

## Tuberculin Skin Testing (TST)

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### Objectives

- Describe the steps in placing and reading a TST
- Describe the classification system (cut-offs) for Mantoux skin test
- Define “TST conversion”
- Describe the “booster” phenomenon
- Explain how TST results are interpreted for Bacille Calmette-Guerin (BCG) vaccinated individuals
- Compare and contrast TST and QuantiFERON®-Gold (QFT-G) results
- Describe best practices for targeted testing

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### Overview

- Background
- Definition of the TST
- Review of administration and reading of the TST
- Identifying the classification system
- “TST conversion” vs. “booster phenomenon”
- BCG
- TST vs. QFT
- Best practices for targeted testing
- Discussion/questions

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## Background on the TST

- March 24, 1882, Robert Koch announced to the Berlin Physiological Society that he had discovered the cause of TB
- Koch announces the discovery of tuberculin, a substance derived from tubercle bacilli, which he thought was capable of arresting bacterial development *in vitro* and in animals
- Development of the TST by Von Pirquet and Mantoux in 1907-1908, and preparation of purified protein derivative (PPD) of tuberculin by Seibert in 1931



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## Just What Does PPD Stand For?

### Purified Protein Derivative

- Tuberculin is a glycerine extract of the tubercle bacilli. PPD tuberculin is a precipitate of non-species-specific molecules obtained from filtrates of sterilized, concentrated cultures
- The test is named after Charles Mantoux, a French physician who built on the work of Koch and Clemens von Pirquet to create his test in 1907

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## Why Do a Skin Test?



- “Screening is done to identify **infected** persons at high risk of disease who would **benefit from treatment of latent TB (formally preventive therapy)** and to find persons with clinical disease in need of treatment.”

*1998 APIC Guidelines Committee*

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### Before You Give That Skin Test...

- Question the client carefully:
  - Have you ever had a skin test before? When? Why?
  - Have you ever been tested for TB?
  - If you had a skin test, did it swell up?
  - If you had a skin test, did you have a chest x-ray after the skin test was read?
  - Did anyone ever say your skin test was "positive"?

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### Before You Give That Skin Test... (2)

- For you to consider:
  - Can we give this person another PPD if they say they were positive in the past?
  - What will happen if we do?

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### Mantoux TST

- Standard
  - Historically the preferred and most accurate method of identifying persons infected with *Mycobacterium tuberculosis (M. tb)*



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## Administration of the Skin Test

- Use an area free of veins or lesions
- A discrete, pale elevation (or tense, white, wheal) should be produced
  - Approximately 6 mm-10 mm



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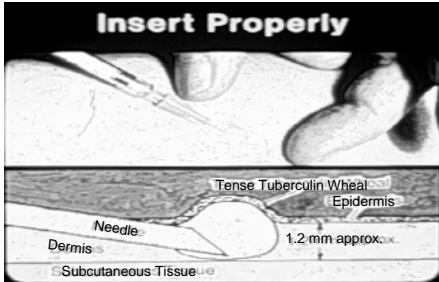
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### Insert Properly



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### Measure Induration Only Across the Arm



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### Reading the Skin Test

- Optimally read @ 48-72 hours
- Look for the presence or absence of palpable induration
- Just measure "induration"
- Must be read by a healthcare professional **trained** to read TST



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### Classifying the Tuberculin Reaction

**\*5 mm or more is positive:**

- Persons known to have or suspected of having HIV infection
- Close contacts of a person with infectious TB
- Persons who have a chest radiography suggestive of previous TB

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### Classifying the Tuberculin Reaction (2)

**\*10 mm is positive in:**

- Persons with certain medical conditions, excluding HIV infection
- Persons who inject drugs (if HIV negative)
- Foreign-born persons from areas where TB is endemic
- Medically underserved, low-income populations
- Residents of long-term care facilities
- Children younger than 4 years of age
- Locally identified high-prevalence groups

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## Classifying the Tuberculin Reaction (3)

\*15 mm or more is positive in:

- Persons with no known risk factors for TB

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## Yeah, But...

- 00 mm test does **NOT** exclude the possibility of TB infection or disease
- **False-negative**
  - improper administration
  - recent infection
  - immunosuppression
  - active disease



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## The Client Had Measles, Mumps, and Rubella (MMR) Recently...



- Determine when **exactly** the vaccination was administered
- If > 4-6 weeks, give the PPD
- Recent vaccination may produce false negative result

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## BCG

- Stands for Bacille Calmette Guerin
  - derived from a strain of *M. Bovis*
  - not accepted/recognized in U.S. as protection against TB
  - not standardized vaccine
  - efficacy studies range from 0-80%
  - consider patient to be **TB infected** if PPD positive

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## Booster Phenomenon

- A patient infected in the distant past, may lose the ability to “mount” a response to PPD
- Reaction to PPD gradually “waned” over time
- For example, an adult infected with TB during childhood, may demonstrate a “negative reaction” (00 mm-9 mm) to an initial PPD
- Subsequent PPDs may “boost” or “tease” the reaction to a larger reaction  $\geq 10$ mm and wrongfully be considered a conversion

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## Conversion

- A tuberculin test conversion is defined as an **increase of 10 mm** or more **within a 2-year period**, regardless of age
- For example:
  - 5/10/05 PPD 4 mm
  - 3/17/07 PPD 16 mm

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## Two-step Testing

- In an effort to avoid misinterpretation of “new” infection/or conversion, the two-step testing procedure is advised and ideal especially in those situations where persons will be retested periodically, such as in the case of healthcare workers (HCWs)
- It follows the idea that often persons may demonstrate a negative skin test reaction when tested years after they were initially infected. An initial skin test may stimulate the ability to react to tuberculin (aka the “Booster Phenomenon”)

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## Two-step Testing (2)

- The procedure is as follows:
  - Initial PPD is placed followed by the reading 48-72 hours later
    - If first test is positive, consider the person infected
    - If first test is negative, repeat PPD within 1-3 weeks, followed by the reading 48-72 hours later
  - If second test is positive, consider person infected
  - If second test is negative, consider person uninfected

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## A Word About Anergy Testing

- Anergy basically is an inability to mount a reaction by the body's defense mechanisms when foreign substances come into contact with the body
  - For example, the tuberculin reaction will occur weakly, thus compromising the value of Mantoux testing
- Anergy is present, for example, in AIDS and other co-morbidities which impair the immune system
- Routine anergy skin testing is **NOT** recommended

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### Points to Ponder

- TST is **NOT** simple
- If done correctly, TB testing can yield valuable information
- When done incorrectly, potential problems arise
- Education of providers and consumers is critical
- Is there something easier...?

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### Let's Put Your Knowledge To the Test!

- Juan Valdez presents with a request for a PPD today. He is from the Dominican Republic and needs a PPD for work. He has heard prior vaccination with BCG in his country prevents him from getting a PPD today. You tell him...
- Mrs. O'Malley is pregnant for the 9<sup>th</sup> time and is being sent for a PPD after her latest vacation in Hong Kong. She is not too keen on the PPD and fears she may be placing her baby at risk. Is she correct?

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### Let's Put Your Knowledge To the Test! (2)

- Oscar, an 87 year old new resident from your favorite nursing home has a PPD reading of 4 mm. He thinks he has picked it up from Lois, his new girlfriend. How do you want to proceed with this?

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## QuantiFERON®-Gold (QFT-G)

- As a potential replacement for the Mantoux test in time, QFT-G is a blood test that measures the ability of the patient's immune system to react to the presence of TB bacteria ignoring other artifacts such as BCG and other commonly encountered non-tuberculous bacteria
- This new method intends to be useful for initial and serial testing of persons with an increased risk of *M. tb* infection
- Guidelines for the use of QFT-G were released by the CDC in December 2005

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## QFT-G (2)

- QFT-G is FDA approved in the U.S.
- Uses TB specific antigens in place of PPDs
  - ESAT-6 and CFP-10
- Blood culture stage is unchanged from *QFT-TB*
- Uses a more sensitive ELISA for IFN- $\gamma$ 
  - 2 hour incubation
  - Limit of detection 0.05 IU/mL (compared with 1.5 IU/mL for QFT-TB)

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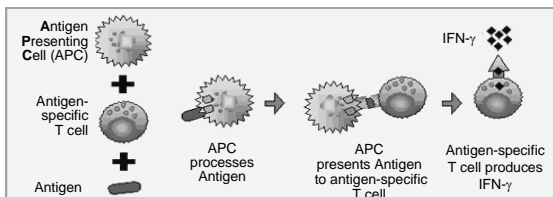
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## QFT: Ag recognition and IFN-g Secretion



This (ELISA) test detects the release of interferon-gamma (IFN-g) in fresh heparinized whole blood when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tb*: ESAT-6 and CFP-10. ESAT-6 and CFP-10 are secreted by all *M. tb* and pathogenic *M. bovis* strains.

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## QuantiFERON®-TB Gold Method

**Stage 1 Whole Blood Culture**

**Stage 2 IFN- $\gamma$  ELISA**

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## Species Specificity of ESAT-6 and CFP-10

Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
<i>M. tuberculosis</i>	+	+	<i>M. abscessus</i>	-	-
<i>M. africanum</i>	+	+	<i>M. avium</i>	-	-
<i>M. bovis</i>	+	+	<i>M. branderi</i>	-	-
BCG substrain			<i>M. celatum</i>	-	-
gothenburg	-	-	<i>M. chelonae</i>	-	-
moreau	-	-	<i>M. fortuitum</i>	-	-
tice	-	-	<i>M. gordonii</i>	-	-
tokyo	-	-	<i>M. intracellulare</i>	-	-
danish	-	-	<i>M. kansasii</i>	+	+
glaxo	-	-	<i>M. malmoense</i>	-	-
montreal	-	-	<i>M. marinum</i>	+	+
pasteur	-	-	<i>M. oenavense</i>	-	-
			<i>M. scrofulaceum</i>	-	-
			<i>M. smegmatis</i>	-	-
			<i>M. szulgai</i>	+	+
			<i>M. terre</i>	-	-
			<i>M. vaccae</i>	-	-
			<i>M. xenopi</i>	-	-

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## QFT-G Advantages

- Single patient visit
- Does not “boost” subsequent test responses
- Less likely positive in BCG-vaccinated
- Objective read-out
- Results available in < 24 hours
- Cost benefits
- Culture- and ethnic-naïve
- **Substitute for PPD**

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## QFT-G 2006

- **CDC recommends** that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for HCWs)
- *But ...*

*CDC: MMWR 54, 12/16/2005*

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## QFT-G Limitations

- 12 hour to primary culture
- HIV-infected individuals?
- Chronic corticosteroids?
- Recipients of TNF- $\alpha$  inhibitors, immunomodulators?
- Children?
- Likely more specific, but less sensitive?

*CDC: MMWR 54, 12/16/2005*

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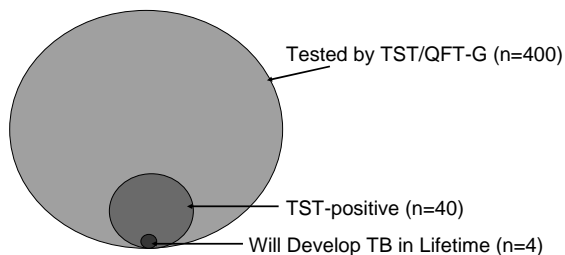
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## QFT-G 2006: Sensitivity for LTBI?



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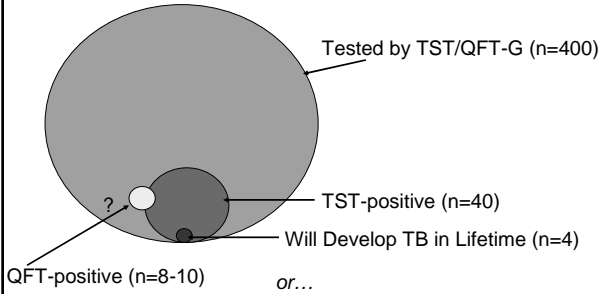
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### QFT-G 2006: Sensitivity for LTBI? (2)



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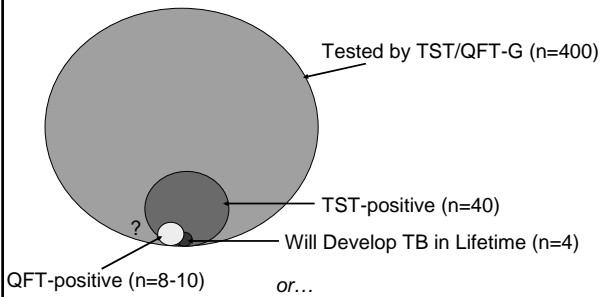
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### QFT-G 2006: Sensitivity for LTBI? (3)



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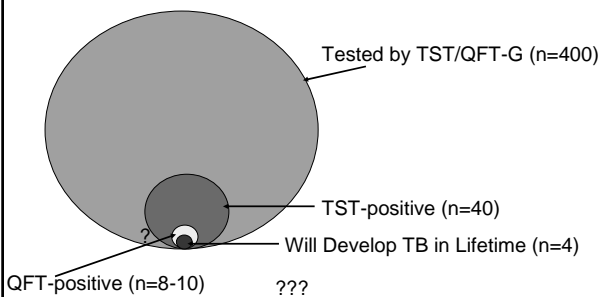
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### QFT-G 2006: Sensitivity for LTBI? (4)



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## A Few Words on QFT

- QFT not happening yet for many due to \$\$\$, lab availability, fear of the unknown...
- Continue surveillance by monitoring
- Keep up-to-date on the skills of skin testing

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## Ideas for Best Practices “Targeted Testing”



TB among homeless persons traditionally is a great public health concern. Boston's Pine Street Inn (PSI) shelter has been the center of several TB outbreaks

### TB Prevention in the Homeless




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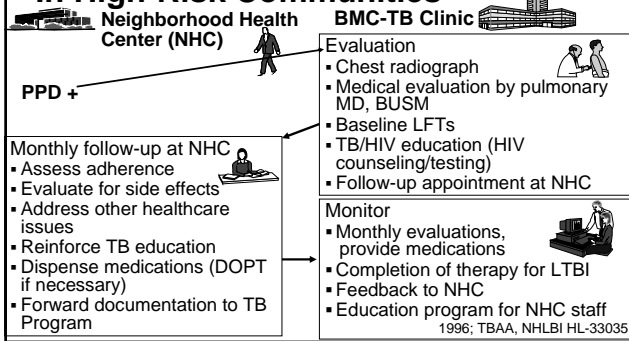
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## Community-Based TB Prevention In High-Risk Communities




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## Challenge: TB in Boston's Haitian Community



- High-risk population in Boston-metro area
  - Represent 9-13% of Massachusetts cases annually
    - Many failed to complete treatment of LTBI in past
- Divergent health belief systems
  - Use of folk healers, herbal treatments common
    - Frequent travel to Haiti to address health issues

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## Challenge: TB in Boston's Haitian Community (2)

- Divergent health belief systems (continued)
  - Distrust of Western medicine
    - Favored use of *private (ethnic) providers*
  - *Prevention of disease* not within health framework
- TB is highly stigmatized
  - Avoidance of association with TB/TB programs

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## Finally, The End... Questions?



OFFICE OF  
NATIONAL ASSOCIATION FOR THE PREVENTION OF TUBERCULOSIS,  
1 Victoria Square, London, W.C.1.

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