Testing for Latent TB Infection (LTBI)

(TST vs IGRA)

2023 GTBI TB 101 Series
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Disclosure and Disclaimer

Faculty:

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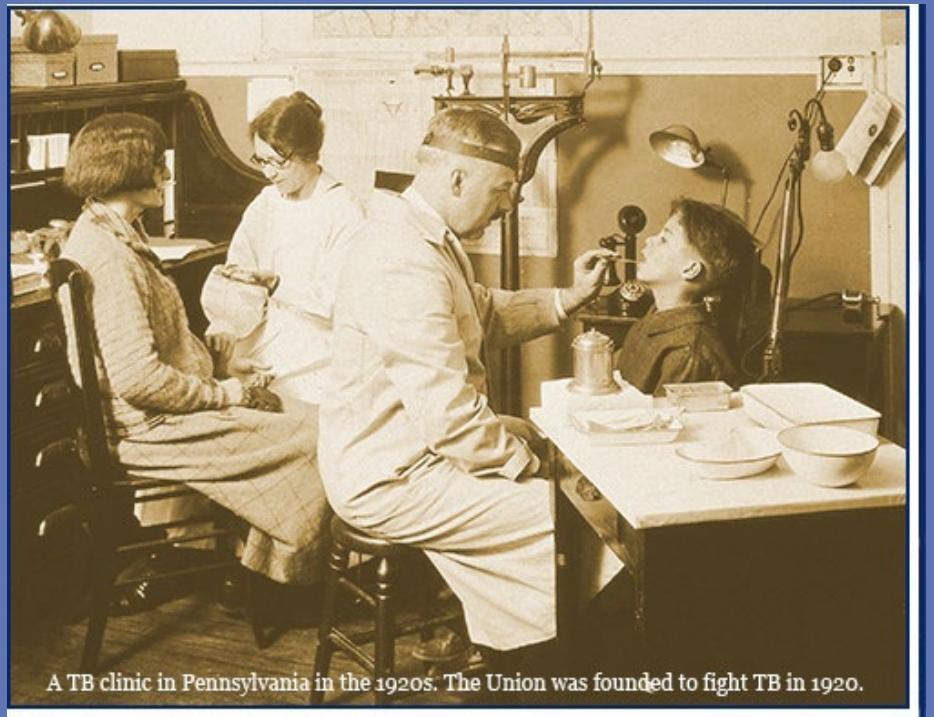
Disclosure: I have no real or perceived vested interests that relate to this presentation nor do we have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.

Tuberculosis in Pennsylvania



A TB clinic in Pennsylvania in the 1920s. The Union was founded to fight TB in 1920.

Global Burden of TB, 2021

WHO Global TB Report, 2022

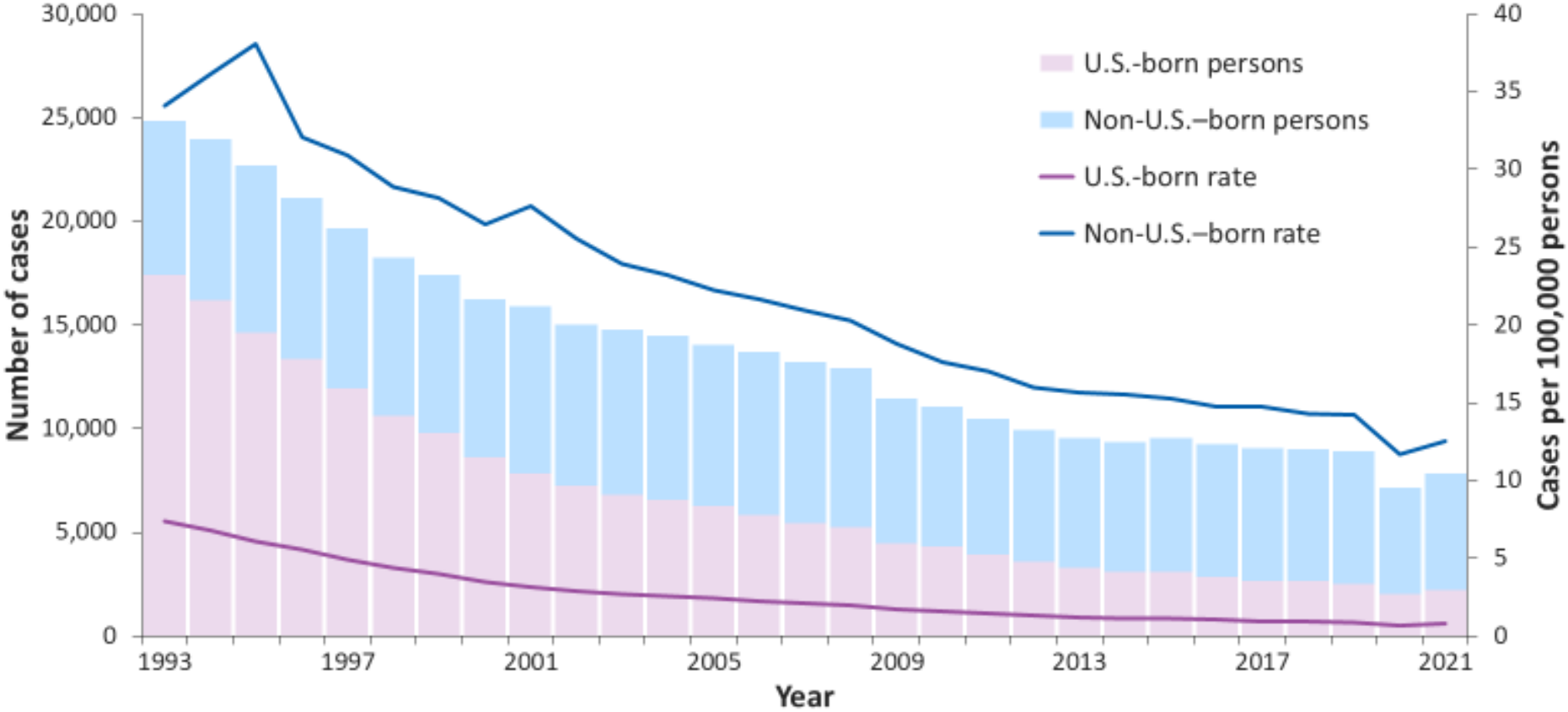
	Estimated Number of Cases	Estimated Number of Deaths
All forms of TB	10.6 million (9.6 in 2014)	1.6 million*
HIV-Associated TB	1.2 million (12%)	374,000
Multidrug-resistant TB (MDR-TB)	558,000**	~150,000

- Approx. 1/4 of the world (2 billion people) is infected with *M.tb*
- Estimated that 53 million lives were saved between 2000 and 2016 through effective diagnosis and treatment of TB and HIV
- In Children 1,000,000 cases and 140,000 deaths a year

*including 0.2 million deaths among PLHIV

**Fewer than 25% of those thought to have MDR TB were detected

TB Cases and Incidence Rates by Origin of Birth,* United States, 1993–2021



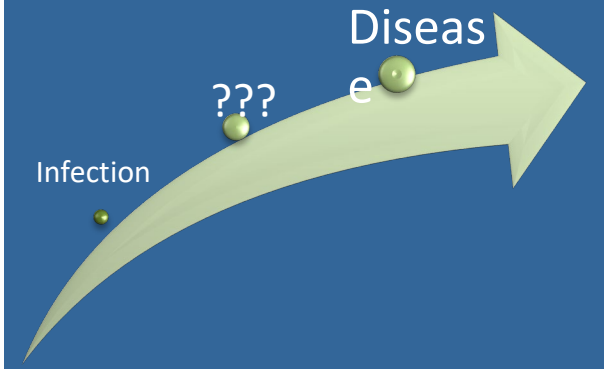
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

What are the “Hidden Stats” on TB

- Active TB cases 7,882
- Contact investigation* identifies average of 17.9 contacts/active case; 1% new active case identified; 20% LTBI; estimated over 141,000 individuals that need to be evaluated, tested and offered preventive treatment if infected.
- TB Infection (LTBI) Estimated >13,000,000 with ~ 10% risk of active TB in lifetime

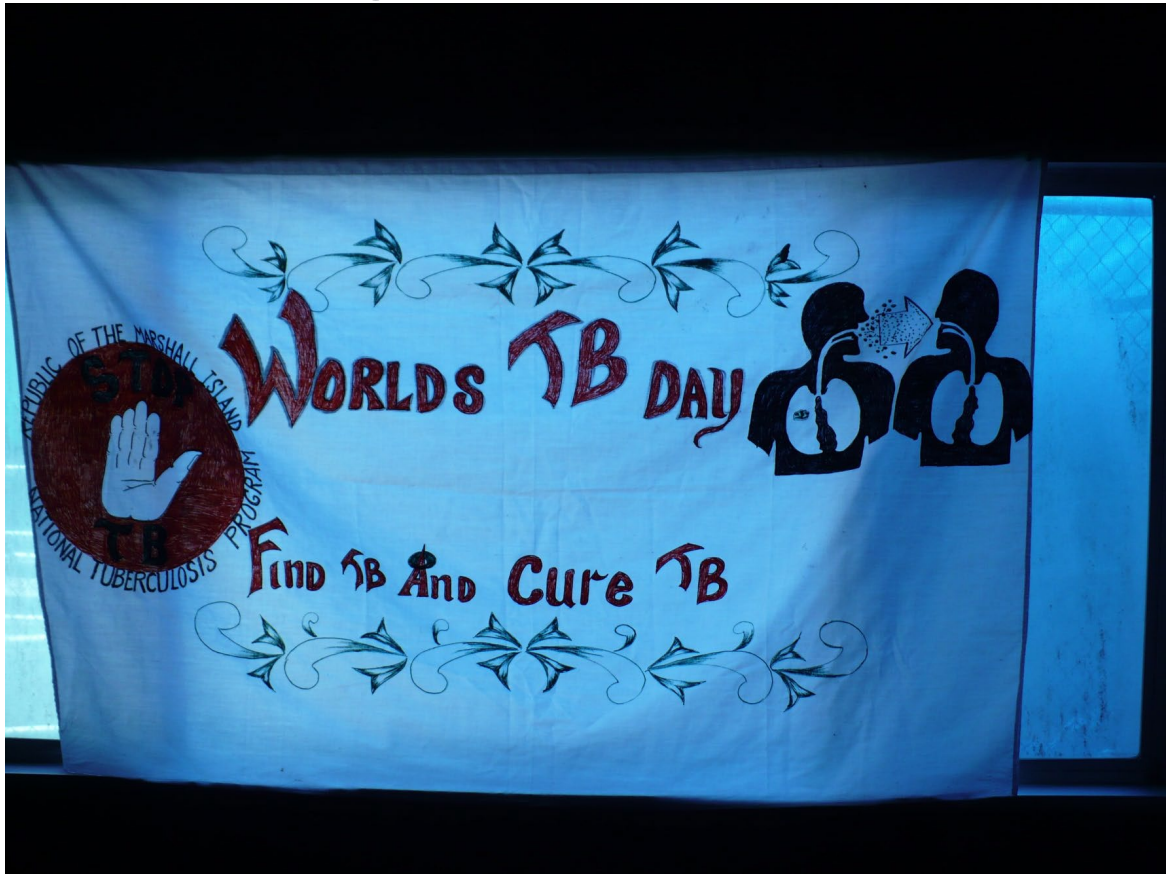
*ARPE Report US, 2010 (CDC data 2/1/2015)

Conditions that increase the risk of progression to TB disease…



- HIV infection
- Recent infection
- Chest radiograph findings suggestive of previous TB
- Diabetes mellitus
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy (chemo for CA)
- History of inadequately treated TB
- Children under 5

Testing for TB Infection



Who is NOT REQUIRED to be TB Tested before entering the US??

- Student Visa holders
- Temporary Work Visa holders
- Tourist Visa holders
- Diplomats
- Undocumented Individuals

Who No Longer Needs Yearly TB Testing: Health Care Workers

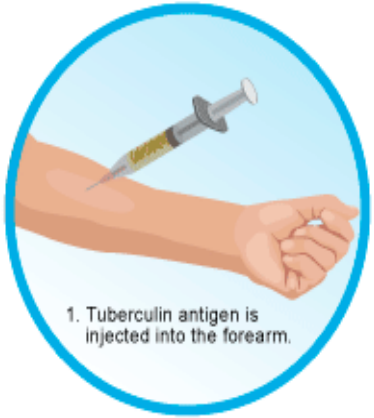
"Tuberculosis Screening, Testing and Treatment of US Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019"*

"In the absence of known exposure or evidence of ongoing TB transmission, U.S. health care personnel without LTBI should not undergo routine serial TB screening or testing at any interval after baseline (e.g., annually)"

*(MMWR, May17, 2019:Vol. 68 No. 19)

Approved tests for LTBI

QuantiFERON®-TB Gold In-Tube (Qiagen) measures interferon gamma



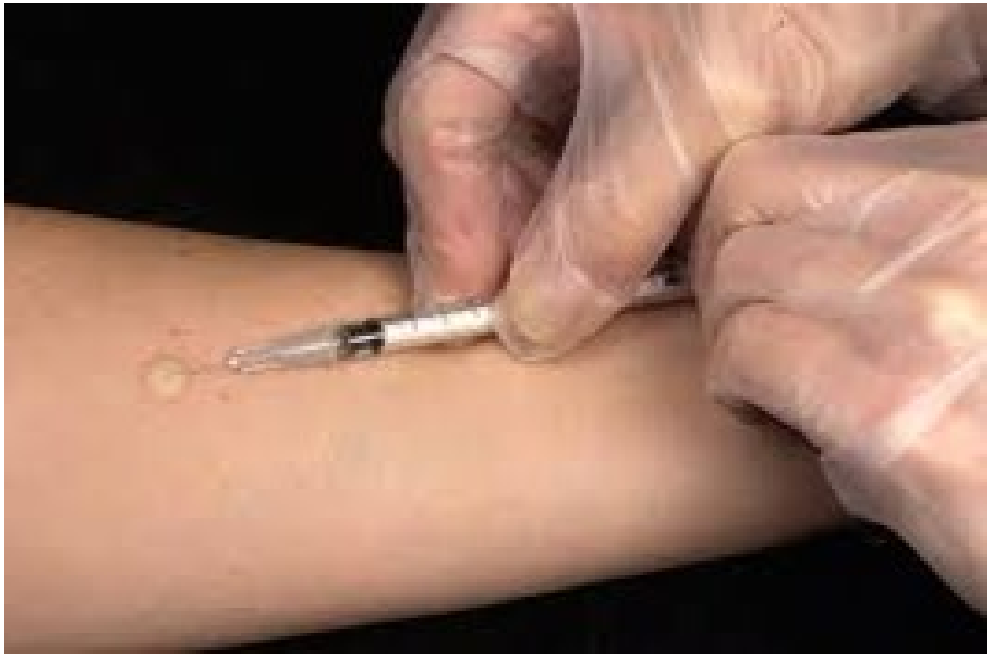
Tuberculin Skin Test

T-SPOT®.*TB* test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma

Beware of data….

TB infection testing interpretation, PPD, TST, Mantoux test (created in 1907)

- Intradermal injection of tuberculin material
- Stimulates a delayed-type hypersensitivity response mediated by T lymphocytes
- In patients with prior mycobacterial exposure, causes induration at the injection site within 48 to 72 hours



TB infection testing interpretation, PPD, TST, Mantoux test

- Interpretation depends on the risk for TB infection and the risk for progression to active TB disease

≥ 5mm	HIV + (any CD4 count)	Close contact of active contagious case	Abnormal chest radiograph with fibrotic changes consistent with old TB	Immunosuppressed patients: -TNF-alpha inhibitors -chemotherapy -organ transplantation -glucocorticoid treatment (equivalent of ≥15 mg/day prednisone for ≥1 month)
≥ 10mm	Certain conditions that increase the risk of reactivation -HD -Silicosis -Certain malignancies -DM -Malnutrition -Jejunal bypass -IVDU	Residents and employees in high-risk settings -Prisons -Jails -Healthcare facilities - Mycobacteriology labs -Homeless shelters	Children < 4 yrs age	Foreign born from countries with high incidence TB, in particular those immigrated in past 5 years
≥15mm	Healthy individuals age 4 years and older with low likelihood of true TB infection			

TB infection testing interpretation, booster phenomenon vs. conversion

- Booster response:
  - Positive PPD performed 1-4 weeks after an initial negative PPD in the absence of TB exposure
  - Sometimes done in a person who is planned for serial testing, ie.. health care workers
  - May be a sign of a remote TB infection
  - Helps to avoid misclassifying someone as a new conversion
- Conversion:
  - An increase in induration of ≥10 mm since the previous test in the setting of ongoing risk of exposure to TB
- Remember: serial PPDs will not lead to a false + PPD!

TST Return Rates

- **Return rates vary from 18% to 72%** depending on the population*
- This is especially important in high risk groups

Population	LTBI screening completion rate	Source
HIV	57%	Cheallaigh et al. (2013) *Plos One*
Immigration employees	39%	De Perio et al. (2011) *J Occup Environ Health*
Children	< 50%	Jacono et al. (2006) *Arch Pediatr Adolesc Med*

Failure to come for result reading undermines the TST

* Cheng et al. (2011) *Pediatrics* 100;210

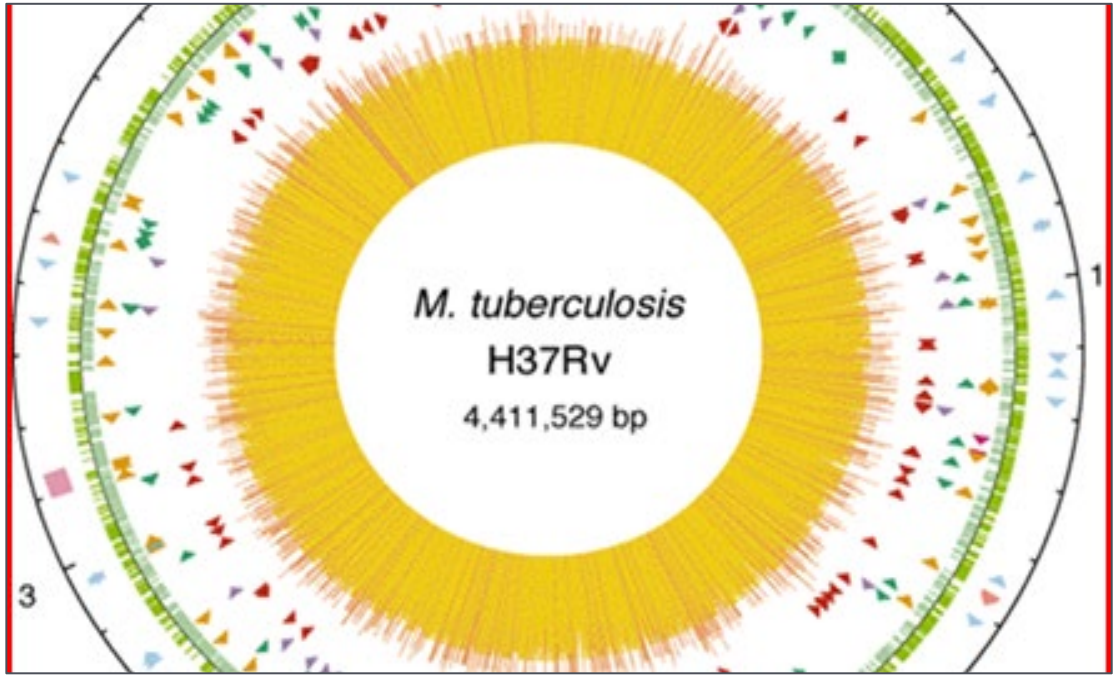
TB infection testing interpretation, PPD false +

- Non-TB mycobacteria
  - Remember TB is not the only mycobacteria- in fact there are approximately 200 NTM species out there!
- BCG vaccine, made from *Mycobacterium bovis*
  - More likely if received a booster BCG after infancy
  - Effect on the PPD wanes with time (12mm PPD in a 8 yr old vs. 12mm PPD in a 60 yr old)
  - Can look for the scar on the upper lateral arm
- Misreading
  - Should read horizontally across the forearm
  - Read induration, not erythema! Close your eyes!

TB infection testing interpretation, PPD false -

- Immunosuppression
  - HIV (esp low CD4), steroids, malignancy, TNF alpha
  - Malnourished
  - CRI
- Any active infection including active TB!
- Recent infection
  - Close contact of an active case repeat PPD in 8 wks to look for conversion
- Recent live vaccine, MMR
- Improper storage, improper administration, improper reading

Interferon γ Release Assays



TB infection testing interpretation, IGRAs

- Blood tests
- Measure T cell release of interferon-gamma following stimulation by antigens more specific to *Mycobacterium tuberculosis*
- 2 IGRA tests:
  - Quantiferon gold (plus)
    - enzyme-linked immunosorbent assay (ELISA)
  - T-spot
    - enzyme-linked immunospot (ELISPOT) assay

TB infection testing interpretation, IGRAs

- Main advantages over PPD
  - Do not cross react to a prior BCG vaccine and most other NTM
  - One stop shop
  - More automated (ie… less room for error)
  - Built in measure of immune function

- Main disadvantage over PPD
  - Not well studied children < 2 yr old
  - **Most Experts now testing all children**

TB infection testing interpretation, Quantiferon gold plus

Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

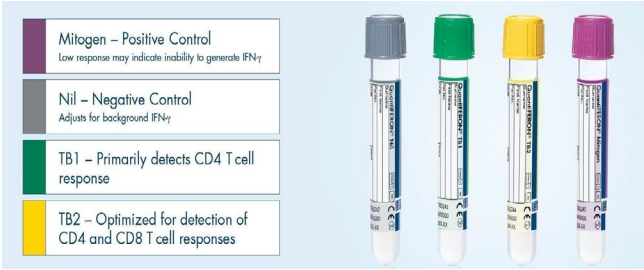
Nil – Negative Control
Adjusts for background IFN-γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

TB infection testing interpretation, Quantiferon gold plus

- Results in IU/ml
- Positive result
  - + Mitogen, - Nil, + result in **EITHER** tube 1 or tube 2
  - tube 1 or tube 2 minus nil > 0.35 IU/ml
- Negative result
  - + Mitogen, - Nil, - result in **BOTH** tube 1 and tube 2
- Indeterminate result
  - - Mitogen: immunosuppression
  - + Nil: high background noise
  - Inproper testing technique
- Remember: no test is perfect!
  - False -
    - Window period after TB infection, up to 8-12 wks
  - False +
    - *M bovis* (but NOT BCG)
    - *M kansasii, M szulgai and M marinum*
    - *Low risk patients with low TB1 or TB2 positive results*



LabCorp

SPECIMEN INFORMATION

[redacted]

Lab ref no:

COLLECTED: 02/18/2022 07:51AM LOCAL
RECEIVED: 02/18/2022
REPORTED: 02/20/2022 04:07PM ET

PATIENT INFORMATION

[redacted]

GENDER: Male
FASTING: Yes

[redacted]

Clinical Info:

REPORT STATUS: FINAL

ORDERING PHYSICIAN

[redacted]

CLIENT INFORMATION

[redacted]

Test Name	Result	Flag	Reference Range
QuantiFERON®-TB Gold Plus			
QuantiFERON Incubation	Incubation performed.	NORMAL	
QuantiFERON-TB Gold Plus	Positive	ABNORMAL	Negative
Chemiluminescence immunoassay methodology			
QuantiFERON-TB Gold Plus			
QuantiFERON Criteria	Comment	NORMAL	
The QuantiFERON-TB Gold Plus result is determined by subtracting the Nil value from either TB antigen (Ag) tube. The mitogen tube serves as a control for the test.			
QuantiFERON TB1 Ag Value	1.77	NORMAL	IU/mL
QuantiFERON TB2 Ag Value	1.79	NORMAL	IU/mL
QuantiFERON Nil Value	0.08	NORMAL	IU/mL
QuantiFERON Mitogen Value	>10.00	NORMAL	IU/mL

Performing Laboratory Information:

01: Labcorp Dublin, 6370 Wilcox Road, Dublin OH, 430161269, phone: 800-282-7300, Director: PhD Vincent Ricchiuti

Results

QUANTIFERON TB GOLD PLUS [LAB3522] (Order 693690631)

Lab Collection Information

Specimen ID: [redacted]

Specimen: Blood
Specimen: Blood, Venous Venipuncture

Collection Date and Time: 2/3/2022 4:06 PM
Collected By: [redacted]
Received: 2/3/2022 4:06 PM

QUANTIFERON TB GOLD PLUS

Order: [redacted]

Status: Final result Visible to patient: Yes (not seen) Next appt: None Dx: Sacroiliitis (HCC)

	Ref Range & Units	5 d ago
QUANTIFERON-TB PLUS,1T	NEGATIVE	POSITIVE !

Comment: In healthy persons who have a low likelihood both of M. tuberculosis infection and of progression to active tuberculosis if infected, a single positive QFT result should not be taken as reliable evidence of M. tuberculosis infection. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis.

NIL	IU/mL	0.06
MITOGEN-NIL	IU/mL	>10.00
TB1-NIL	IU/mL	0.39
TB2-NIL	IU/mL	0.37

Comment: The Nil tube value reflects the background interferon

QUANTIFERON(R)-TB GOLD
PLUS, 1 TUBE

QVE

POSITIVE NEGATIVE
In healthy persons who have a low likelihood both of M. tuberculosis infection and of progression to active tuberculosis if infected, a single positive QFT result should not be taken as reliable evidence of M. tuberculosis infection. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis.

NIL	0.04	IU/mL
MITOGEN-NIL	>10.00	IU/mL
TB1-NIL	0.47	IU/mL
TB2-NIL	0.27	IU/mL

The Nil tube value reflects the background interferon gamma immune response of the patient's blood sample. This value has been subtracted from the patient's displayed TB and Mitogen results.

Lower than expected results with the Mitogen tube prevent false-negative Quantiferon readings by detecting a patient with a potential immune

CLIENT SERVICES: [redacted]3 SPECIMEN: [redacted]

12/08/2021 3:12PM (GMT-05:00)

TB infection testing interpretation, Quantiferon gold plus

QFT PLUS INTERPRETATION	INDETERMINATE !	

Comment:

An Indeterminate interpretation can be caused by a number of factors, including sample collection. Testing should be reordered and a new sample collected on patients with indeterminate results. Samples with a low mitogen response (<0.5) may be due to anergy or immune suppression. Samples with a high Nil response (>8.0) may be due to interferon gamma production independent of TB stimulation or heterophile antibodies. For more details, please see TB Testing Guidance on Staffnet.

QFT PLUS NIL VALUE	10.000	IU/mL
QFT PLUS TB AG1 MINUS NIL	0.000	IU/mL
QFT PLUS TB AG2 MINUS NIL	0.000	IU/mL
QFT PLUS MITOGEN MINUS NIL	0.000	IU/mL

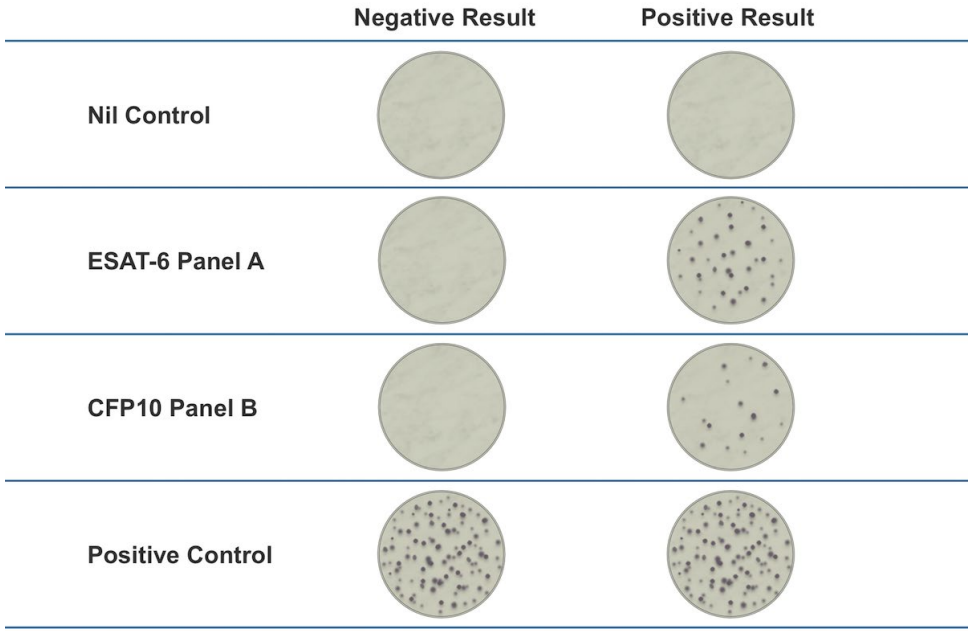
QUANTIFERON TB GOLD

Collected:	11/19/15 1021
Resulting lab:	LABCORP
Reference range:	Negative
Value:	Indeterminate !
Comment:	Mitogen (positive control) gave low response. This may indicate anergy or immune suppression. Early draws and extended transit time may also result in low positive control and indeterminate results. The specimen received for QuantiFERON testing was incubated by the ordering institution. Specific procedures outlined in our Directory of Services and in the package insert for the QuantiFERON Gold (In Tube) test must be followed to enable for proper stimulation of cells for the production of interferon gamma.

QFT TB AG VALUE	0.04
QFT NIL VALUE	0.04
QFT MITOGEN VALUE	0.14
QFT TB AG MINUS NIL VALUE	0.00
QFT INTERPRETATION	

TB infection testing interpretation, T spot

- Results are interpreted by subtracting the spot count in the negative (Nil) control from the spot count in Panels A and B
- **Positive:** if Panel A minus Nil and/or Panel B minus Nil is ≥ 8 spots
- **Negative:** if both Panel A minus Nil and Panel B minus Nil is ≤ 4 spots
- **Equivocal:** if the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6, or 7 spots



TB infection testing interpretation

- Remember
  - Neither PPD or IGRAs differentiates b/w latent or active TB infection
  - Neither is used to follow response the treatment in a patient with active TB
  - After TB infection both should remain + for life

8 yr old healthy girl from Brazil, PPD 10MM, IGRA neg

- What questions about this child's history do you want to ask?
  - Did she receive a BCG vaccine?
  - Is she a close contact of an active case of TB?
  - Who placed and read the PPD?
  - Is she immunocompromised in any way?

60 yr old female from Brazil, uncontrolled DM and CRI, PPD 10mm, IGRA neg

- What historical questions do you want to ask this individual?
    - Close contact of active case of pulmonary TB in the past?
    - Is she on any immunosuppressive medications?
    - Is she on a renal transplant list?

8 yr old healthy girl from Brazil, PPD 30mm, IGRA neg

- What questions about this child's history do you want to ask?
  - Did she receive a BCG vaccine?
  - Is she a close contact of an active case of TB?
  - Who placed and read the PPD?
  - Is she immunocompromised in any way?

30 yr old patient from Haiti with HIV. PPD 2 yrs ago 0 mm. Now IGRA +

- What historical questions do you want to ask this individual?
  - Was she on antiretrovirals 2 years ago?
    - **NO**
  - Is she a close contact of an active case of TB?
    - **NO**
  - Is she on antiretrovirals now?
    - **YES**
  - Would you treat her as an LTBI?
  - **YES**

40 yr healthy male from Brazil, PPD 10mm, IGRA neg, works in a neonatal ICU

- What historical questions do you want to ask this individual?
  - Close contact of active case of pulmonary TB in the past?
    - **NO**
  - Is he on any immunosuppressive medications?
    - **NO**
  - Has he had a previous PPD and was it positive or negative?
    - **10 mm 2 yr ago**
  - Would you treat him as an LTBI?
  - **YES, if converts to active disease/disaster**

18 yr US born patient, healthy, no h/o international travel or known exposures to TB, TB testing done b/c required for entry to college, PPD 0mm, QFT plus: TB 1 0.35 IU/ml TB 2 0.22 IU/ml. Reported as a "Positive QFT"

- What would you do next with this individual?
  - Obtain CXR and if normal offer LTBI treatment
    - **NO**
  - Obtain a PPD to verify positive test
    - **Possibly** could help if it is negative but requires two visits
  - Repeat QFT plus
    - **Best Answer <90% chance repeat test will be negative**

TB infection testing interpretation

Most important take home message

- When interpreting results of PPD or IGRA, always interpret in context of the patient
- No gold standard to diagnose latent TB infection, pre-test probability matters!
- Ask yourself:
  - what risk factors does this patient have for being infected with TB?
  - what risk factors does this patient have for reactivation of a latent TB infection?
  - what are the consequences of TB reactivation?
  - what are the possible reasons for a false + or a false - PPD or IGRA?

Contact

Ed Zuroweste, MD (814-571-7395)
ezuroweste@migrantclinician.org

TB infection testing interpretation, Context matters!

- + PPD, - IGRA test
  - 8 yr old healthy girl from Brazil, PPD 10MM, IGRA neg
  - 60 yr old female from Brazil, uncontrolled DM and CRI, PPD 10mm, IGRA neg
  - 60 yr old female from Brazil, PPD 10mm, IGRA neg, getting ready to start TNF alpha inhibitor
  - 60 yr female from Brazil, PPD 0mm 2 yrs ago, now a contact of an active smear + case, current PPD 10mm, IGRA neg
  - 8 yr old healthy girl from Brazil, PPD 30mm, IGRA neg
  - 40 yr healthy male from Brazil, PPD 10mm, IGRA neg, works in a neonatal ICU

TB infection testing interpretation, Context matters!

- -PPD, + IGRA (not as common)
  - 30 yr old healthy patient from Haiti, PPD 2 yrs ago 0 mm. Now IGRA +
  - 30 yr old patient from Haiti with RA. PPD 2 yrs ago 0 mm. Now IGRA+
  - 30 yr old patient from Haiti with HIV. PPD 2 yrs ago 0 mm. Now IGRA +
  - 18 yr US born patient, healthy, no h/o international travel or known exposures to TB, TB testing done b/c demanded for entry to college, PPD 0mm, quant gold plus Positive in 1 of the tubes at 0.35 IU/ml

TB infection testing interpretation, Context matters!

- Indeterminate IGRA
  - 30 yr male from Haiti, on 40mg prednisone for RA, IGRA indeterminate due to low mitogen response
  - 30 yr male from Haiti, healthy, IGRA indeterminate due to high nil