

Population Screening and Treatment of LTBI in TB Control in the US

Margarita Elsa Villarino MD MPH
Division of TB Elimination, CDC
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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



For Tuberculosis
Cure = Prevention



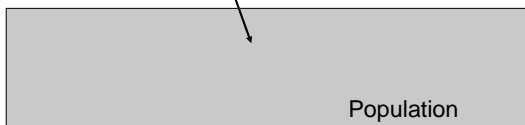
Therapy for Latent Tuberculosis Infection

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



Compartment Model of TB Epidemiology

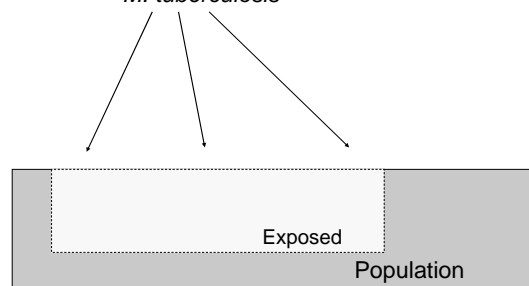
(The TB-Naïve Hosts)



Population



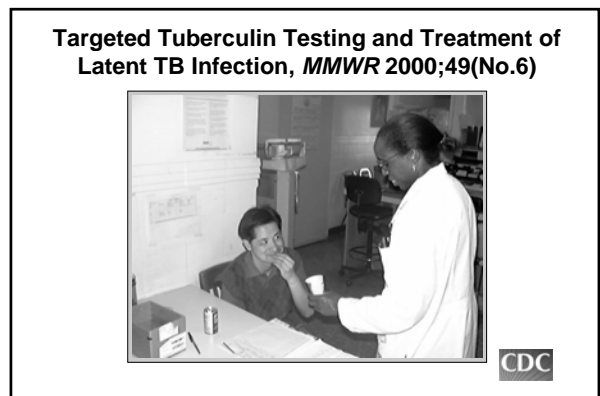
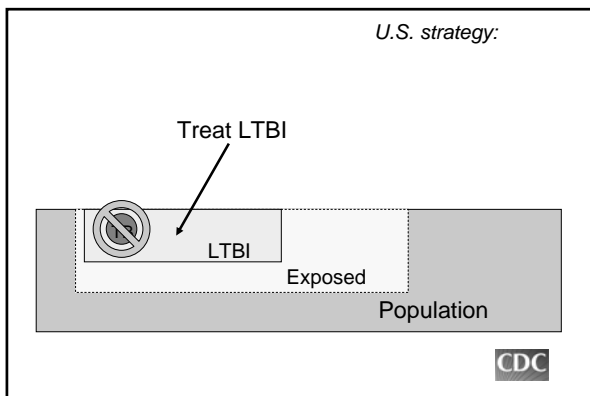
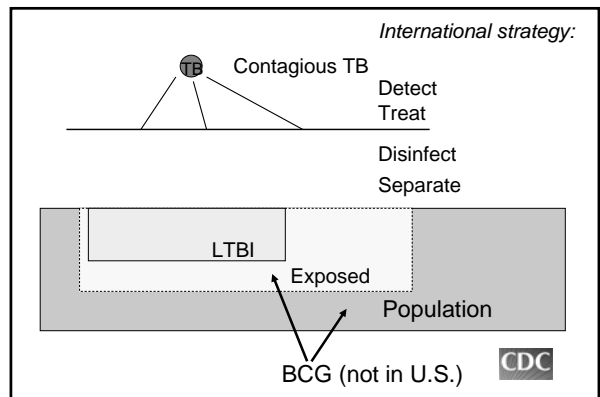
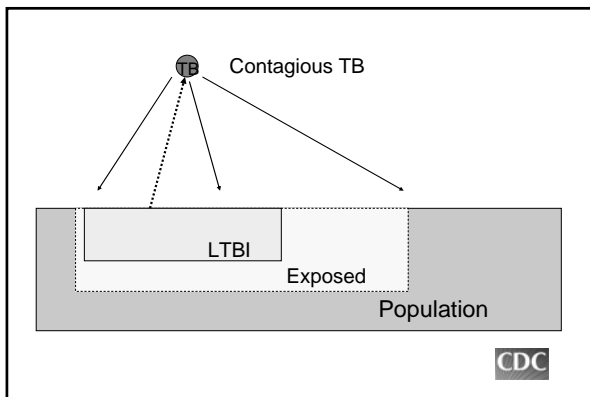
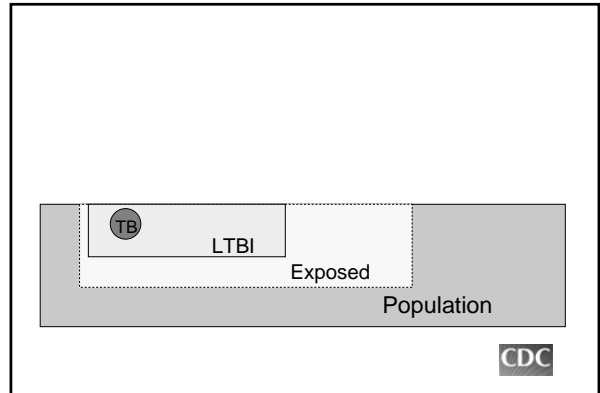
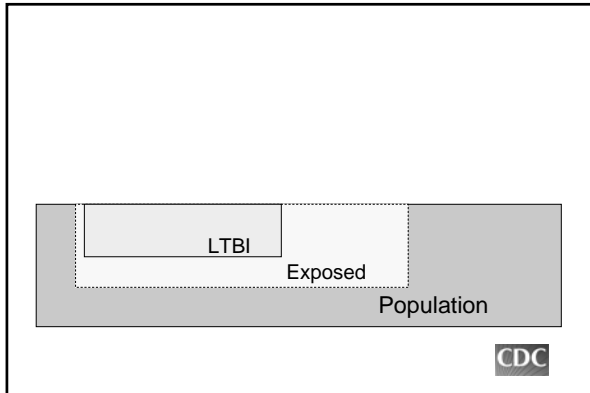
M. tuberculosis



Exposed

Population





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 intensive 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
 Gastrectomy, or jejunioileal bypass
 Age ≥ 5 years
 Recent exposure to TB



Circumstances that are counted under Pop. (population) Risk

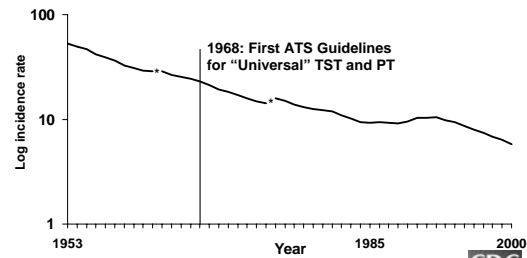
Residency or occupation in high-risk congregate settings:
 Prisons and jails
 Health care facilities
 Nursing homes and long-term facilities for the elderly
 Shelters for homeless persons

Birth in a country having a high prevalence or incidence of TB. Includes
 Immigrants
 Refugees
 Students
 Some migrant workers

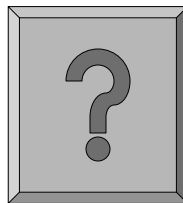
Socioeconomic predictors of exposure:
 Low income
 Inner-city residence
 Migrant labor



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



*Change in case definition

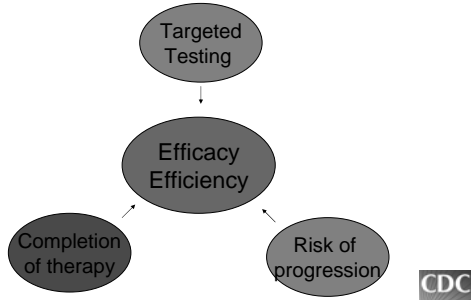


Factors Affecting the Impact of TTTLTBI

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

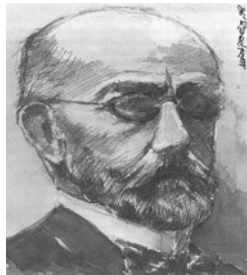


TB Prevention Effectiveness



The Tuberculin Skin Test (TST)

- Some 2-12 wks after infection with *M. 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
- CDC

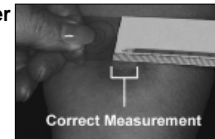


Robert Koch (1843 -1910)

CDC

Reading the Tuberculin Skin Test

- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters



CDC

Prevalence rate of LTBI

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

Positive Predictive Value of a Tuberculin Test

Am J Respir Crit Care Med; 2000, Vol 161, p 1389

Positive Predictive Value

Prev of TB infection (P₊) Specificity of 0.95 Specificity of 0.99

CDC

Classifying the Tuberculin Reaction

≥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

≥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

≥15 mm is classified as positive in

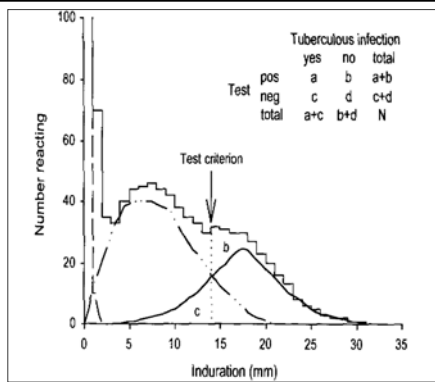
- Persons with no known risk factors for TB



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...”

von Reyn CF, Horsburgh CR, Olivier KN. International Journal of Tuberculosis & Lung Disease. 2001;5:1122-1128.



Tuberculosis Screening in Private Physicians' Offices, Pennsylvania, 1996

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

Schulte JM, Moore M, Kistler V, Margraf P, Christman R, Valway SE, Onorato IM, Stader B. American Journal of Preventive Medicine 1999;16:178-181.



QuantIFERON®-TB (QFT)

whole-blood IFN γ release assay for the detection of *M. tuberculosis* infection



QFT vs. TST

- | | |
|---|--|
| <ul style="list-style-type: none"> • <i>in vitro</i> • multiple antigen mixes • no boosting • 1 patient visit • minimal inter-reader variability • results in 1 day • stimulate w/i 12 hrs | <ul style="list-style-type: none"> • <i>in vivo</i> • 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.

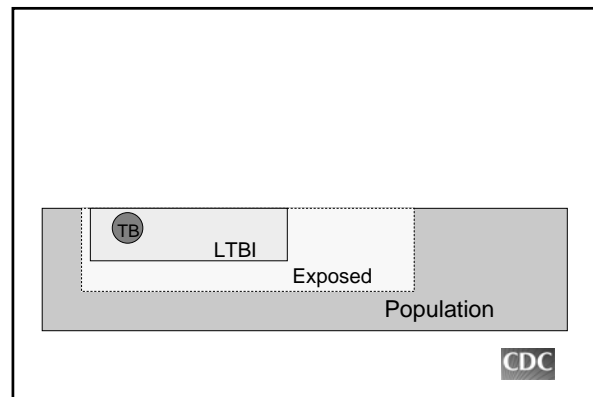
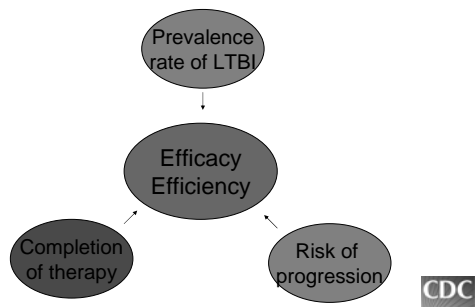


Factors Affecting the Impact TTTTLTBI

- 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

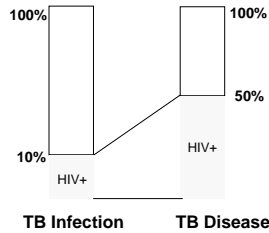


Table 2. Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors

Risk factor	TB cases/1,000 person-years
Recent TB infection	
Infection <1 yr past	12.9 (6) ^a
Infection 1-7 yr past	1.6
Human immunodeficiency virus (HIV) infection	35.0-162 (28)
Injection drug use	
HIV seropositive	76.0 (37)
HIV seronegative or unknown	10.0 (37)
Silicosis	68 (36)
Radiographic findings consistent with prior TB	2.0-13.6 (32-34)
Weight deviation from standard	
Underweight by ≥15%	2.6 (35)
Underweight by 10-14%	2.0
Underweight by 5-9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

^a Numbers in parentheses are reference numbers.



Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

Clinical condition	Relative risk
Silicosis	30 (37,38) [†]
Diabetes mellitus	2.0-4.1 (24-41)
Chronic renal failure/hemodialysis	10.0-25.3 (39-41)
Gastroctomy	2-5 (45-47)
Jejunoileal bypass	27-83 (49-49)
Solid organ transplantation	
Renal	37 (60)
Cardiac	20-74 (51,52)
Carcinoma of head or neck	16 (53)

* Relative to control population, independent of tuberculin test status.
[†] Numbers in parentheses are reference numbers.



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
- Students
- Some migrant workers

Socioeconomic predictors of exposure:

- Low income
- Inner-city residence
- Migrant labor

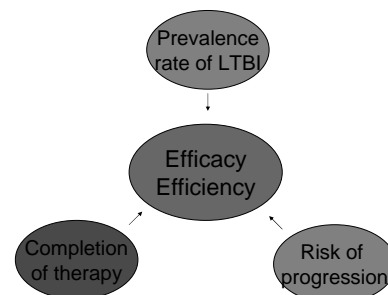


Factors Affecting the Impact of TTTLTBI

- Tuberculin skin testing
- Prediction of progression to disease
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TB Prevention Effectiveness



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)

↓
260-fold drop

Bock N N, Rogers T, Tapia J R, Herron, G D, DeVoe, B, Geiter, L J. Chest 2001;119:833-837.



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

Bock NN, Metzger BS, Tapia JR, Blumberg HM. American Journal of Respiratory & Critical Care Medicine. 1999;159:295-300.



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

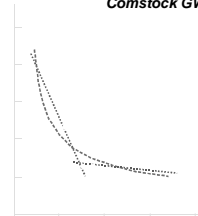
	TB Case Rates		Reduction in TB
	Placebo	INH	(10 yr. follow-up)
Patients taking ≥80% of medication for:			
10-12 mo	24.9	7.9	68.3
0 - 9 mo	18.6	15.6	16.1
Patients taking medication ≥10 months compliant for:			
60%-79%	26.2	11.2	57.3
40%-59%	19.0	9.1	52.1

Ferebee, SH. Adv Tub Res 1970;17:28-106



How Much Isoniazid Is Needed for the Prevention of Tuberculosis?

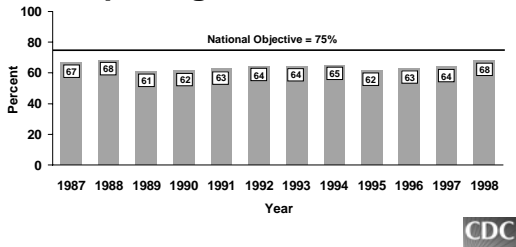
Comstock GW, Int J Tuberc Lung Dis 1999;3:847-50



- 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

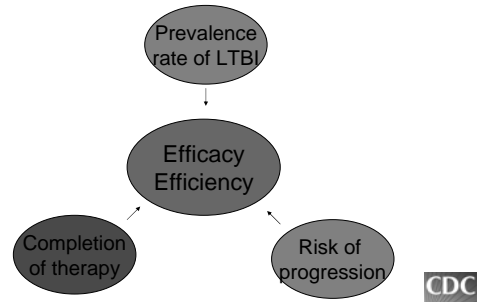


Percentage of Infected Contacts Age 15 - 34 Completing Treatment for LTBI



CDC

TB Prevention Effectiveness



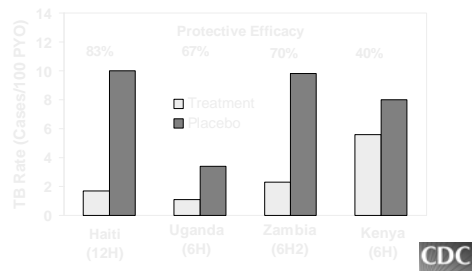
CDC

Use of Isoniazid for the Prevention of TB Among Patients Not Known to Be Infected with HIV

Trial -- regimen	Population	Years of Observation	% Reduction
USPHS -- 12-mo INH	primary tuberculosis	10	88
Pediatrics clinics	primary tuberculosis		
Health departments	contacts	4-10	57
Mental institutions	hospital/school	10	62
Alaskan villagers	community	6	59
Health departments	inactive lesions	5	60

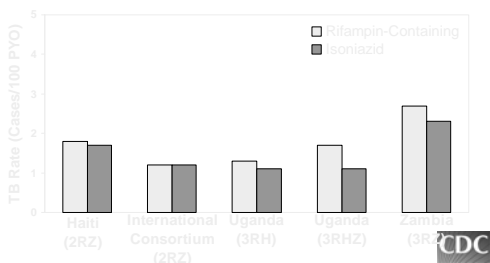
CDC

Isoniazid Preventive Therapy HIV Infection - TST Positive



CDC

Short-Course Regimens HIV Infection - TST Positive



CDC

Problems Associated with TLBTI

- Low adherence with INH therapy, mostly associated with long duration
- Potential better adherence with shorter (2RZ) regs
- 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

CDC

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 TTTLTBI

- Tuberculin skin testing
- Prediction of progression to disease
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Toxicity of Isoniazid in Persons Without HIV Infection

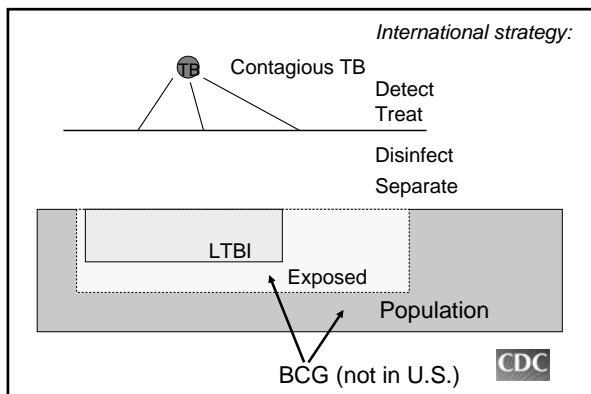
- Hepatitis 10.3/1000 persons
- Death due to hepatitis 0.6/1000 persons
- Age-related hepatotoxicity
 - ≤ 35 years 0.6-1.3/100 persons
 - > 35 years 2.0-3.1/100 persons
- Risk factors
 - Active liver disease, Alcohol
- Mortality risk associated with pregnancy, Hispanic ethnicity



Reports of Severe Liver Injury Associated with RZ Treatment of LTBI October 2000 – May 23, 2002

- 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



Prevention and Control of Tuberculosis
in Correctional Facilities

Vaccination Against Tuberculosis



CDC

NATURAL PROTECTION AGAINST TB

Risk of TB among Student Nurses, Oslo, 1924-6

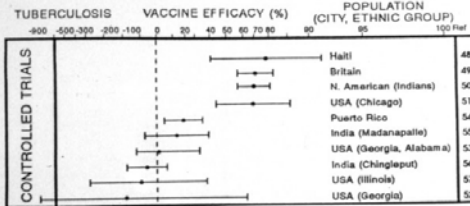
PPD STATUS AT ENROLLMENT	NUMBER	CASES OF TB (%)
Negative	185	62 (34)
Positive	152	3 (2)

from Heimbeck, 1949

EFFECT OF PARENTERAL BCG ON RATES OF TB IN STUDENT NURSES, OSLO, 1927-35

PPD STATUS	BCG STATUS	NUMBER	TB CASES (%)
Positive	No	436	27 (6)
Negative	Yes	368	37 (10)
Negative	No	95	42 (44)

from Heimbeck, 1949



PROBLEMS WITH BCG

Different vaccine strains
Dose-dependent protection
Age-dependent protection
Interaction with "natural immunization" by environmental mycobacteria
PPD skin test conversion
BCG disease

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

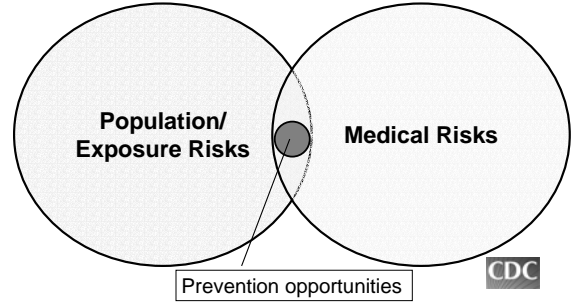
CDC

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



**For Tuberculosis
Cure = Prevention**

