Latent Tuberculosis Infection

Controversies in Diagnosis and Management of LTBI

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The opinions expressed in this talk are mine and should not be construed as official views of the US Department of State.
LTBI

Why at the CME meeting?

• TB is still common in much of the developing world

• Many of the participants in today’s conference are responsible for health care of individuals living in, traveling to, or coming from, high TB threat zones.

TB is a perennial concern
  – DoD and other USG agencies
  – Multinational companies
  – Health Care organizations

• Current state of affairs:
  – Confusion in the medical literature
  – Hysteria in the media whenever TB is mentioned
So many confusing and contradictory recs?!  
A bewildering number of studies with markedly different findings

- Different studies address the needs of different audiences: WHO, CDC, DoD, DoS, multinational corps, Health Corps organizations
  - High TB prevalence vs low TB prevalence (developing vs industrialized)
  - High BCG background vs no BCG background (Europe vs US)
  - Feasibility in resource limited settings (LTBI testing of any type)
  - Cost in high resource settings (IGRAs for $$$ vs TST for pennies)

- No true “gold standard” for the diagnosis of TB
  - Sensitivity and specificity when tested in highly prevalent settings does not translate to low prevalence settings and vice versa

- New diagnostic tests (i.e. IGRA) are continuing to evolve
  - Makes even recently performed studies “apples vs oranges”
• **Latent TB Infections (LTBI) Controversies**
  - **Who should we be screening?**
    • Americans working in CONUS
    • Americans working in high TB threat areas
    • Host nation employees in high TB threat areas
  - **TST (Tuberculin Skin Test) vs IGRA (Interferon γ Release Assay)**
    • Which PPD product should we use? *Tubersol* vs *Aplisol* vs others
    • Which IGRA should we use? *Quantiferon Gold* vs *T Spot-TB*
  - **Treatment of LTBI**
    • 9 months Isoniazid vs 4 month rifampin vs 12 doses of weekly isoniazid and rifapentine

• **Literature discussion**

• **Recommendations**
  - Few clear answers to most questions
TB and LTBI Worldwide
Markedly decreasing but still incredibly prevalent

• 2nd only to HIV/AIDS as the greatest killer due to an infectious agent.

• In 2012, 8.6 million ill and 1.3 million died from TB.

• >95% of TB deaths occur in low- and middle-income countries.

• In 2012, ~530,000 children became ill and 74,000 HIV-negative children died of TB.

• TB is a leading killer of people living with HIV causing ¼ of all deaths.

• The TB death rate dropped 45% between 1990 and 2012.

• Sub Saharan Africa has highest TB rates (>500/100,000) while many industrialized nations are <10/100,000.

• LTBI is present in ~ 2.2 billion people or ~ ⅓ of the world’s population.

http://www.who.int/mediacentre/factsheets/fs104/en/
US TB and LTBI rates in 2012
Decreasing annually since 1993 to lowest levels

- 9,945 TB cases (rate of 3.2 cases/100,000)
  - 63% of reported US TB cases in the United States occurred among foreign-born
  - foreign-born TB rate (15.9/100,000) ~11x that among U.S.-born (1.4/100,000).

- Rates among US born ethnic groups:
  - American Indians or Alaska Natives: 6.3/100,000
  - Asians: 18.9/100,000
  - Blacks or African Americans: 5.8/100,000
  - Native Hawaiians and other Pacific Islanders: 12.3/100,000
  - Hispanics or Latinos: 5.3/100,000
  - Whites: 0.8/100,000

- Estimated 11 million LTBI infections (~4% of the population)
Why Targeted Testing?
Study of 39,920 US TB cases in 2006-08

• 79.7% of TB cases in the US are from reactivation

• Reactivation rates appear to be greater among foreign born vs US born in 2006-08.
  • Foreign born: 0.098 cases per 100 person-years
  • US born: 0.084 cases per 100 person-years
  • US reactivation rates in the 1950s: 0.100–0.160 per 100 person-years

• Reactivation rates are 5x higher in those with old, healed TB lesions who were never treated
  – Over the last 50 years these individuals are much less common in the US but are more common in much of the developing world

LTBI screening for employees?

- All staff in the US and overseas?
  - Focused screening for higher risk populations are the recs from the WHO and CDC. Especially HCWs.
  - TSTs or IGRAs in low risk populations yields many false positives

- DoD screens at accession and is moving to decrease number of TSTs performed after accession. Risk questionnaires annually.
  - Very low rates in the DoD

- DoS continues to screen all US direct hires at accession and then every 1-2 years while OCONUS

- Staff at embassies in high TB risk areas are generally screened with CXR at hiring and then screened with questionnaires
Scope of the Problem

Department of State (USG employees and families only)

DoS Health Unit LTBI 2013
Jan thru 15 Nov 2013

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<thead>
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<th>POST</th>
<th>New Positive TSTs</th>
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<td>Washington, DC</td>
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<tr>
<td>Mexico City</td>
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<td>Taipei</td>
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<tr>
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<tr>
<td>Monrovia</td>
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<td><strong>Total</strong></td>
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DoS Skin Test Conversions
2008-2013

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<th>Year</th>
<th>New Positive TSTs</th>
<th>WASH</th>
<th>OCONUS</th>
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<td>244</td>
<td>121</td>
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<td>2010</td>
<td>240</td>
<td>240</td>
<td>63</td>
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<tr>
<td>2011</td>
<td>151</td>
<td>151</td>
<td>91</td>
<td>242</td>
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<tr>
<td>2012</td>
<td>100</td>
<td>100</td>
<td>123</td>
<td>223</td>
</tr>
<tr>
<td>2013 (thru 15 Nov)</td>
<td>105</td>
<td>105</td>
<td>74</td>
<td>179</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>1137</strong></td>
<td><strong>1137</strong></td>
<td><strong>577</strong></td>
<td><strong>1714</strong></td>
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</tbody>
</table>

Total TSTs performed MED DC 2008-13: 18,008
TST conversion rate in MED DC: 6.31%

2 documented active TB cases over last 10 years
TB cases in the US military
1998-2012

• 128 cases of active TB or 0.6 cases/100,000.
  – Rate < ⅕ of that in the overall US population

• Of cases from 2008 to 2012:
  – 58% of the TB disease cases diagnosed were associated with + TST at the time of accession
    • 21% of the above had active TB at accession
  – 45% were born outside the US

• 24% associated with deployment to Iraq or other high risk areas

Risk in Immigrants from High Incidence areas
Mainly India, Pakistan and Bangladesh

- 402 immigrants to the UK with + TST and normal CXRs followed for 15 years
  - 10 years: 13.5% with active TB
  - 15 years: 16.3% with active TB
- US TB rate in 2012:
  - 3.2 cases per 100,000
- Rate in this study cohort:
  - 1297 per 100,000

Coming from and going to High TB Risk Countries

Sutton’s Law applies

- Local epi profiles are most useful to identify high risk countries
  - base testing and treatment on local immigration patterns and epi

- 2011, ~ 62% of US TB cases occurred in foreign-born individuals.
  - The majority of U.S. cases among foreign-born individuals are in people from 7 countries:
    - Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala

- Identify high risk nations where employees may be posted as focus areas for TB screening
  - Those going to and coming from low and moderate risk areas of Western Europe, Australia, New Zealand, Japan and many areas of the Americas are in low/mod risk areas and may not need screening. Similar for host nation staff in these areas.
  - Travelers and local staff visiting medium and high incidence should have increased scrutiny and be focused on for screening

http://www.stoptb.org/countries/tbdata.asp
What defines a high TB risk nation?

WHO categories by country-level TB incidence

1. Low incidence: less than 30 per 100,000.
2. Moderate incidence: 30-100 per 100,000.
3. Medium incidence: 100-300 per 100,000.
4. High incidence: >300 per 100,000.

80% of global TB from these 22 nations
TB Screening Host Nation Staff
State Department “Policy”

• Medical screening is NOT performed by embassy Health Units but in the local community

• New hires have a screening questionnaire and CXR as part of initial appt
  – Drivers have TB screening as part of a required driver’s physical performed every 2 years

• Most staff, even in high TB threat areas, are NOT screened subsequently (except HCWs)
  – Health Units are encouraged to develop policy depending on the local situation
LTBI Screening of Overseas Staff?
Are TSTs worth the trouble in high prevalence countries?

• What is the best way to monitor staff in high prevalence countries who may infect American staff?

• With very high background rates of TB in nations that do not treat LTBI is testing worthwhile? Maybe should test
  – Study of 107 healthy Ethiopians
    • 46.7% had a positive TST result (TST≥10 mm),
    • 43.9% had a positive QFT-GIT assay result
    • 44.9% (95%CI: 35.2% to 54.8%) had BCG scar.
    • There was strong agreement between TST (TST ≥10mm) and QFT-GIT assay

• Current policy has been NOT to perform TSTs on LES (Locally Engaged Staff) in high risk nations. Maybe shouldn’t test
  – 23/26 of State Dept drivers in Guyana were TST positive >10 mm

Testing for Latent TB
Perennial confusion

- **TST (Tuberculin Skin Test)**
  - *Tubersol vs Aplisol vs local PPD product*

- **IGRA (Interferon Gamma Release Assay)**
  - Most commonly *Quantiferon Gold in Tube*
    - Measures IFN produced by T cells
  - *T-Spot.TB* is similar test
    - quantifies IFN producing T cells (spots)

- Routinely performing an IGRA on all those with a positive TST is NOT RECOMMENDED by WHO or CDC
Latent TB Infections
TST vs IGRA
(aka PPD vs Quantiferon)

• Advantages of TST
  – Inexpensive
  – Can be used in young children

• Disadvantages
  – Subjective interpretation
  – Different PPD different results
  – Requires two visits
  – Cross reactivity with other mycobacteria esp BCG
  – Booster phenomenon

• Advantages of IGRA
  – More objective results
  – Single visit
  – Results may be in 24 h
  – Prior BCG does NOT cause false positives
  – No booster phenomenon

• Disadvantages
  – Expensive
  – Limited data for use in:
    • children <5yo
    • Recently exposed
    • Immunocompromised
  – Specimen handling
Interferon \( \Gamma \) Release Assays

Quantiferon Gold\textsuperscript{®} or T Spot\textsuperscript{®}

- 6-7 mL blood sample is incubated with synthetic versions of two \( M.\text{tb} \) antigens (ESAT-6 and CFP-10) for 16-24 hours.

- Patients infected with \( M.\text{tb} \) will produce interferon which is bound by anti IFN \( \Gamma \) Ab assayed via ELISA.

- Advantages:
  - Requires a single patient visit to draw a blood sample.
  - Results available within 24 hours.
  - No “booster phenomenon” with subsequent tests
  - Not subject to reader bias that can occur with TST.
  - Not affected by prior BCG vaccination
  - Not affected by prior non tuberculous mycobacteria infxn

Guidelines for Using the QuantiFERON\textsuperscript{®}-TB Gold Test for Detecting \textit{Mycobacterium tuberculosis} Infection, United States

MMWR2005;54(No. RR-15)
Interferon Gamma Release Assay (IGRA)
T cell release of interferon in response to *M tb* infection

*Quantiferon Gold®* or *T Spot.TB®*

An immune system that has experience with TB has T lymphs that are sensitized to TB antigens and will produce interferon gamma when re-exposed.

Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting *Mycobacterium tuberculosis* Infection, United States MMWR2005;54(No. RR-15)
Which test to use for LTBI?

You can find a study to support every option

• Among US staff
  – Screening Questionnaire – if TB risk identified then do TST or IGRA or in some cases CXR; if previously positive TST or IGRA assess for onset of new sx c/w active TB
  – TST performed initially and then with what periodicity?
  – IGRA performed in those with prior hx BCG or equivocal TST
  – CXR – in those with possible LTBI or active disease or in those with previously positive tests and a new exposure
Which test to use for LTBI?
You can find a study to support every option

• Among host nation staff in high risk countries
  – Screening Questionnaire
  – TST performed initially and then with what periodicity?
  – IGRA performed in those with prior hx BCG or equivocal TST
  – CXR:
    • screen all employees upon initially starting position
    • Repeat if periodic questionnaire is positive
    • Consider repeat if clinical signs of TB, (typically chronic cough)
Dump TSTs in Favor of IGRAs for Screening?
Maybe not as good an option as we originally thought

• Stanford University Medical Center screens >10,000 employees for TB annually:
  – TST conversion rate of 0.4% in 2006
  – (US hospitals TST conversion rates range <0.1 to 1.2%)

• Changed to IGRA in 2007
  – Numerous individuals with no new TB risk factors were positive with conversion rate of 4.4%
  – Repeat IGRA within 6 weeks for newly positive
  – Significant discordance on serial testing
  – Tendency for Occ Health staff to repeat IGRAs until negative
".. IGRA results have proved more dynamic in serial testing than anticipated"

- 9,153 HCWs with ≥ 2 IGRA tests.
  - 8,227 individuals with a negative result:
    - 361 (4.4%) converted their IGRA result over 2 years.
    - 261 (72.3%) of the HCWs with conversions underwent repeat short-term testing after the first positive result with 169 (64.8%) reverting.
    - IFN-γ cutoff of ≥5.3 IU/ml (manufacturer’s cutoff ≥0.35 IU/ml) yielded a conversion rate of 0.4%, equal to institution’s historical TST conversion rate.

- Conclusions:
  - Manufacturer’s definition of IGRA conversion results in an inflated conversion rate incompatible with a low-risk setting.
  - Significantly higher Quantiferon cutoff value needed to match historical TST conversion rate.
  - Nonreproducible conversions in most converters suggested false-positive results.
  - the IGRA as currently designed is too sensitive in a low risk population.

HCWs at Beth Israel Deaconess

Discordant QuantiFERON-TB Gold Test Results Among US Healthcare Workers With Increased Risk of Latent Tuberculosis Infection: A Problem or Solution?

- 143 TSTs + tested with QFT-G only 18% +.
  - Those with high TB risk 28% QFT-G +
  - Those with high TB risk and QFT-G (−) were tested with an extended stimulation T-Spot.TB IGRA and an additional 33% were identified as positive.

- CONCLUSIONS—The extreme discordance between the results of the clinical diagnostic algorithm and the IGRA results raises concern about the sensitivity of the IGRA for detection of LTBI in HCWs.
  - Results of extended stimulation assays suggest that many increased TB risk HCWs have indeed been sensitized to *M. tuberculosis*.
  - It is possible that the QFT-G assay identifies those at higher reactivation risk rather than all previously infected,
  - the absence of long-term follow-up data, we should interpret negative QFT-G results with some caution.

While back in Norway
TST gave more positive results than IGRA among 387 HCWs

- 13 (3.4%) demonstrated a persistent positive IGRA
- 214 (55.3%) had a TST \( \geq 6 \) mm and 53 (13.7%) a TST \( \geq 15 \) mm.
- 10 (4.7%) of HCW with a positive TST were IGRA positive.
- Origin from a TB-endemic country was the only risk factor associated with a positive IGRA (OR 14.13, 95% CI 1.37 - 145.38, \( p = 0.026 \))

- Conclusion: the concordance between TST and IGRA is poor and IGRA only is preferable in a low prevalence group with BCG and TST boosting

Gran et al. Screening for latent tuberculosis in Norwegian health care workers: high frequency of discordant tuberculin skin test positive and interferon-gamma release assay negative results. BMC Public Health 2013, 13:353
TST vs IGRA in the DoD?

Not an easy answer

• Recruits who were born in countries with a high prevalence of TB were 26–40 times more likely to have discordant results involving a positive TST result and a negative IGRA result than were recruits born in countries with a low prevalence of TB.
  – 19 (50%) of 38 recruits with this type of discordant results had TST induration >15 mm

• Conclusion:
  – Negative QFT-G results for recruits born in countries where TB is highly prevalent and whose TST induration was ≥ 15 mm suggest that the QFT-G may be less sensitive than the TST in detecting LTBI.

Mazurek GH et al. Detection of *M. tuberculosis* infection in USN recruits using the TST or whole-blood IGRA. Clin Infect Dis. 2007; 45:826–836.
IGRA too sensitive or TST too sensitive?

Testing in low prevalence populations

Hypothesis:
• It appears that some individuals with LTBI of long duration may lose their IGRA response while maintaining a positive TST
• When a more sensitive IGRA is used, many of the TST +, IGRA – have concordant results

Implications:
• Do we want to capture all the LTBI cases even if they are “old convertors/reactors” who are beyond the highest risk period (1st 2 years) for reactivation TB and offer them treatment?
• Would we prefer to leave the IGRA at it’s current level of sensitivity and capture primarily more recently acquired LTBI that is still at the highest risk for reactivation.
TST vs IGRA?

- Still contentious
- Possibly some modification of IGRA cutoffs for those in serial testing programs
- As the CDC recs: pick one or the other but not both
  - Do not routinely follow all positive TSTs with an IGRA
- DoS MED recs:
  - Continue TSTs in American staff
    - due to cost in the US and availability OCONUS
  - Tubersol is PPD of choice over Aplisol (no non US PPD used)
  - Use IGRA in equivocal cases or TST positives with hx BCG
Therapies for LTBI

- **INH** daily for 9 months
- **Rifampin** daily for 4 months (6 months peds)
- **PZA-Rifampin** qd for 2 months:
  - 78% vs 66% (INH 9 months) completion
  - 6.1% with reversible hepatotoxicity (2.0% in INH group)
  - Deaths in some studies (poor follow up)
  - NOT recommended by CDC
- **INH - Rifapentine** q week for 12 weeks via DOT
  - Rec as an alternative by CDC Dec 2011 based on a number of studies
  - RCT in Brazil, Canada, Spain, and USA compared 12 doses of INH-RPT given as weekly DOT with 9 months of self-supervised daily INH in 773 participants ≥2 yo who had LTBI
  - completion rate was 82% for INH-RPT and 69% for INH (p<0.01).
  - Of 22 TB cases, seven were in INH-RPT recipients, and 15 were in INH recipients (hazard ratio: 0.38 for INH-RPT, CI = 0.15–0.99, adjusted for TB risk factors).


CDC. *Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.* MMWR 2011; 60:1650-3
# Treatment Regimens for Latent TB Infection

<table>
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<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
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<tbody>
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<td>Daily</td>
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<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

**Note:** Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.
LTBI Conclusions

• Despite decades of studies still no definitive answers
  – With diminishing TB rates screening focused on high risk groups is most cost effective and WHO & CDC recommended

• As experience with IGRAs increases it’s exact role will be better defined

• The TST, as imperfect as it is, remains a good choice

• Short course DOT is probably the best treatment option for LTBI
Tuberculosis
Natural History

The natural history of tuberculosis can be divided into several stages:

1. **Exposure**
   - **Dendritic cell** contact with bacteria.

2. **4–6 weeks**
   - **Elimination of bacteria** by the immune system.
   - **T cell** response.
   - **Innate response**.

3. **Years – decades**
   - **Latent TB**.
   - **Re-infection and re-activation**.
   - **Elimination of bacteria**.

4. **Active TB**
   - **Macrophage** activity.

The process is illustrated with a timeline and detailed cells and pathways.
Thanks for your attention!

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