Tuberculosis and Latent Tuberculosis Infection

Developments in diagnosis and treatment

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APIC Meeting
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Global burden of TB

EVERY 3 SECONDS
A NEW INFECTION HAPPENS

30% OF THE WORLD'S POPULATION IS INFECTED

EVERY 21 SECONDS
SOMEONE DIES OF TB

2

WHO GLOBAL TB REPORT 2016

Actions and investments to End TB fall far short

Turbuculosis among top 10 causes of death worldwide last year

Here are the statistics from 2015

10.4 million people
FELL ILL FROM TB
That's 28,500 people every day

1.8 million people
DIED FROM TB
including 400,000
WITH HIV + TB
That's over 4,900 people every day

60% of TB cases worldwide occurred in just SIX COUNTRIES

CHINA · INDIA · INDONESIA · NIGERIA · PAKISTAN · SOUTH AFRICA

More action and investment in these countries will drive down the TB burden

3 MILLION LIVES WERE SAVED BY THE GLOBAL TB RESPONSE IN 2015

ACCESS TO CARE

6.1 million people had
ACCESS TO QUALITY TB CARE

4.3 million people
MISSED OUT

DRUG RESISTANCE

Only 1 in 5 people needing treatment for **multidrug-resistant TB in 2015**
ACTUALLY RECEIVED IT

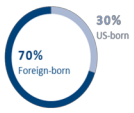
Only half of those who started MDR-TB treatment **WERE CURED**

3

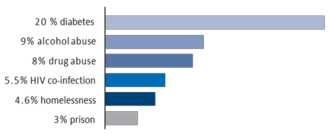
According to the CDC, eliminating TB in the US requires expanded testing and treatment of latent TB infection.

An estimated 13 million people in the US are infected with latent TB (1). The US Preventative Services Task Force (USPSTF) now recommends proactive screening for asymptomatic adults who are at risk for TB – including persons who are immunocompromised and those living in congregate settings or originating from countries where TB is prevalent (2).

US TB cases 2017



Common risk factors (3)



What Did the LTBI Researchers Do and Find?

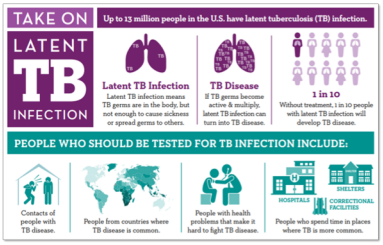
- We generated an annual risk of infection between 1934 and 2014 and applied this to a country-level demographic model, quantifying uncertainty wherever possible.

- We estimated that approximately **1.7 billion individuals were infected with LTBI** in 2014; just under a **quarter of the global population.**

- If left unaddressed, the current LTBI burden alone will likely prevent achieving the global TB targets for TB elimination.

Houben RMGJ, Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling

To eliminate active TB, focus on latent TB infection



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Evolution of TB laboratory technologies

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Evolution of new TB/MDR TB technologies in the last five years

Stop TB Partnership

Year	Technology	Turnaround time
Before 2007	Solid Culture DST (Phenotyping) (1st/2nd line)	30-60 days
2007	Liquid Culture DST (Phenotyping) (1st/2nd line)	15-30 days
2008	Line Probe Assay (Genotyping) (1st line, Rif & INH)	2 days
2010	Genotyping second generation (1st line, Rif & INH)	90 minutes

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Turn around time

Result - TAT

- AFB smear – 24 hrs
- NAAT – 48 hrs
- Molecular susceptibility – 3-5 days?
- Culture – approximately 7-14 days but cultures are held for 42 days/6 weeks
- Conventional susceptibility – 3-6 weeks

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TB Diagnosis

- Culture
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media
  - Need ~100 organisms/ml to get 1 colony
  - Sensitivity-Positive in 80% of CDC Verified Cases
  - Specificity- 1-2% False Positive
- Susceptibility
  - Takes 1-2 weeks after positive culture
  - Molecular Techniques have the ability to give more rapid results

Most of the world does not have access to these critical laboratory tests!!!

Southeastern National Tuberculosis Center

Diagnosis of Drug Resistance

- Line Probe Assays
  - commercially available in Europe – not cleared yet by FDA
  - Hain: detects presence of TB complex and gene mutations associated with Rifampin resistance (*rpoB*) and INH resistance (*kat G and inhA*)
  - In smear positive specimens:
    - Rifampin resitance: Sensitivity (98.9%) Specificity (99%)
    - INH resistance: Sensitivity (94%) Specificity (99%)
  - Turnaround times: 1-2 days

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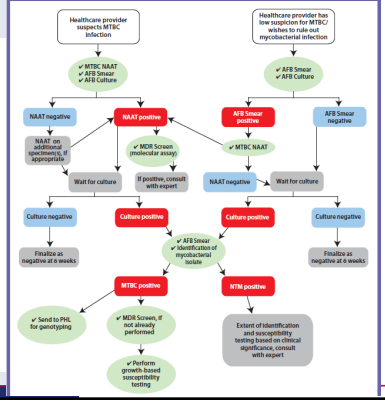
Ideal Algorithm for Mycobacteriology Testing in Clinical and Public Health Laboratories



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Agenda for today

- what is Tuberculosis ?
- Impact and burden of tuberculosis (World, USA, Georgia)
- U.S. Preventive Services Task Force recommendations for primary care screening for Latent Tuberculosis Infection.
- Diagnosis– Active tuberculosis and LTBI
- Research and Development Updates
- Questions and discussion

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What Is Tuberculosis?

Tuberculosis (TB) overview

- Infectious communicable disease
- Caused by *Mycobacterium tuberculosis* complex organisms
  - ***M. tuberculosis***
  - ***M. bovis***
  - ***M. africanum***
  - ***M. canetti***
  - ***M. microti***
- Affects different parts of the body:
  - Lungs - **Pulmonary TB** (> 70% of all TB cases)
  - Other organs - **Extra-pulmonary TB**

Photo courtesy of WHO Stop TB initiative. Website: www.stoptb.org

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What Is Tuberculosis?

Transmission of TB

- TB is spread through the air from one person to another
  - Droplets aerosolized when a person with active pulmonary TB disease coughs, sneezes, speaks, spits, or sings
- A single sneeze can release up to 40,000 infectious droplets 0.5 to 5.0 μm in diameter
- People nearby may breathe in these bacteria and become infected
  - Inhalation of fewer than 10 bacteria may cause infection
- TB infection begins when mycobacteria reach pulmonary alveoli
  - Invade and replicate within endosomes of alveolar macrophages

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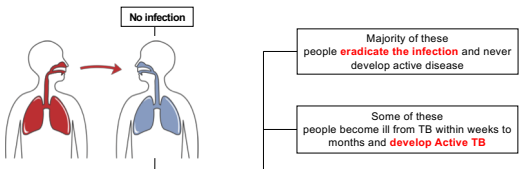
What Is Tuberculosis?

Outcomes of transmission of TB infection



Outcome depends on the person's immune status

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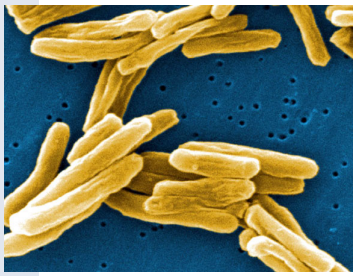
A History Lesson

Scientists Describe 7,000-Year-Old Case of Tuberculosis in Europe
Oct 31, 2013 by News Staff / Source



Scientists Describe 7,000-Year-Old Case of Tuberculosis in Europe
Oct 31, 2013 by News Staff / Source

The scientists examined seventy-one human skeletons from a 7,000-year-old site of Hódmezővásárhely-Gorzsa in the south of Hungary. They found numerous cases of infections and metabolic diseases, and some skeletons showed signs of Hypertrophic Pulmonary Osteopathy and therefore potentially tuberculosis.

The team then focused on one skeleton in particular to verify this hypothesis, and analyzed the ancient DNA and lipids from its bones to do so.
Both tests confirmed the presence of the *Mycobacterium tuberculosis* complex associated with tuberculosis.

History lesson

Skeletal remains show that prehistoric humans (4000 BC) had tuberculosis, and tubercular decay has been found in the spines of Egyptian mummies (3000-2400 BC).

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Poor understanding of the TB spectrum contributes to fuzzy terminology

- Latent infection
- Active infection
- Inactive infection
- Subclinical infection
- Acute infection
- Chronic infection
- Persistent infection
- Dormant infection
- Recent infection
- Remote infection
- Quiescent infection
- Incipient disease

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The journey from LTBI to active TB

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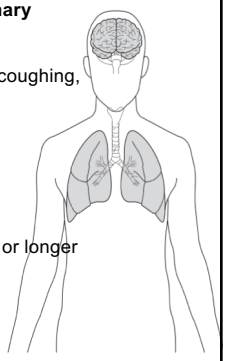
What Is Tuberculosis?

Active TB: Pulmonary

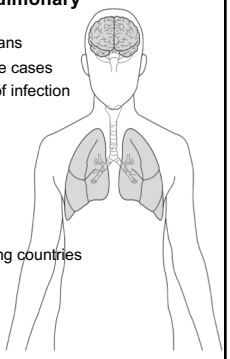
- Infectious
- Typically spreads through talking, coughing, sneezing or singing
- Symptoms:
  - Weakness or fatigue
  - Weight loss
  - No appetite
  - Bad cough for the last 3 weeks or longer
  - Chest pain
  - Coughing up blood or sputum
  - Chills, fever and night sweats



What Is Tuberculosis?

Active TB: Extra-pulmonary

- Infection spreads outside respiratory organs
- Occurs in approximately 15-20% of active cases
- Symptoms vary, especially with the site of infection
- Common sites for extra-pulmonary TB:
  - Lymph nodes
    - Especially common in children
  - Genital tracts
    - May lead to infertility
  - Meninges
    - Often fatal, particularly in developing countries
  - Pleura
  - Bone
  - Many others



What Is Tuberculosis?

Groups at higher risk of LTBI progression to active TB

Persons who have been recently infected with TB bacteria:

- Contacts of people with active TB
- Children < 5 years of age
- Immigrants from high-prevalence countries

Persons with medical conditions that weaken the immune system:

- HIV/AIDS
- Substance abuse
- Diabetes mellitus
- Severe kidney disease
- Low body weight
- Head and neck cancer
- Immunosuppressive medical treatments
  - Corticosteroids
- Specialized treatments for rheumatoid arthritis or Crohn's disease
  - anti-TNF-α therapy
- Organ transplants
- Silicosis

What Is Tuberculosis?

Progression from latent to active TB

- People with LTBI have a ***lifetime risk of developing TB of 10%*** (1)
- The ***greatest risk occurs within the first 2 years after infection***
- Some groups of people are at even higher risk of TB:

Risk group	TB risk, times
HIV/AIDS	21-34[1]
TNF-α therapy	4-8[2]
Diabetes	2-3[1]
Healthcare workers	2-5[3]
Corticosteroid therapy	> 5[4]

- LTBI treatment can prevent later development of TB

1. World Health Organization
2. Winthrop KL et al. *Arthritis Rheum* 2005, Gardam MA et al. *Lancet infect Dis* 2003
3. Baussano I et al. *Emerg Infect Dis 2011*
4. Cisneros JR at al. *Ann Pharmacother* 1996

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Tuberculosis Epidemiology

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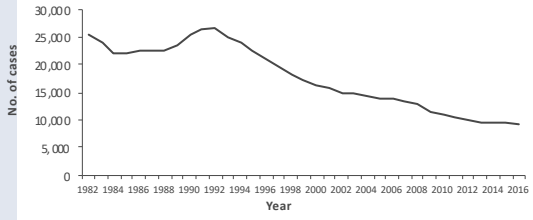
Reported Tuberculosis (TB) Cases United States, 1982–2016*



In 2017, a total of **9,093** new cases of tuberculosis (TB) were provisionally* reported in the United States, representing an incidence rate of 2.8 cases per **100,000** population. The case count decreased by 1.8% from 2016 to 2017, and the rate declined by 2.5% over the same period.

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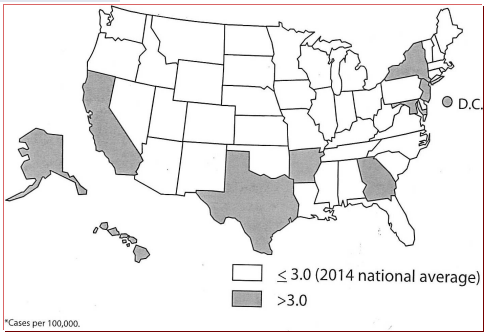
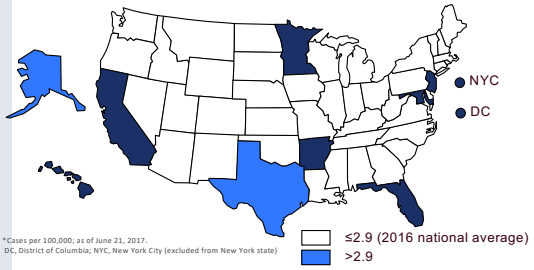
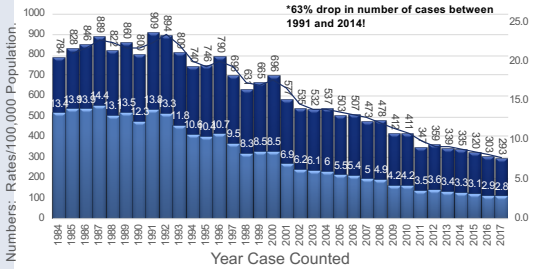
Rate of TB Cases*, By State – United States, 2014



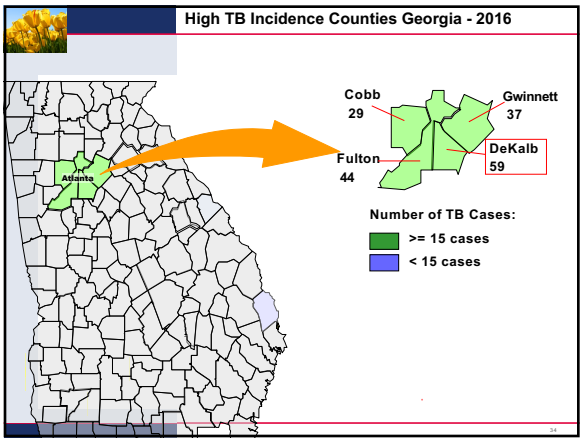
TB Case Rates,* United States, 2016

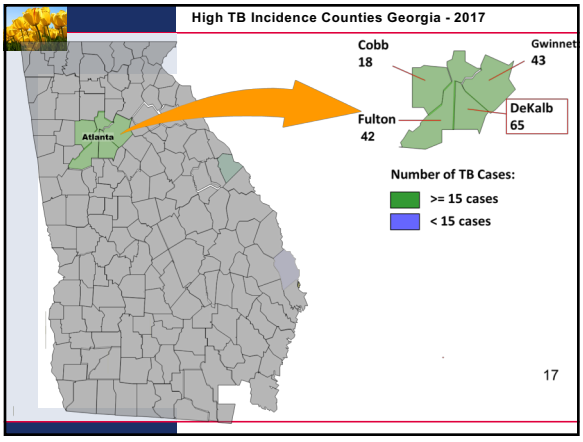


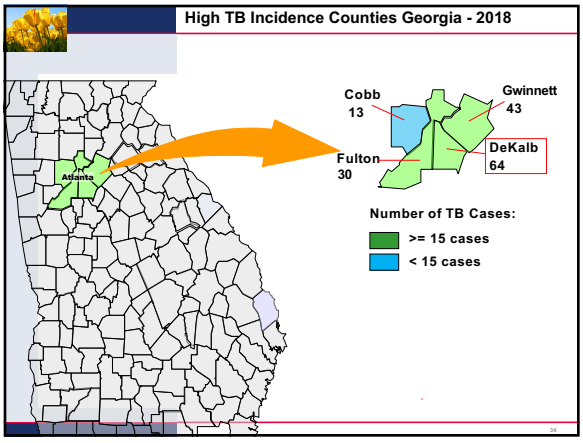
TB Cases and Case Rates Georgia : 1984 - 2018

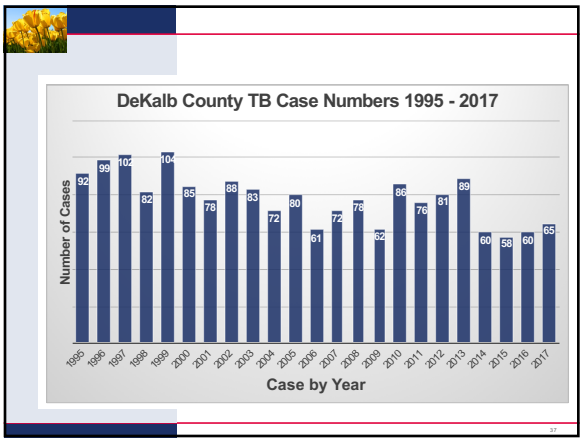


As of February 2019, 273 TB cases have been counted in Georgia for 2018 – representing a significant decrease from 2017.


High TB Incidence Counties Georgia - 2016
Cobb
29
Gwinnett
37
DeKalb
59
Fulton
44
Atlanta
Number of TB Cases:
>= 15 cases
< 15 cases


High TB Incidence Counties Georgia - 2017
Cobb
18
Gwinnett
43
DeKalb
65
Fulton
42
Atlanta
Number of TB Cases:
>= 15 cases
< 15 cases
17


High TB Incidence Counties Georgia - 2018
Cobb
13
Gwinnett
43
DeKalb
64
Fulton
30
Atlanta
Number of TB Cases:
>= 15 cases
< 15 cases


DeKalb County TB Case Numbers 1995 - 2017
Number of Cases
92
99
102
82
104
85
78
88
83
72
80
61
72
78
62
86
76
81
89
60
58
60
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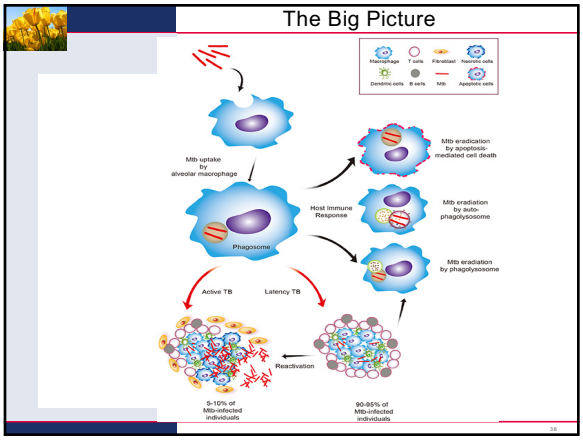
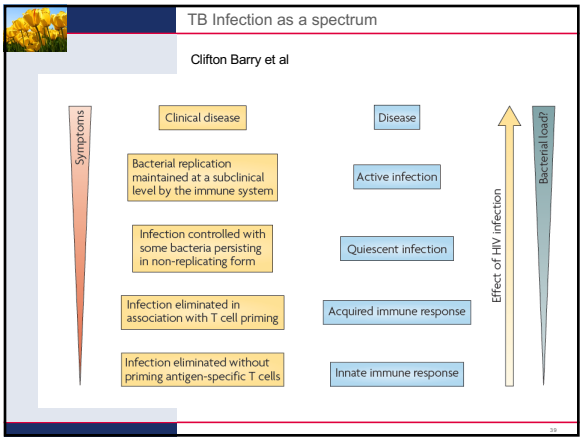
2017
Case by Year


The Big Picture
Macrophage
T cells
Fibroblast
Necrotic cells
Dendritic cells
B cells
Mtb
Apoptotic cells
Mtb uptake by alveolar macrophage
Phagosome
Host Immune Response
Mtb eradication by apoptosis-mediated cell death
Mtb eradiation by auto-phagolysosome
Mtb eradiation by phagolysosome
Active TB
Latency TB
Reactivation
5-10% of Mtb-infected individuals
90-95% of Mtb-infected individuals


TB Infection as a spectrum
Clifton Barry et al
Symptoms
Clinical disease
Bacterial replication maintained at a subclinical level by the immune system
Infection controlled with some bacteria persisting in non-replicating form
Infection eliminated in association with T cell priming
Infection eliminated without priming antigen-specific T cells
Disease
Active infection
Quiescent infection
Acquired immune response
Innate immune response
Effect of HIV infection
Bacterial load?

LTBI in the United States

- Up to 13 million people in the United States are estimated to have LTBI.
  - While TB disease is a nationally notifiable disease, LTBI is not reported to CDC.
  - Despite declines of TB disease in the United States, there has been no significant change in the rate of LTBI over the last decade.
- People who have latent TB infection were exposed to TB in the past.
- More than 85% of U.S. TB cases are believed to be associated with longstanding untreated LTBI.

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ACA and the U.S. Preventive Services Task Force

Under ACA, preventive services with a USPSTF Grade of A or B are covered without cost-sharing (e.g., copayment or deductible) by many health insurance plans or policies

Plans subject to this requirement (i.e. "non-grandfathered" plans) must comply within the first plan year that begins one year after the September 6, 2016 USPSTF recommendation

For example, plan years that begin January 1st will have to comply by January 1,2018 at the latest

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LTBI Diagnosis

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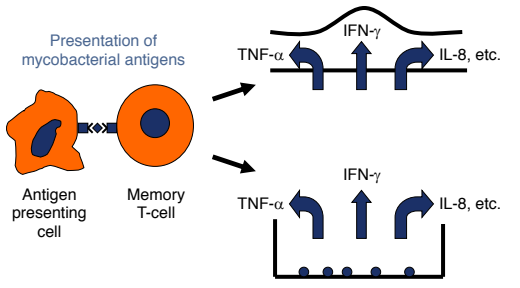
Diagnosis And Treatment: LTBI

Current practices

- There is no "gold standard" to determine if a person has LTBI
- Currently there are two classes of diagnostic test for LTBI:
  - Interferon-gamma release assays (IGRAs)
  - Tuberculin skin test
- No test can discriminate between old and new infection
- LTBI testing is usually only performed on those:
  - At increased risk of being infected:
    - Healthcare workers, contacts of active TB cases, etc.
  - At risk of developing active TB:
    - Immunosuppressed, etc.

In Vivo and *In Vitro* Diagnostic Tests

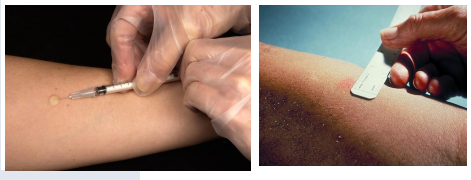


Andersen P, et al. Lancet 2000;356:1099

Diagnosis And Treatment: LTBI

Tuberculin Skin Test (TST)

- First used in 1906 as a diagnostic for TB
- Measures a person's cell mediated immune (CMI) response to *M. tuberculosis*
- Tuberculin Purified Protein Derivative (PPD) is injected intra-dermally into the forearm and 48 – 72 hours later the size of the resultant reaction is measured:
  - Induration (firm area)
  - Erythema (redness)
- Requires two visits: to have the test administered and read



What exactly does the TST detect?

LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement

U. Mack, G.B. Migliori, M. Sester, H.L. Rieder, S. Ehlers, D. Goletti, A. Bossink, K. Magdorf, C. Hölscher, B. Kampmann, S.M. Arend, A. Detjen, G. Bothamley, J.P. Zellweger, H. Milburn, R. Diel, P. Ravn, F. Cobelens, P.J. Cardona, B. Kan, I. Solovic, R. Duarte, D.M. Cirillo and C. Lange for the TBNET

ERJ 2009

"Latency, as assayed by the tuberculin skin test and IGRA, is a state of persistent mycobacteria-specific T-cell responses in the absence of clinical evidence for tuberculosis disease"

TST and IGRAs measure "lasting TB immune responses" and not "latent TB infection"

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Diagnosis And Treatment: LTBI

Limitations of the TST

- People without TB are **often falsely positive** due to many reasons, including:
  - BCG vaccination
  - Immune reactivity to non-tuberculous mycobacteria (NTM)
    - In US-born individuals, up to 50% of TST responses can be due to NTM infections (1)
- People with TB are **often falsely negative**
- Difficulty in proper intradermal **injection** of PPD
- Must read the test **2-3 days** after PPD injection
  - Often people do not return for reading
- **Subjective**:
  - Two different readers, two answers
  - Different cut-offs for different situations (≥ 5mm, ≥ 10mm, ≥ 15mm)
- **Boosting**: as PPD antigen is injected into the person, this can lead to the boosting of a subsequent test and a false-positive result, especially in those BCG vaccinated

1. von Reyn CF, Horsburgh CR, Olivier KN, et al. Skin test reactions to Mycobacterium tuberculosis purified protein derivative and Mycobacterium avium sensitin among health care workers and medical students in the United States. Int J Tuberc Lung Dis 2001; 5 (12): 1122-1128

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Limitations of the Tuberculin Skin Test (TST)

Reasons for False Positive TST

- Non-tuberculosis mycobacteria
  - e.g. *M. avium*
- Reading errors
- Cross-reactivity with BCG
- Allergic reaction to PPD

Reasons for False Negative TST

- Technical Factors
  - Too little antigen, too deep, leakage
  - Reading errors
- Purified protein derivative injectable
  - Improper storage or dilution
- Biologic Factors
  - Co-morbidity: Diabetes, HIV, MMR
  - Poor nutrition
  - Drugs (steroids, methotrexate, immunosuppressive drugs, e.g. RA, Lupus)
  - Chronic renal failure, malignancy
  - Age (newborn, elderly booster)

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IGRA TESTS

Interferon-Gamma Release Assays (IGRAs) are in vitro blood tests that address many of the limitations of the TST

- IGRAs are more specific and sensitive than the TST for TB screening (1)
- IGRAs measure the secretion of the cytokine interferon-gamma (IFN-γ) as a marker of cell mediated immune response to TB
- IFN-γ is produced by T cells stimulated in vitro with TB-specific antigens
- IFN-γ is:
  - Measurable, stable
  - Absent from normal circulation

Differences in Currently Available IGRAs

	QFT-Gold In Tube (QFT-GIT)	QuantiFERON-TB Gold Plus (QFT-PLUS)	T-Spot
Format	Process whole blood Stimulates CD4+ T Cells	Process whole blood *CD4+ & CD8+ T Cells	Process peripheral blood mononuclear cells (PBMCs)
***M. Tuberculosis* antigen**	Single mixture of synthetic peptides representing ESAT-6 & CFP-10, and TB 7.7	TB1: Long Peptides (MHC Class II) ESAT 6, CFP10; TB2: Long Peptides (MHC Class II) ESAT 6, CFP10, Short Proprietary Peptides (MHC Class I)	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-γ concentration	IFN-γ concentration	# of IFN-γ producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate	Positive, negative, indeterminate (invalid), borderline

QFT vs T-SPOT Results

QFT-GIT

- Positive (> 0.35 IU/mL)
- Negative (< 0.35 IU/mL)
- Indeterminate
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

T-SPOT TB

- Positive (> 8 spots) (≥6)
- Negative (< 4 spots) (≤5)
- Borderline (5-7 spots)
- Invalid (Indeterminate)
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

IGRAs are unaffected by BCG and most NTMs

BCG Sub-strain	QFT TB-Specific Antigens			TST Antigens
	ESAT-6	CFP-10	TB-7.7 (p4)	PPD
Gothenberg	-	-	-	+
Moreau	-	-	-	+
Tice	-	-	-	+
Tokyo	-	-	-	+
Danish	-	-	-	+
Glaxo	-	-	-	+
Montréal	-	-	-	+
Pasteur	-	-	-	+

Environmental Strains	QFT TB-Specific Antigens			TST Antigens
	ESAT-6	CFP-10	TB-7.7 (p4)	PPD
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. terra	-	-	-	+
M. vaccae	-	-	-	+
M. xenopi	-	-	-	+

Higher specificity leads to fewer false positive results and unnecessary workup

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LTBI Diagnosis

The currently available diagnostic tools

In summary, three tools are currently in use for the diagnosis of LTBI, two of which fall under the same category:

•The time-honored Tuberculin Skin Test (TST)

•The Interferon-Gamma Release Assays (IGRAs), including:

- the QuantiFERON-TB Gold plus(QFT-Plus)
- the T-SPOT.TB test (T-Spot)

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Diagnosis And Treatment: LTBI

IGRAs and the TST

- A large body of published data demonstrates that IGRAs are:
  - More specific than the TST
    - Unaffected by BCG vaccination and most NTMs
    - More accurately identify those who have a TB infection
  - More sensitive than the TST in detecting active TB
  - Less affected by immunosuppression than the TST
  - Objective – not subjective – interpretation (at least for QFT)
  - More efficient due to single visit
  - More cost-effective for screening programs
- Currently, IGRAs and the TST are used for LTBI diagnosis
- TST is > 110 years old

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Interferon-gamma

Interferon-gamma is crucial to immune defense against intracellular pathogens such as *Mycobacterium tuberculosis.* Post infection, naïve T cells become sensitized to TB-specific antigens and develop into TB-specific effector T cells (both CD4+ and CD8+), which then migrate to the site of infection and secrete interferon-gamma to activate macrophages to ingest and destroy mycobacteria. TB-infected patients have TB-specific effector T cells circulating in their peripheral blood, which secrete interferon-gamma *in vitro* when stimulated by specific antigens

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Diagnosis And Treatment: LTBI

Interferon-gamma release assays (IGRAs)

- In response to the limitations of the TST, IGRAs have been developed and have become available over the last decade
- More specific and sensitive than TST for diagnosis of LTBI
- Two IGRAs commercially available in USA
- Both IGRAs measure the secretion of the cytokine interferon-gamma (IFN-γ) by lymphocytes stimulated in vitro with TB-specific antigens

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Interferon Gamma Release Assays (IGRAs)

Quantiferon-TB Gold In-Tube Assay

- ESAT-6, CFP – 10, TB7.7
- Measure IFN- Gamma ELISA

T-spot.TB Assay

- ESAT-6, CFP – 10
- Count spots which are related to the number of cells releasing Gamma Interferon.

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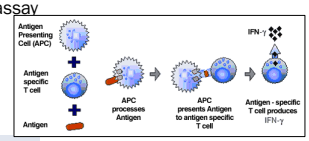
Diagnosis And Treatment: LTBI

Whole Blood Interferon Gamma Release Assay

- IGRAs use **purified antigens from MTB to stimulate peripheral-blood lymphocytes to produce gamma interferon**
- QuantiFERON tests (QFT) measures gamma interferon (IFN-gamma) in the supernatant of the cell suspension
- TSPOT measures cells producing gamma interferon using ELISpot assay



The QFT Journey

2001 a new test became available, the **QuantiFERON-TB test** (QFT) (Cellestis)

2005 replaced by its slightly more reliable descendant: the **QuantiFERON-TB Gold test** (QFT-G)

2007 replaced by an even more reliable version : the **QuantiFERON-TB In-Tube test** (QFT-IT)

2008 the T-SPOT.TB test (T-Spot) (Oxford Immunotec)

2011 Acquisition of **QuantiFERON** technology by QIAGEN

2018 (Now available in USA) **QuantiFERON-TB Gold Plus** (QFT®-Plus)

A benchmark of clinical support for the new QFT-Plus format

Barcellini et al. confirm the accuracy of QFT-Plus and begins to reveal the increased value of the new TB1 and TB2 format:

1. Excellent sensitivity and specificity for QFT-Plus
   - QFT-Plus has excellent sensitivity, particularly in patients living with HIV, and maintains high specificity.
2. Verification of new format efficacy – agreement between TB1 and TB2
   - Significant difference is seen between both the TB1 and the TB2 Nil-subtracted IFN-γ results in smear positive patients compared to smear negative patients, supporting the value of the new test format and CD8 antigens.
3. Clinical significance for CD8 technology
   - The novel, optimized CD8 technology may be advantageous in patients with low CD4 counts. CD8-dependent IFN-γ values correlate with bacterial load and smear-positivity.

NTMs - MOTT BCG

What Is Tuberculosis?

Bacillus Calmette-Guérin (BCG) vaccination

- Attenuated (weakened) live *M. bovis* that is avirulent
- Thought to be effective in preventing severe complications of TB in children if given soon after birth
- No reliable protection for adults
  - Some studies show good efficacy, others none
- ~100 million doses/yr administered to children in 170 countries
  - The WHO recommends that BCG be given to all children born in highly-endemic countries
  - Some countries recommend >1 vaccination throughout life
- Confounds results of the tuberculin skin test (TST)
- For country information on BCG practices, go to **www.bcgatlas.org**

Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues related to the use of BCG in immunization programmes: a discussion document. World Health Organization, Geneva, Switzerland; 1999;WHO/V&B/ 99.23:1-44.)
World Health Organization, Global Tuberculosis Programme and Global Programme on Vaccines.
Statement on BCG revaccination for the prevention of tuberculosis. *Wkly Epidemiol Rec* 1995;72:229-231.)

When BCG is given after infancy or repeated many times, it can affect TST results

INT J TUBERC LUNG DIS 10(11):1192–1204
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REVIEW ARTICLE

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

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- Analysis of 24 studies with N = 240,243 subjects
- When BCG is given in infancy, false-positive TST results due to BCG occur in 6% of vaccinated subjects
- When BCG is given after infancy, false-positive TST results due to BCG occur in 40% of vaccinated subjects

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US QFT Product Training QM31635261A Approval date 06/2013

MTB Genome

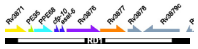
MTB has 4,000 genes including the RD1 region encoding proteins ESAT6, CFP10

The IGRA TB antigen is peptides from ESAT6, CFP10, ± TB7.7

TB peptides stimulate memory T-cells in blood that release IFN-gamma upon exposure to the peptides

CFP10 and ESAT6 test for immune memory to these MTB proteins

MTB Genome



RD1 = Region of Difference 1

deleted in BCG: fundamental advantage over TST

deleted in almost all non-tuberculous mycobacteria

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What Is Tuberculosis?

Non-tuberculous mycobacteria (NTM)

- These NTM, and many others, can cause infections in humans:

M. abcessus	*M. avium*	*M. scrofulaceum*	
M. fortuitum	*M. gordonii*	*M. malmoense*	***M. flavescens***
M. intracellulare	***M. kansasii***	***M. marinum***	***M. szulgai***

- Most NTM infections treated with different drugs than those used for TB
- Definitive differentiation from TB is by culture or nucleic acid amplification (NAA) tests
- Usually occurs in:
  - Immunosuppressed
  - Generally not pulmonary, but does occur
- People with NTM infections are usually TST-positive, but most are IGRA-negative
- NTM also known as "Mycobacteria other than tuberculosis (MOTT)"

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QFT is not affected by BCG vaccination (1)

Tuberculosis Complex	QFT TB-Specific Antigens			TST Antigens
	ESAT-6	CFP-10	TB 7.7	PPD
M. tuberculosis	+	+	+	+
M. africanum	+	+	+	+
M. bovis	+	+	+	+
BCG Sub-Substrain	**QFT TB-Specific Antigens**			**TST Antigens**
	ESAT-6	CFP-10	TB 7.7	PPD
Gothenberg	-	-	-	+
Moreau	-	-	-	+
Tice	-	-	-	+
Tokyo	-	-	-	+
Danish	-	-	-	+
Glaxo	-	-	-	+
Montréal	-	-	-	+
Pasteur	-	-	-	+

Environmental strains	QFT TB-Specific Antigens			TST Antigens
	ESAT-6	CFP-10	TB 7.7	PPD
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. terra	-	-	-	+
M. vaccae	-	-	-	+
M. xenopi	-	-	-	+

Screening for LTBI in inflammatory rheumatic patients receiving Disease-modifying Antirheumatic Drugs therapy using QFT is not influenced by BCG vaccination status.(2)

1. QuantiFERON-TB Gold Package Insert, March 2013
2. Matulis G., et al. (2008). Ann Rheum Dis 67(1), 84-90

66

Diagnosis And Treatment: LTBI

- Although TB rates are falling worldwide, TB remains a major health burden
- To truly impact TB case rates, it requires screening of both LTBI and active TB
- Some groups of people are at increased risk of TB, and LTBI screening and treatment of those populations can help to reduce the risk of potential TB disease
- IGRAs have significant advantages over TST in LTBI screening:
  - More specific
  - More accurate
  - Do not cross-react with BCG-vaccination
  - Requires single visit
  - Not subject to human interpretation (QFT)

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Research & Developments

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Moving towards TB Elimination:

Modeling data support importance of LTBI tx

Nadir in TB disease and transmission in U.S.

New tests for Mtb infection

New shorter treatments for LTBI, high completion rates

Engagement of global partners in LTBI tx as a component of TB control

Expansion of health coverage through ACA

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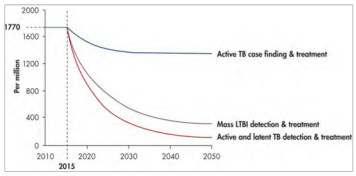
Potential impact of an LTBI approach to TB elimination

By using an LTBI-focused elimination strategy, there is the potential to dramatically reduce US incidence of active TB.



[1] Adapted from Abu-Raddad et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. PNAS. 2009; 106: 13980-5.

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Link between USPSTF and mandated coverage

- Under existing US healthcare law, medical/laboratory services that receive an A or B recommendation by USPSTF are covered by private health plans as a preventive service
  - No copays
  - No deductibles
  - No coinsurance
- By definition, as a 'B' level recommended service, TB testing for patients at increased risk for LTBI is covered as a preventive service under private health plans.
- TB testing is routinely covered under Medicare and most state Medicaid plans as well.

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LTBI Treatment

Isoniazid	**9 mo DAILY**
Rifampin	**4 mo / 6 mo DAILY**
Isoniazid + Rifapentine	**12 wk WEEKLY**
***Rifapentine**	**6 wk DAILY**

***currently under trials**

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LTBI Research

TBESC
TUBERCULOSIS EPIDEMIOLOGIC STUDIES CONSORTIUM-II

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Analytic Approach

- Assess agreement between IGRAs
  - Stratified by diameter of TST induration
  - Using different IGRA test cut-points
- Compare sensitivities and specificities at different test cut-points
- Assess performance of LTBI tests in different high risk populations
  - U.S.-born and foreign-born
  - HIV-infected and HIV-uninfected
  - <5 years old and ≥5 years old

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Study Design

10-year prospective cohort study

14 urban sites; 40,000 to be enrolled; began 2012

Each enrollee receives all 3 tests and is followed for 2-10 years or until TB disease develops

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Primary Study of TBESC II

The primary study of TBESC II:

Evaluates tests used to detect latent TB infection. These tests include the tuberculin skin test (TST) and the interferon-gamma release assays (IGRAs): QuantiFERON®-TB Gold In-Tube (QFT-GIT), and T-SPOT®.TB test (T-Spot).

Compares the ability of the TST and IGRAs to predict progression from latent TB infection to TB disease. This study is one of the largest of its kind. Approximately 6,000 patients will be enrolled each year for a total enrollment of about 42,000 patients over a 7 year period.

TBESC II will also evaluate:

Strategies to ensure latent TB infection treatment acceptance and completion.

Shorter, safer, and cost-effective latent TB infection treatment regimens.

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Preliminary Conclusions (1)

IGRAs have greater specificity than TST in foreign-born persons, particularly young children

QFT and TSPOT perform comparably in most high-risk groups

At the current cut-point, TSPOT is less sensitive than QFT in— (or are TST and QFT "overly sensitive"?)

- Children <5 years old
- HIV-infected persons

QFT may be a better choice for young children and HIV infected persons (Sens QFT and TST same for <5, but more spec; Spec QFT and TST same for HIV, but lower Sens TST for USB HIV)

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TBRU project, *Role of Antigen-Specific T Cell Responses in the Control of TB*

The Tuberculosis Research Units (TBRU) program was established in 1994 by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. In an effort to expand to program and drive innovation in tuberculosis (TB) research, in 2015 the NIAID selected four institutions, including one led by Emory University, to act as a collaborative TBRU network. The Emory-led TBRU will conduct a tuberculosis research projects over seven years with a NIH award of approximately $18.7 million.

Collaborating institutions include Emory University, NYU School of Medicine, Tulane National Primate Research Center, the La Jolla Institute of Allergy and Immunology, Aeras, the DeKalb County (Georgia) Board of Health, Kenya Medical Research Institute, and the U.S. Centers for Disease Control and Prevention.

The project is funded by the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)

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TBRU

Our TBRU project, *Role of Antigen-Specific T Cell Responses in the Control of TB*, is led by investigators at Emory University and NYU School of Medicine. Human studies will be conducted in both Atlanta, GA, and Kenya in collaboration with investigators at the DeKalb County (Georgia) Board of Health, the Kenya Medical Research Institute and CDC-Kenya. Studies of TB in nonhuman primates will be done by experts at Yerkes National Primate Research Center and the Tulane National Primate Research Center. Other collaborating institutions include the La Jolla Institute of Allergy and Immunology, Aeras, and the U.S. Centers for Disease Control and Prevention. The assembled team possesses a wide range of knowledge and expertise, and is poised to generate improved understanding of TB immunity to contribute to the elimination of TB.

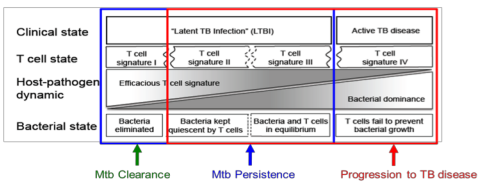
TBRU

The central theme of TBRU-ASTRa and its individual projects is to identify T cell signatures (the antigens recognized, the phenotypes, and the functions, of *Mtb*-specific T cells) associated with distinct states and outcomes of infection with *Mtb*.

The overall goal of TBRU-ASTRa is to contribute to the elimination of tuberculosis by generating a comprehensive understanding of antigen-specific T cell responses and their relationship to distinct outcomes of *Mtb* infection, including mycobacterial clearance, prolonged latent TB infection (LTBI), or progression from LTBI to active TB disease. The general hypotheses that TBRU-ASTRa will address are:

1) there are distinct states of *Mtb* infection that are currently considered to be a single category, LTBI;
2) that differences in antigen-specific T cell responses accompany distinct states of *Mtb* infection;
3) that these differences in antigen-specific T cell responses can be detected through analysis of peripheral blood T cells; and
4) that distinct antigen-specific T cell responses contribute to determining the outcome of infection with *Mtb*.

Relationship between antigen-specific T cell responses and bacterial load in different Mtb infection states



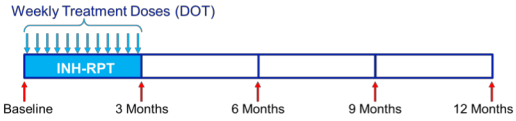
- What proportion of IGRA⁺ asymptomatic individuals have "true" Mtb infection? How do we identify them?
  - Highest risk for progression to TB / reactivation
  - Target Rx to those with persistent Mtb infection
- T cell signatures (antigens recognized, phenotypes, functions of antigen-specific T cells) associated with LTBI *vs* clearance

T cell signatures of persistent versus cleared Mtb infection

Aim 1. Test the hypothesis that Mtb-specific CD4 and CD8 T cell responses associated with chemotherapy-mediated bacterial clearance are distinct from persistent Mtb infection.

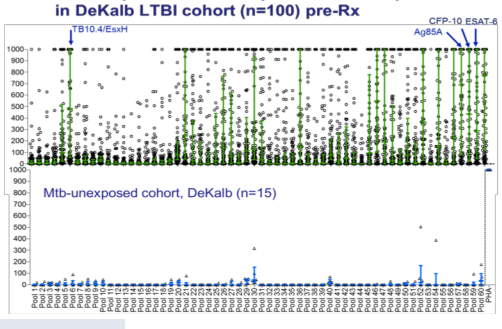
- Examine the spectrum of antigens recognized by Mtb-specific memory T cells in in untreated asymptomatic QFT+ individuals
- Is there a shift in the breadth of antigen-specific T cell responses after of INH-RPT treatment? (Aim 1a)
- Define the phenotypes and functional capacities of Mtb-specific memory T cells before and after treatment. (Aim 1b)

Do antigen-specific T cell responses change following 3 months of INH-RPT treatment?



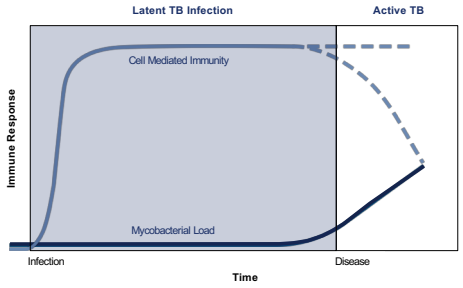
LTBI cohort at the DeKalb County Board of Health Refugee Clinic, GA

Divers spectrum of Mtb-specific T cell responses in DeKalb LTBI cohort (n=100) pre-Rx

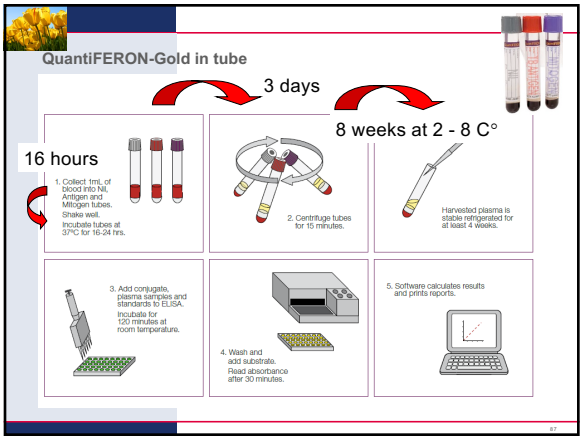


Immunological Basis of IGRAs

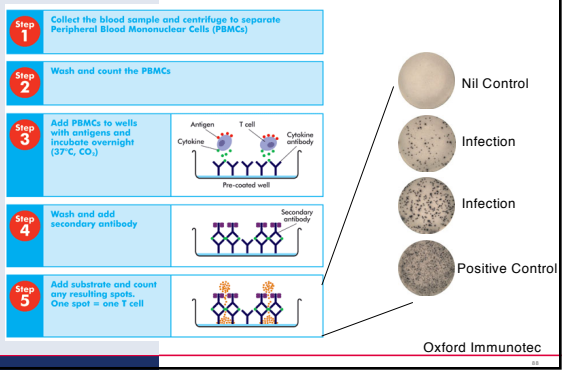
Measuring CMI is the key for a diagnostic test for LTBI



QuantiFERON-Gold in tube



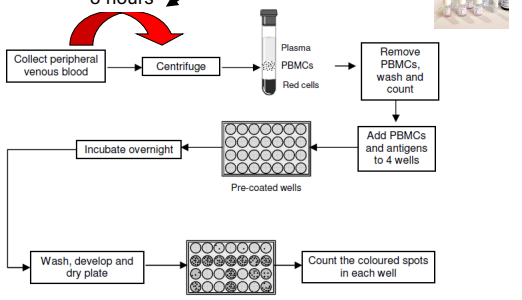
T-Spot.*TB*™: "Six easy Steps"



T-SPOT.TB

T-Cell *Xtend* – 32 hours

8 hours



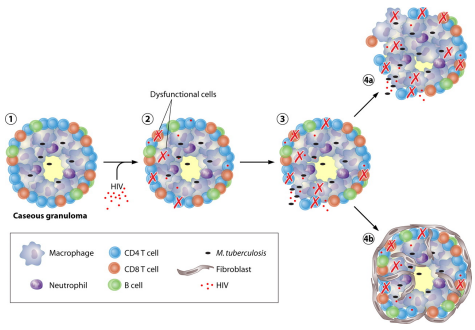
Meta -Analysis: IGRA – TST sensitivity & specificity

Deil R, et al Chest 2009

	QFT	T Spot.TB	TST
Sensitivity	81%	87.5%	69.9%

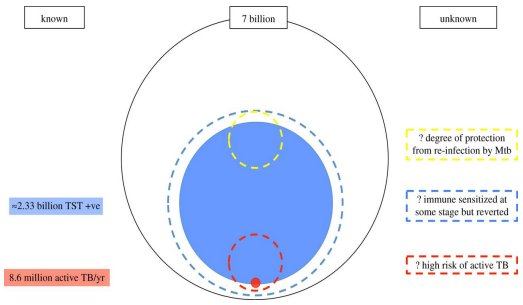
		T Spot.TB	TST
Specificity	99.2%	86.3%	59%

Proposed mechanism of HIV-induced reactivation of latent TB. (Stage 1) Necrotic granuloma functioning "normally" in an individual with latent TB. (Stage 2) HIV enters the granuloma and induces functional changes within T cells and macrophages.



Diedrich C R , and Flynn J L Infect. Immun. 2011;79:1407-1417

The known vs. the unknown



The Process LTBI ----→ TB