TB Prevention and Control in the United States

- The fundamental strategies include:
  - Early detection and treatment of patients who have active TB disease
  - Therapy for persons with latent TB infection to prevent the development of TB
  - Prevention of institutional transmission of M. tb
  - BCG vaccination is not recommended as a routine strategy

Therapy for Latent Tuberculosis Infection

- Rationale
  - Reduce individual risk for developing active disease
  - Shrink pool of infected persons at risk for tuberculosis

Compartment Model of TB Epidemiology

(The TB-Naive Hosts)
Population Exposed LTBI Population Exposed LTBI

TB Contagious TB Treat LTBI

International strategy:
Detect Treat
Disinfect Separate

BCG (not in U.S.)

U.S. strategy:
Targeted Tuberculin Testing and Treatment of Latent TB Infection, *MMWR* 2000;49(No.6)
Newest Terminology

- Latent tuberculosis infection (LTBI)
- Treatment of LTBI (TLTBI)
- Targeted testing (TTTLTBI)
- “Decision to test is a decision to treat.”

Conditions that are counted under Medical Risk

- HIV infection
- Tuberculin skin test conversion
- Fibrotic lesions (on chest X-ray) consistent with old, healed TB
- Injection drug use
- Diabetes mellitus
- Prolonged high-dose corticosteroid therapy or other intense immunosuppressive therapy
- Chronic renal failure
- Some hematologic disorders, such as leukemia or lymphoma
- Specific malignant neoplasms, such as carcinoma of the head or neck
- Weight at least 10% less than ideal body weight
- Pulmonary silicosis
- Gastric surgery, or jejunoileal bypass
- Age 50 years
- Recent exposure to TB

Circumstances that are counted under Pop. (population) Risk

- Residency or occupation in high-risk congregate settings:
  - Prisons and jails
  - Health care facilities
  - Nursing homes and long-term facilities for the elderly
  - Shelters for homeless persons
- Birth in a country having a high prevalence or incidence of TB: Includes
  - Immigrants
  - Refugees
  - Asylum seekers
  - Some migrant workers
- Socioeconomic predictors of exposure:
  - Low income
  - Inner-city residence
  - Migrant labor

Reported TB Cases per 100,000 Population
United States, 1953 – 2000

Factors Affecting the Impact of TTTLTBI

- Tuberculin skin testing: the diagnosis
- Prediction of progression to disease
- Completion of therapy and programmatic costs
- Efficacy of treatment
- Safety of treatment
The Tuberculin Skin Test (TST)
- Some 2-12 wks after infection with \( M. \text{tb} \), there is a delayed-type hypersensitivity (DTH) reaction at the site of tuberculin injection
- DTH reactions begin 5-6 hrs after injection and reach a maximum at 48-72 hrs
- Since the 1930s, TST has been used to screen persons or populations for LTBI

Reading the Tuberculin Skin Test
- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters

Prevalence rate of LTBI
- Yield of testing
  - higher rate gives higher yield
- Predictive value of a positive result
  - higher rate gives better predictive value

Positive Predictive Value of a Tuberculin Test
*Am J Respir Crit Care Med; 2000, Vol 161, p 1389*

<table>
<thead>
<tr>
<th>Prevalence rate of TB Infection (%)</th>
<th>Specificity of 0.95</th>
<th>Specificity of 0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>0.99</td>
<td>0.999</td>
</tr>
<tr>
<td>50</td>
<td>0.95</td>
<td>0.99</td>
</tr>
<tr>
<td>25</td>
<td>0.86</td>
<td>0.97</td>
</tr>
<tr>
<td>10</td>
<td>0.67</td>
<td>0.91</td>
</tr>
<tr>
<td>5</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>1</td>
<td>0.16</td>
<td>0.49</td>
</tr>
<tr>
<td>0.1</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>0.01</td>
<td>0.002</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Classifying the Tuberculin Reaction

$\geq 5$ mm is classified as positive in:
- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

$\geq 10$ mm is classified as positive in:
- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

$\geq 15$ mm is classified as positive in:
- Persons with no known risk factors for TB

Skin Test Reactions to Mycobacterium tuberculosis Purified Protein Derivative and Mycobacterium avium Sensitin Among Health Care Workers and Medical Students in the United States

"Infections with NTM are responsible for the majority of 5-14 mm PPD reactions among US-born health care workers..."


Tuberculosis Screening in Private Physicians' Offices, Pennsylvania, 1996

"Only 8/59 (14%) physicians followed published guidelines for placement and reading of tuberculin tests."


QuantiFERON®-TB (QFT)

whole-blood IFN $\gamma$ release assay for the detection of $M. tuberculosis$ infection

QFT vs. TST

- in vitro
- multiple antigen mixes
- no boosting
- 1 patient visit
- minimal inter-reader variability
- results in 1 day
- stimulate w/ 12 hrs

- in vivo
- single antigen mix (PPD)
- boosting
- 2 patient visits
- inter-reader variability
- results in 2 - 3 days
- read in 48 - 72 hrs
Learning Objective (QuantiFERON)

Name prospective new blood tests that could detect latent infection as well as a skin test can?

QuantiFERON®-TB (QFT) is approved for specific indications. Research is underway for robust tests with broader applications.

Factors Affecting the Impact TTTLTBI

- Tuberculin skin testing
- Prediction of progression to disease
- Completion of therapy and programmatic costs
- Efficacy of treatment
- Safety of treatment

TB Prevention Effectiveness

Risk of Progression to TB

- Markers for risk:
  - recent infection
  - contacts
  - converters
  - underlying medical conditions: HIV infection

Risk of TB Disease by Time of M. tb Infection

- Among 1,472 persons enrolled in the placebo arm of 2 trials of the efficacy of LTBI (Ferebee SH. Adv Tuberc Res. 1970)
  - 19 developed TB in 1st yr of follow-up (FU)
  - 7 developed TB in subsequent 7 yrs of FU
  - Difference in case rate 12.9 vs 1.6 per 1,000 person-yrs

- Among 2,550 British children enrolled in the unvaccinated arm of TB vaccine study (Sutherland I. TSRU Prog Rep. 1978)
  - 121 (5%) developed TB in 15 yrs of FU
  - Of these, 54% cases during 1st yr, 82% within 2 yrs
Proportion of Persons with TB Infection and Disease Co-infected with HIV

<table>
<thead>
<tr>
<th>HIV+</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Infection</td>
<td>50%</td>
</tr>
<tr>
<td>TB Disease</td>
<td>10%</td>
</tr>
</tbody>
</table>

Factors Affecting the Impact of TTTLTBI

- Tuberculin skin testing
- Prediction of progression to disease
- Completion of therapy and programmatic costs
- Efficacy of treatment
- Safety of treatment

Table 1: Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>TB cases/1,000 persons-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of TB infection (1 year prior)</td>
<td>120.0 (1)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.0</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>36.0 (2)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>10.0 (1)</td>
</tr>
<tr>
<td>HIV seropositivity</td>
<td>100.0 (2)</td>
</tr>
<tr>
<td>Injected drug use</td>
<td>10.0 (1)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>36.0 (2)</td>
</tr>
<tr>
<td>Underweight for height (BMI &lt; 18.5)</td>
<td>2.8 (0-5)</td>
</tr>
<tr>
<td>Underweight for height (BMI &lt; 18.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Underweight for height (BMI &lt; 18.5)</td>
<td>3.0</td>
</tr>
<tr>
<td>Weight gain in 10% or more</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Factors that are counted under Pop. (population): Risk

- Residence or occupation in high-risk congregate settings: Prisons, jails, health care facilities, nursing homes, group homes
- Birth in a country having a high prevalence or incidence of TB: Includes refugees, immigrants
- Circumstances that are counted under Pop. (population): Risk
  - Low income
  - Inner-city residence
  - Migrant labor
  - Some migrant workers
  - Socioeconomic predictors of exposure: Low education, inner-city residence, migrant labor

TB Prevention Effectiveness

- Prevalence rate of LTBI
- Efficacy
- Efficiency
- Completion of therapy
- Risk of progression
Issues Associated With Completion of TLTBI

• Programs and systems
• Duration of regimen

Acceptability of Short-Course Rifampin and Pyrazinamide Treatment of Latent Tuberculosis Infection Among Jail Inmates

>21,000 admissions (1 yr.)
75% of inmates tested
68% of tests read
07.3% reactor rate
12.3% start rate
48% completion rate (81 inmates; 2-mo regimen)


A Tuberculin Screening and Isoniazid Preventive Therapy Program in an Inner-city Population

7,246 participants, various community settings
4,701 (65%) tests read
809 (17%) reactors
409 eligible for treatment
84 completed treatment
86-fold drop


Optimal Duration of INH Therapy for the TLTBI, MMWR 2000;49(No.6)

• The duration of INH therapy should be >6 months to provide maximum protection.
• Therapy for 9 months appears to be sufficient, with little or no value of longer treatment.

Effect of the Duration of INH Therapy on the Prevention of Active TB

<table>
<thead>
<tr>
<th>TB Case Rates</th>
<th>Reduction in TB Placebo INH (10 yr. follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients taking ≥80% of medication for:</td>
<td></td>
</tr>
<tr>
<td>10-12 mo</td>
<td>24.9</td>
</tr>
<tr>
<td>0 - 9 mo</td>
<td>18.6</td>
</tr>
<tr>
<td>Patients taking medication ≥10 months compliant for:</td>
<td></td>
</tr>
<tr>
<td>60%-79%</td>
<td>26.2</td>
</tr>
<tr>
<td>40%-59%</td>
<td>19.0</td>
</tr>
</tbody>
</table>


How Much Isoniazid Is Needed for the Prevention of Tuberculosis?


• Longer duration of therapy corresponded to lower TB rates among those who took 0-9 mo
• No extra increase in protection among those who took >9 mo
Use of Isoniazid for the Prevention of TB Among Patients Not Known to Be Infected with HIV

<table>
<thead>
<tr>
<th>Trial -- regimen</th>
<th>Population</th>
<th>Years of Observation</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPHS -- 12-mo INH</td>
<td>Pediatrics clinics</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>Health departments</td>
<td>contacts</td>
<td>4-10</td>
<td>57</td>
</tr>
<tr>
<td>Mental institutions</td>
<td>hospital/school</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Alaskan villagers</td>
<td>community</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>Health departments</td>
<td>inactive lesions</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

Isoniazid Preventive Therapy HIV Infection - TST Positive

- Protective Efficacy
  - Haiti: 83%
  - Uganda: 67%
  - Zambia: 70%
  - Kenya: 40%

Short-Course Regimens HIV Infection - TST Positive

- Rifampin-Containing
  - Haiti: 2RZ
  - Uganda: 3RH, 3RHZ
  - Zambia: 3RZ

Problems Associated with TLTBI

- Low adherence with INH therapy, mostly associated with long duration
- Potential better adherence with shorter (2RZ) reg
- Effectiveness of 2RZ has not been studied in
  - HIV-seronegative persons (decreased tolerability?)
  - children
- High pill burden, drug toxicity, drug interactions with 2RZ
- DOT necessary for intermittent regimens
USPHS Study 26: Highly intermittent short-course treatment of LTBI

- Patients with LTBI at high risk for developing active disease will receive INH for 9 months OR once weekly INH/rifapentine for 12 doses (3INH/RPT)
- Main study outcome: rate of development of active tuberculosis
- Almost ~3,000 enrolled to date, sample size = 8,000 total or 4,000 per arm

Factors Affecting the Impact of LTBI

- Tuberculin skin testing
- Prediction of progression to disease
- Completion of therapy and programmatic costs
- Efficacy of treatment
- Safety of treatment

Toxicity of Isoniazid in Persons Without HIV Infection

- Hepatitis 10.3/1000 persons
- Death due to hepatitis 0.6/1000 persons
- Age-related hepatotoxicity
  - \( \leq 35 \) years 0.6-1.3/100 persons
  - \( > 35 \) years 2.0-3.1/100 persons
- Risk factors
  - Active liver disease, Alcohol
  - Mortality risk associated with pregnancy, Hispanic ethnicity

Reports of Severe Liver Injury Associated with RZ Treatment of LTBI

- 40 *cases (17 jurisdictions)
  - 32 hospitalized
  - 8 fatal
  - 33 investigated
- 96 other reports of liver injury

* A case is defined as a person who was hospitalized or died due to liver injury associated with RZ.

Essential TB Infection Control Activities

- Screening. Measures to identify persons with active TB disease or LTBI
- Containment. Measures used to prevent transmission
- Assessment. Collection and analysis of data to monitor whether the S&C activities are being implemented

[Diagram of TB infection control activities]
**Recommendations for BCG Vaccination**

- Not recommended in immunization programs or TB control programs in the U.S.
- BCG vaccination undertaken after consultation with health department
  - Infant or child with negative skin test and continuous exposure
  - HCW in areas of high MDRTB and deficient TB infection control precautions
- Contraindicated for persons with impaired immunity
BCG Vaccination and Tuberculin Skin Testing

- Tuberculin skin testing not contraindicated for BCG-vaccinated persons
- LTBI diagnosis and treatment for LTBI considered for any BCG-vaccinated person whose TST is positive, if any of these circumstances are present:
  - Was contact of another person with infectious TB
  - Was born or has resided in a high TB prevalence country
  - Is continually exposed to populations where TB prevalence is high

TB Control in the US

Population/Exposure Risks
Medical Risks

Prevention opportunities

For Tuberculosis
Cure = Prevention