944 high risk
 - 94 TB suspects
 - 87 culture-confirmed TB after Rx
- QFT - TST Agreement = 83.1%

Mazurek J, et al. JAMA 2001;286:1740-1747

QFT Advantages

- Single patient visit
- Less placement variability
- Does not "boost" subsequent test responses
- Less likely positive in BCG-vaccinated
- Objective read-out – less reading variability
- Assess response to M. tuberculosis and avium
- Results available in < 24 hr.
- Cost benefits
- Culture- and ethnic-naive

Major Components of TST Program Costs

- Cost analysis of health care workers (HCW)* TST screening program
 - 4 hospitals, 2 public health departments
- Major cost components
 - TB program personnel costs
 - Time taken off by HCW
- Supplies (tuberculin, etc) only 0.5–0.9% of TST screening program costs

*L. Lambert et al, Infect Cont Hosp Epidemiol; 2003: 814-820

Conclusions

- QFT-Gold is highly specific (~100%)
 - Unaffected by BCG
 - Specificity for the TST (@ 10mm) was 35.6%
 - Many had been BCG vaccinated up to 4 times
- Excellent sensitivity (89%) in untreated TB
 - Sensitivity of the TST was 65.6% (untreated TB)

QFT - 3G

- Newest QFT test; *not yet FDA-approved*
- Human PPD antigen replaced with ESAT-6, MCP-10
 - Antigen proteins found on mTB, ***NOT on BCG***
 - Antigen placed into individual blood tubes: *no need to plate out in culture wells to stimulate*
- Preliminary studies demonstrate enhanced sensitivity, ability to discriminate mTB infection vs BCG

Mazurek, J., CDC

QFT Study II: Objectives

(John Bernardo, MD, BUMC)

- TST vs QFT-3G in:
 - ≥ 7 y/o
 - Contacts
 - Cases/suspects
 - Low risk persons (e.g. pre-employment PPD)
- Validate use of 3G tubes
 - to eliminate plating of blood
- Test effect of prior TST on QFT results

Implementation: the San Francisco Experience

SF TB Control Plan - 1st gen QFT

Presented by Chuck Daley, MD, ATS 2004

Plan: Change from TST to QFT for TB screening of high-risk populations

Process:

- Political commitment from DPH
- Generate demand for QFT at community screening sites
- Develop lab infrastructure
- Implement switch and evaluate

TB Control Barriers

- Staff reluctance
- TST suddenly looks great !
- Fear of change and the unknown
- Lack of "green light" from CDC
 - Not yet recommended for key populations: HIV+, suspects, contacts

Solution: TB controller leadership

Political Commitment

- Health Officer supported switch
 - Rationale: improve homeless screening but...
 - General DPH budget – new funds not available
- CTCA QFT position statement
 - Useful foundation for advocacy

Community Providers

- Select sites serving high-risk populations
 - Homeless providers
 - Immigrant / refugee clinics
 - Methadone clinics
- TST screenings –12,000 tests / year
- Problem: community clinics facing service and staff cuts

*"Make the test available and we'll order it."
"We don't have the money to pay for it."*

Lab Resource Estimates to Run 10,000 QFT/year

	TB Control	DPH Lab	Hosp Lab
Hours/day	2	6	8
Staff FTE	0.4	1.0	2.0
Equipment	Existing	New	New

"Find us the money and staff for the test and we'll make it available"

Cost Estimates (Sticker Shock)

10,000 QFT/yr @ \$9/test = \$90,000
 1 FTE for lab (w/ benefits)= \$85,000
 Equipment + misc. = \$5,000

 = \$180,000 per year

Costs and Reimbursements for Recent Laboratory Tests, San Francisco, 2002

Test	Lab FTE Required *	Total Annual Cost *	Medicare Reimburses (per test)
HIV viral load	1.25	\$806,000	\$119
Urine chlamydia screening	1.2	\$902,000	\$27
QuantiFERON	1	\$180,000	n/a

* Per 10,000 tests

Lab Resource Solution

- Program funding identified
 - Unused rollover funds
 - 1 FTE provided to DPH lab

Rationale: As QFT implemented and benefits realized, community support may develop

Site Implementation process

- Discuss QFT with site management
- Provider education
- Clinic site adapts protocols for local program
- Clinic site establishes lab courier – blood to lab by 4 pm

QFT Eligible Populations

- Adults with TB risk factors
 - Targeted testing program sites
- Exclusions based on current FDA approval
 - HIV positive
 - Immunocompromised
 - Children / pregnant
 - TB case contacts

Provider Guidelines

City and County of San Francisco
Department of Public Health
Tuberculosis Control Section

QuantiFERON® TB Blood Test
Provider Information and Guidelines for Interpretation

What is it?
The QuantiFERON TB test (QFT) is a blood test used to help identify latent tuberculosis (TB) infection. It is not intended to detect active TB, only TB infection. The QFT measures the immune system's response to Mycobacterium tuberculosis by measuring interferon-γ (IFN-γ). This test was approved by the U.S. Food and Drug Administration (FDA) in 2010.

How does it work?
Blood samples are mixed with antigen protein substances that are used to elicit immune reactions. After 48 to 72 hours, the immune system naturally controls active infection. The test measures the amount of IFN-γ.

What are the advantages?

- Only needs a single blood draw. Does not require sputum or chest x-rays.
- Does not need a technician. Minimal training, which can be taught and tested (certification is not required).
- Results return to provider within 2-3 weeks.

What are the disadvantages?

- Any TB test should be confirmed with a second test.

Frequently Asked Questions

City and County of San Francisco
TB Control Section
Department of Public Health

QuantiFERON® TB Blood Test
Frequently Asked Questions

What is the purpose of the QFT?

1. To help identify latent tuberculosis infection (LTBI).
2. To help identify individuals who are at high risk of developing active TB disease.
3. To help identify individuals who are at high risk of transmitting TB disease to others.

Who should be tested?

- Individuals who are at high risk of developing TB disease.
- Individuals who are at high risk of transmitting TB disease to others.
- Individuals who are at high risk of developing TB disease and who are also at high risk of transmitting TB disease to others.

How is the test performed?

- A blood sample is drawn from the individual.
- The blood sample is sent to a laboratory for testing.
- The results are returned to the provider within 2-3 weeks.

What are the results?

- Positive: Indicates latent tuberculosis infection (LTBI).
- Negative: Indicates no evidence of TB infection.
- Invalid: Indicates that the test results are unreliable.

TB Screening Log

SFPDH Tuberculosis Screening Log

Subtest ID	Screening	QFT Result	QFT Interpretation	Referral to TB clinic?
1001	QFT	POS	Latent TB Infection	Yes
1002	QFT	NEG	No TB Infection	No
1003	QFT	POS	Latent TB Infection	Yes
1004	QFT	NEG	No TB Infection	No
1005	QFT	POS	Latent TB Infection	Yes
1006	QFT	NEG	No TB Infection	No
1007	QFT	POS	Latent TB Infection	Yes
1008	QFT	NEG	No TB Infection	No
1009	QFT	POS	Latent TB Infection	Yes
1010	QFT	NEG	No TB Infection	No

Communication of QFT Results Back to Ordering Providers

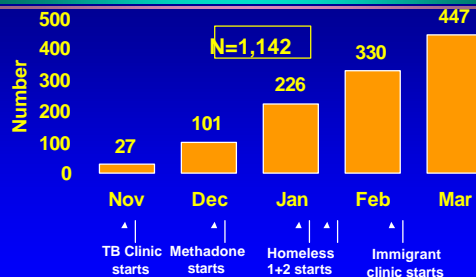
The screenshot shows a web portal interface for viewing test results. A red arrow points to a box labeled "QFT results" on the screen. The interface includes a sidebar with navigation options and a main content area displaying patient information and test results.

SF QFT Implementation Results

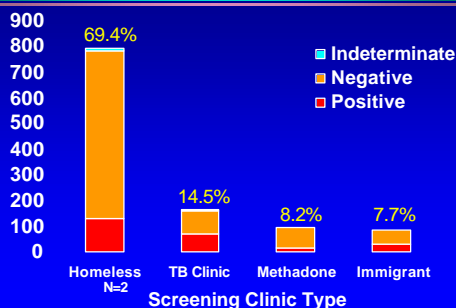
November 2003 – March 2004

- 4 Community clinic sites + TB clinic
 - 2 Homeless, 1 methadone, 1 immigrant
- 1190 patients evaluated by QFT
- 48 (3.8%) specimens rejected
 - Insufficient, clotted, or late sample
- 1142 specimens tested

Number of New Patients Evaluated Monthly by QuantiFERON, San Francisco, Nov. 2003 - Mar. 2004



QFT Test Utilization by Screening Site



QFT Test Results by Screening Site

	Homeless n=794 (%)	TB Clinic n=166 (%)	Methadone n=94 (%)	Immigrant n=88 (%)
Positive	131 (17)	68 (41)	17 (18)	28 (32)
Negative	655 (82)	94 (57)	76 (81)	60 (68)
Indetermin.	8 (1)	4 (2)	1 (1)	0 (0)

*48 (3.8%) not tested due to insufficient or late specimens

QFT Implementation Summary

- Implementation feasible
- Number of participating clinics increasing
- Number of tests increasing
- High satisfaction with TB screening process improvements
- Infrastructure in place for improved QFT tests

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