Diagnosis and Treatment of Active TB Disease in Adults

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74 YO Female

- **Physical Exam**
  - **Temp 97.8°F; BP 136/77; Pulse 136; RR 22**
  - **O_2 Sat. 98% on 3L/min NC O_2**
  - **NAD**
  - **Chest: crackles R base**

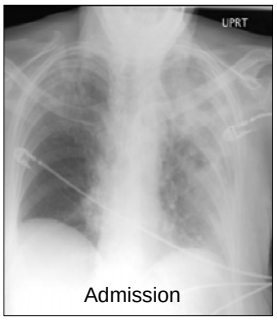
LAB:
WBC 9,700
PMN 86.5%, Lymph 8.2% Mono 5.2%
Hb 9.3 gm/dL; Platelets 570K;
BUN/Creat 12/0.84 mg/dL

Elderly patient with chronic cough and weight loss

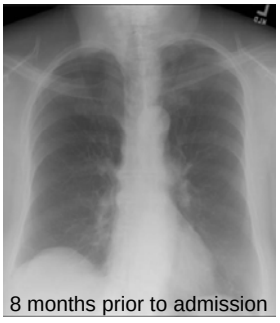
HOPI

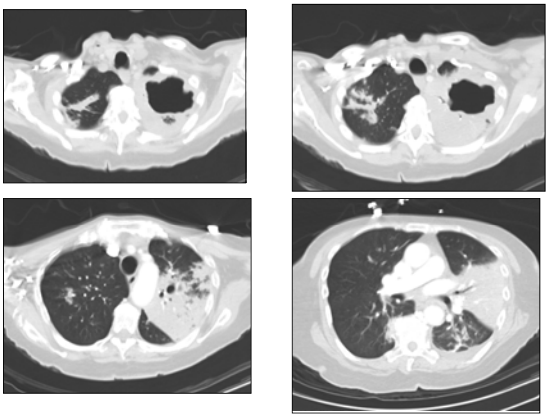
- **74 year-old, African American female**
- **Seen at OSU ER with complaints of shortness of breath and progressive weakness**
- **Increasing SOB over the last 4 days**
- **Associated with fevers, chills, cough, with purulent sputum**
- **Family noted history of cough and weight loss over last several months**

CXR



Admission

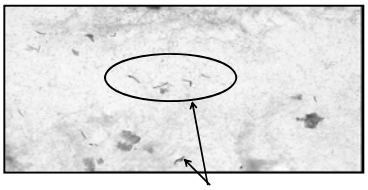

8 months prior to admission



CT Scan: Extensive air-space disease left apical, post cavitary

Hospital Course

- **Admitted to floor – Community Acquired Pneumonia**
- **Treated: ampicillin/sulbactam/azithromycin**
- **Respiratory failure→Intubated 24 hours later**
- **Blood and routine sputum cultures negative.**
- **Bronchial alveloar lavage (BAL)**



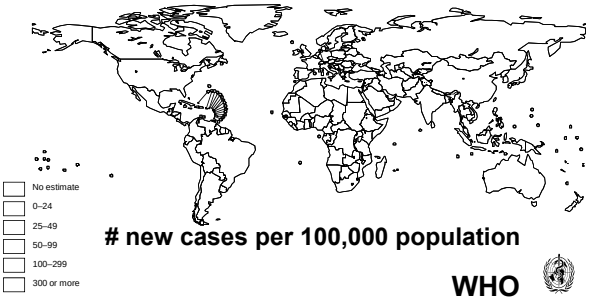
- 5/5 Sputa "Heavy acid fast bacilli (AFB)-Positive"

Hospital Course

- **Admitted to floor – Community Acquired Pneumonia**
- **Treated: ampicillin/sulbactam/azithromycin**
- **Respiratory failure→Intubated 24 hours later**
- **Blood and routine sputum cultures negative.**

Estimated TB incidence rate

- **9 million new TB cases each year**
- **2 million deaths**
- **One life every 20 seconds**



 # new cases per 100,000 population

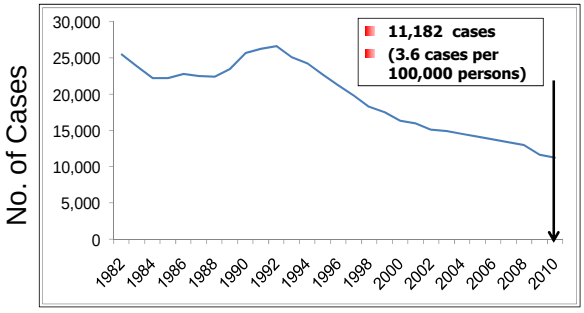
WHO

The hidden Epidemic – Latent TB Infection

- Every one second someone is newly infected with TB
- Two billion people, 1/3 of the world's total population, are infected with TB
- One in 10 people infected with TB bacilli will develop active TB

Slide courtesy of Ian Durrant, PhD

Reported TB Cases United States, 1982–2010*



*Updated as of July 21, 2011

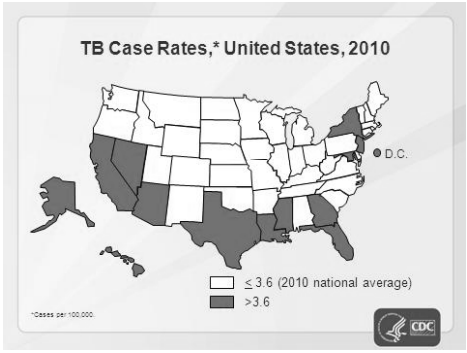
CDC

USA: 1953 84,304 cases of TB Rate 52.6 Cases per 100,000

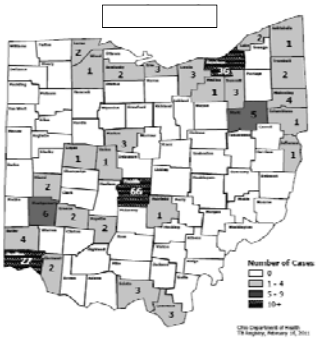
U.S. Public Health Campaign

CDC photo image and A public health campaign poster, lungchicago.org
Historical Collections and Services, The Claude Moore Health Sciences Library, University of Virginia

TB Case Rates,* United States, 2010



Ohio TB Cases by County for 2010
190 Total Cases



Ohio Year	rate	#
2010	1.6	190
2009	1.6	180
2008	1.9	213
2007	2.2	252
2006	2.1	239
2005	2.3	260
2004	1.9	219
2003	2.0	229

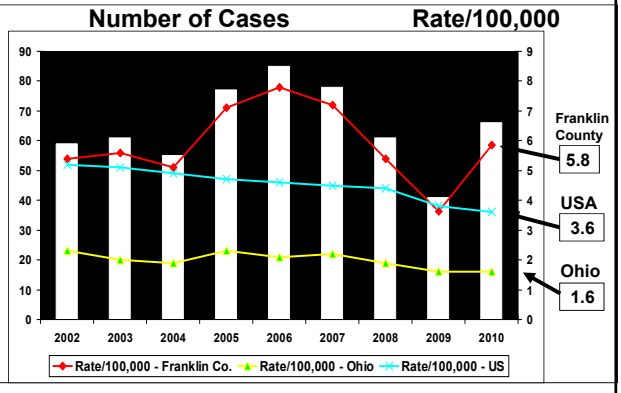
Ohio Department of Health

Clinical Case

HOPI

- 28 year old Chinese female, 32 week pregnant
- Presented to OSH ER with hemoptysis
- C/O cough X 2 days, associated with mild SOB
- No fever, chills, night sweat, appetite loss, fatigue, or weight loss
- Denies any history contact with known active tuberculosis
- History positive TST, no latent TB therapy
- Received BCG vaccine in China as a child

Cases and Rates of Incident TB Disease in Franklin County, OH by Year



Hospital course

Laboratory

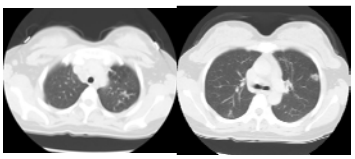
- WBC 6.1, Hgb 10.1gm/dL, Platelets 192, Cr. 0.5, AST 41, ALT 51, HIV negative

Radiology

CXR - Mild asymmetric patchy LUL opacity

CT - No PE

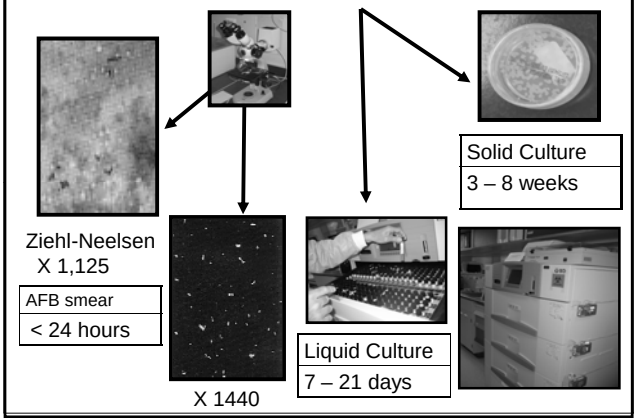
-Extensive diffuse nodular disease



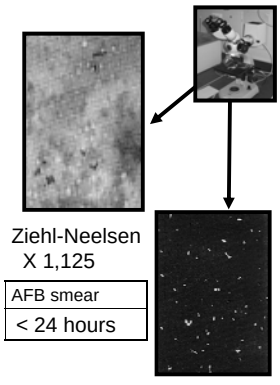
Hospital course

- **Admitted for Community Acquired Pneumonia and**
  - **Azithromycin and ceftriaxone**
- **Rule out TB - in Negative Air Isolation**
  - **Sputum AFB and smear X 3**
  - **Tuberculin Skin Test**
  - **Interferon gamma release assay**

AFB SMEAR and CULTURE



AFB SMEAR and CULTURE



- **PPD 17mm**
- **Interferon gamma release assay**
  (QuantiFERON-TB Gold®)
  - **Positive**

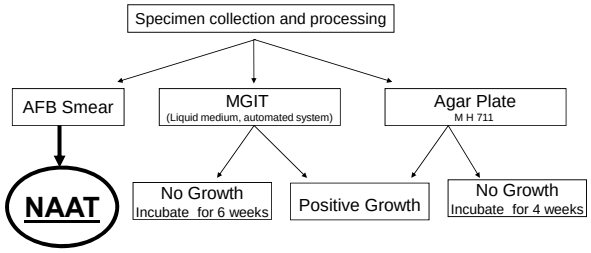
Specimen	Smear
Sputum day 1	**Negative**
Sputum day 2	**Negative**
Sputum day 3	**Negative**
BAL day 4	**Negative**

- **PPD 17mm**
- **Interferon gamma release assay**
  (QuantiFERON-TB Gold®)
  - **Positive**

Specimen	Smear
Sputum day 1	**Negative**
Sputum day 2	**Negative**
Sputum day 3	**Negative**
BAL day 4	**Negative**

•Discharge home on INH for Latent TB Treatment
•Follow up at the Health Department

Is there another test you can order to help you make a diagnosis sooner?



NAAT: Nucleic acid amplification test
Mycobacterium tuberculosis Direct Test (MTD) or Amplicor

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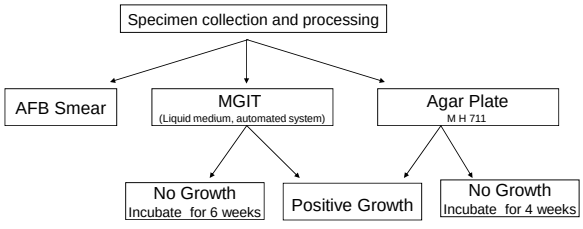


NAAT: Nucleic acid amplification test
Mycobacterium tuberculosis Direct Test (MTD) or Amplicor

Nucleic Acid Amplification Test (NAAT)

- **Direct, rapid, detection of *M. tb* complex (rRNA)**
  - **Patients suspected of TB**
  - **Takes about 4 to 5 hours**
  - **Approved for respiratory specimens only**
    - **Smear positive and smear negative**
  - **Non-respiratory specimen (validated by labs)**
  - **Can detect fewer than 10 organisms**
  - **Does not distinguish live vs dead organism**

MMWR July 7, 2000

CDC Guidelines - 2009 Nucleic Acid Amplification Test

- **Collect specimen for AFB, culture, & NAAT**
- **Interpret results with AFB smear.**

NAAT	AFB	Recommend
+	+	Start treatment. PPV >95% NAAT in AFB+ cases
+	-	Repeat NAAT test. Presume TB if >=2 NAA (+)
-	+	Presume nontuberculous mycobacteria (NTM)
-	-	•Use clinical judgment. •NAAT sensitivity 50-80% in detection AFB (-) Culture (+) pulmonary TB

- **PPD 17mm**
- **Interferon gamma release assay** (QuantiFERON-TB Gold®)
  - **Positive**
- **Nucleic acid amplification test:**
  - **Positive**

Specimen	Smear	Culture
Sputum day 1	Negative	***M. tb***
Sputum day 2	Negative	***M. tb***
Sputum day 3	Negative	***M. tb***
BAL day 4	Negative	Negative
Sputum day 9*	Negative	Negative

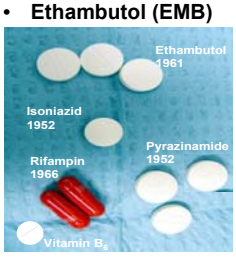
*All subsequent sputum smear and culture negative

- **PPD 17mm**
- **Interferon gamma release assay** (QuantiFERON-TB Gold®)
  - **Positive**
- **Nucleic acid amplification test:**
  - **Positive**

Antimyobacterial Drugs

First-Line Drugs

- **Isoniazid (INH)**
- **Rifampin (RIF)**
- **Pyrazinamide (PZA)**
- **Ethambutol (EMB)**



Second-Line Drugs

- **Streptomycin**
- **Cycloserine**
- **p-Aminosalicylic acid**
- **Ethionamide**
- **Amikacin or kanamycin***
- **Capreomycin**
- **Levofloxacin***
- **Moxifloxacin***
- **Linezolid***

* Not approved FDA for TB Treatment

Treatment of Culture-Positive TB

Initial Phase

2 months - INH, RIF, PZA, EMB daily (56 doses, within 8 weeks)

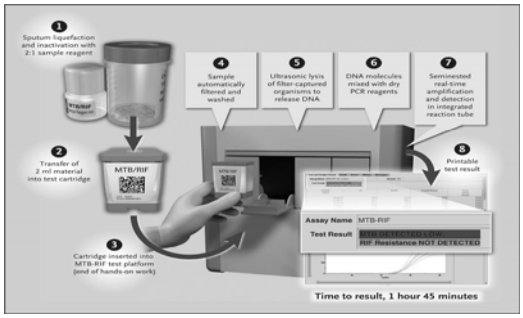
Continuation Phase

Options:

1) 4 months - INH, RIF daily (126 doses, within 18 weeks)
2) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
3) 7 months - INH, RIF daily (217 doses, within 31 weeks)*
4) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

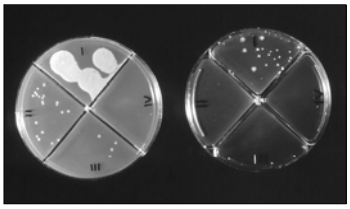
•Continuation phase increased to **7 months**
- •chest x-ray shows cavitation and cx positive at 2 months
- •Or NO PZA in initial phase

Rapid Molecular Detection of Drug Resistance for *M. tuberculosis*



Boehme CC et al. N Engl J Med 2010;363:1005-1015

Drug Susceptibility testing



MDR (Multi-drug resistant) TB
= Resistant to isoniazid and Rifampin
XDR (Extensive Drug Resistance) TB
MDR + Resistance fluoroquinolone +
Resistance injectable (amikacin, capreomycin)

Common Adverse Reactions to Drug Treatment

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergy	Skin rash
Ethambutol	Eye damage	Blurred or changed vision Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea Vomiting Yellowish skin or eyes Dark urine

Common Adverse Reactions to Drug Treatment

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance	Upset stomach, vomiting, lack of appetite
	Arthralgia	Joint aches
	Arthritis	Gout (rare)
Streptomycin	Ear damage	Balance problems
		Hearing loss
		Ringing in the ears
	Kidney damage	Abnormal kidney function test results

LTBI

- **TST positive**
- **CXR Negative**
- **No symptoms or physical findings suggestive of TB disease**

Pulmonary TB Disease

- **TST and IGRA *may* be positive**
- **CXR *may* be abnormal**
- **Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite**
- **Respiratory specimens *may* be smear or culture positive**
- **NAAT *may* be positive**

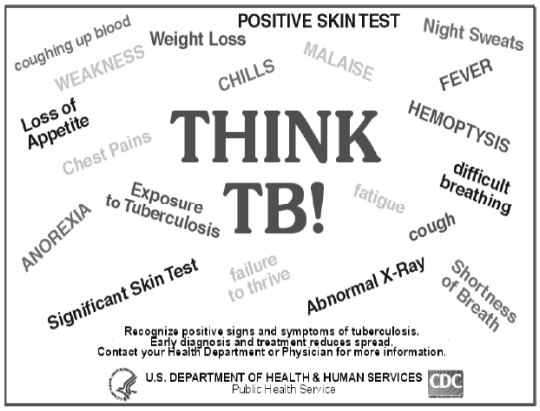
LTBI = Latent TB Infection; TST = Tuberculin skin test, IGRA = interferon gamma release assay
NAAT= Nucleic acid amplification test

Common Adverse Reactions to Drug Treatment

Caused by	Adverse Reaction	Signs and Symptoms
Rifamycins	Thrombocytopenia	Easy bruising
■Rifabutin		Slow blood clotting
■Rifapentine	Gastrointestinal intolerance	Upset stomach
■Rifampin	Drug interactions	Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment

What to do if you suspect TB?

- **Airborne Infection Isolation/precautions –**
  - **Negative airflow room and N-95 respirator mask**
- **CXR**
- **Respiratory AFB smear and culture**
- **Tuberculin skin test/ IGRA -TB blood test**
- **HIV Test**
- **Smear and culture from other sites**
- **Nucleic Acid amplification test on sputum smear**
- **Drug Susceptibility**
- **REPORT ALL TB SUSPECTS to TB Control Program**



Objectives

- To become familiar with the epidemiology of infection and disease caused by *Mycobacterium tuberculosis* complex (TB) in children
- To understand current algorithms for the diagnosis of TB infection and disease in children
- To know the treatment regimens for latent TB infection (LTBI) in children

Pediatric Tuberculosis Update

W. Garrett Hunt, MD, FAAP
Associate Professor of Pediatrics
The OSU College of Medicine
Nationwide Children's Hospital

Pediatric TB

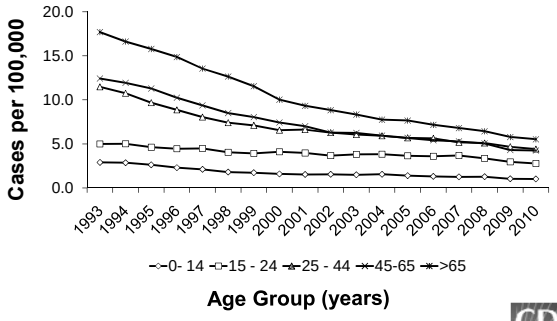
- *Mycobacterium tuberculosis* complex* (TB)
  - *M. tuberculosis*
  - *M. africanum*
  - *M. bovis* and *M. bovis* bacillus Calmette-Guérin
  - *M. microti* and *M. pinnipedii*
  - *M. canettii*, oryx bacillus, and dassie bacillus (proposed)
- Pediatric TB
  - Infection or disease in children or adolescents < 15 years of age

**BMC Infectious Diseases* 2010, 10:80*

TB Case Definitions and Verification

- Incident case of disease
- Case verification categories
  - Laboratory confirmed cases – "Gold Standard"
    - Positive culture, DNA probe, or nucleic acid amplification test
    - Positive AFB smear when culture not attainable
  - Clinical case definition
    - Positive tuberculin skin test
      +
    - Signs and symptoms of TB disease
    - Current treatment for TB disease

TB Case Rates* by Age Group United States, 1993–2010

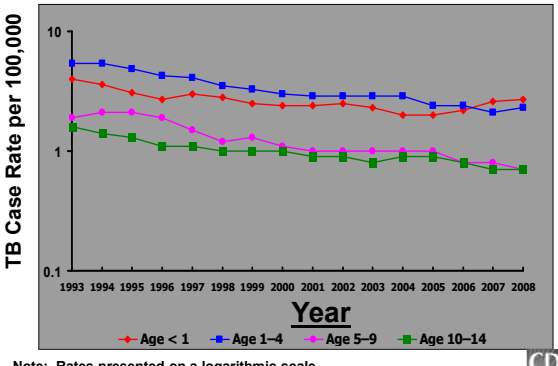


* Updated as of July 21, 2011

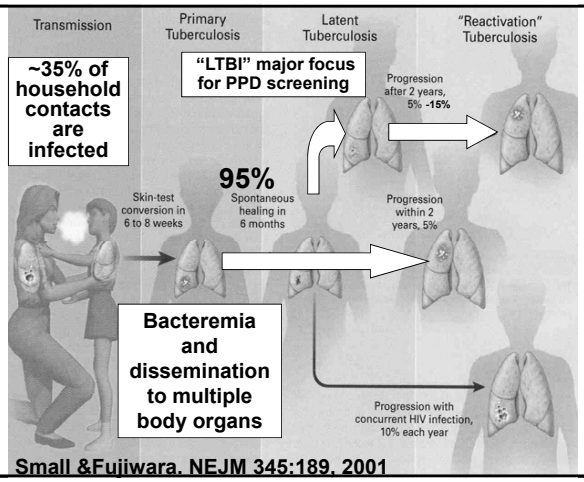
TB Case Definitions and Verification

- Provider diagnosis
  - Diagnosed by health care provider
  - Does not fulfill all criteria necessary to meet laboratory or clinical case definitions

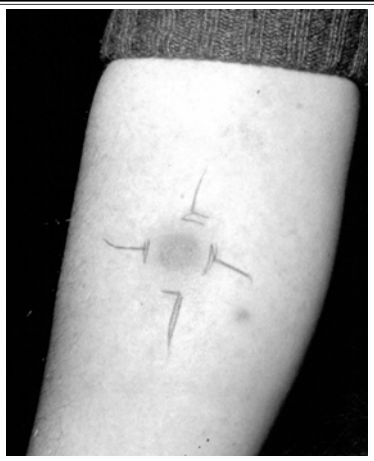
TB Case Rates by Pediatric Age Groups 1993–2008, N=17,502



Note: Rates presented on a logarithmic scale



Small &Fujiwara. NEJM 345:189, 2001

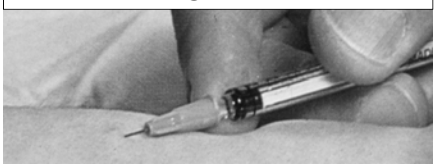


Age-Specific Risk of TB Disease

Age (years)	Disease	Risk of disease after primary infection (%)
<1	None	50
	Pulmonary	30–40
	Meningitis or miliary	10–20
1–2	None	70–80
	Pulmonary	10–20
	Meningitis or miliary	2–5
2–5	None	95
	Pulmonary	5
	Meningitis or miliary	0.5
5–10	None	98
	Pulmonary	2
	Meningitis or miliary	<0.5
>10	None	80–90
	Pulmonary	10–20
	Meningitis or miliary	<0.5

Reproduced with permission from Marais et al. *IJTLD* 2004; 8:392-402

INCORRECT



CORRECT

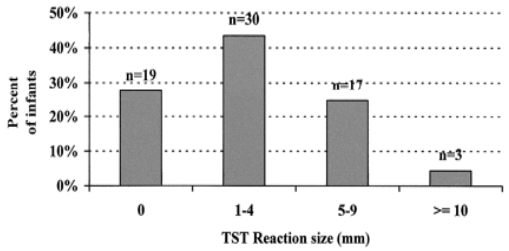
Definition of Positive Mantoux Tuberculin Skin Test (TST) Results in Children

- Induration ≥ 5 mm
  - Children in contact with known active TB
  - Children with clinical or radiographic illness consistent with TB
  - Children who are immunocompromised
- Induration ≥ 10 mm

  Children at increased risk of disseminated disease
  - Age < 4 years of age or underlying medical illness

  Children with increased exposure to TB
  - Born or parents born in high-prevalence countries
  - Frequent exposure to adults with high risk of TB
  - Travel to high-prevalence countries
- Induration ≥ 15 mm
  - Age ≥ 4 years of age without any risk factors

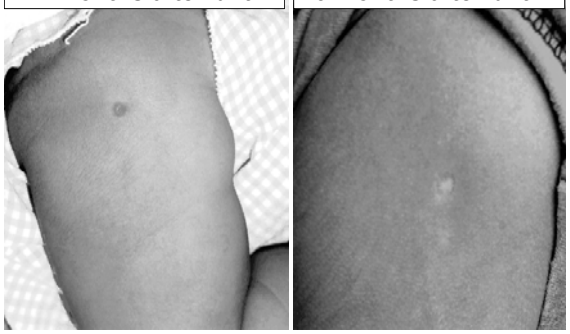
TST 6 Months after BCG at Birth in 69 Infants in Peru



Santiago EM et al. Pediatr 2003;112:e298

BCG Scar after Vaccination at Birth

2 months after birth | 6 months after birth



Santiago EM et al. Pediatr 2003;112:e298

Updated CDC Guidelines 2010

Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010. MMWR 2010;59(No. RR-5):1-16.

Updated CDC Guidelines 2010

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"Using both a TST and an IGRA . . . might be useful . . . when additional evidence of infection is required to encourage compliance."

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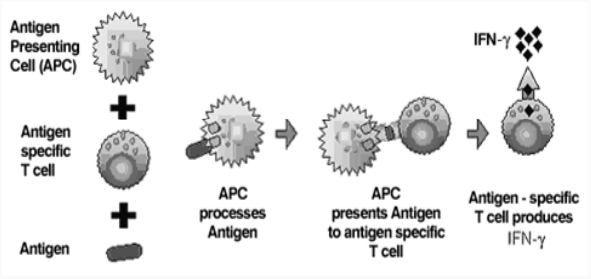
"Using both a TST and an IGRA . . . might be useful . . . when additional evidence of infection is required to encourage compliance."

"For persons who have received BCG and who are not at increased risk for a poor outcome if infected, TST reactions of <15 mm in size may reasonably be discounted as false positives when an IGRA is clearly negative."

Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010. MMWR 2010;59(No. RR-5):1-16.

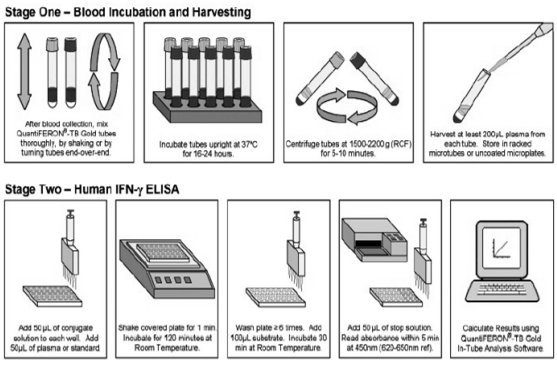
Interferon-γ Release Assay for Detection of TB Infection



Antigens used: ESAT-6, CFP-10, TB 7.7

IGRA	TST
***in vitro* test**	***in vivo* test**
Specific antigens Not affected by prior BCG	**Less specific PPD**
Does not cause boosting	**May cause boosting**
Single patient visit	**2 patient visits**
Results possible in 1 day	**Results in 2-3 days**
Requires phlebotomy	**TST placement skills**
Error in collecting, transporting, lab	**Inter-reader variability**

QuantiFERON-Gold In-Tube



Positive when antigen (–) null elisa = ≥ 0.35 IU/ml

Species Specificity of ESAT-6 and CFP-10

Tuberculosis Complex	ESAT	CFP 10
M. tuberculosis	+	+
M. africanum	+	+
M. bovis	+	+
BCG substrains	-	-

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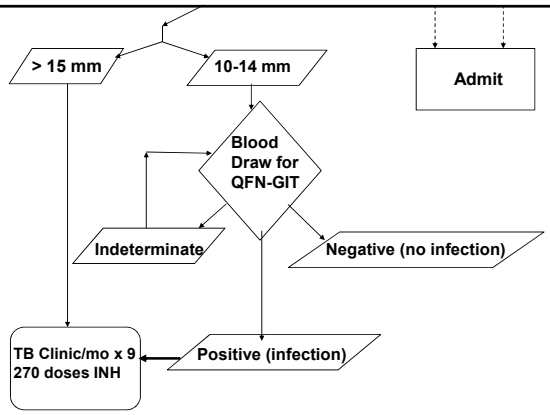
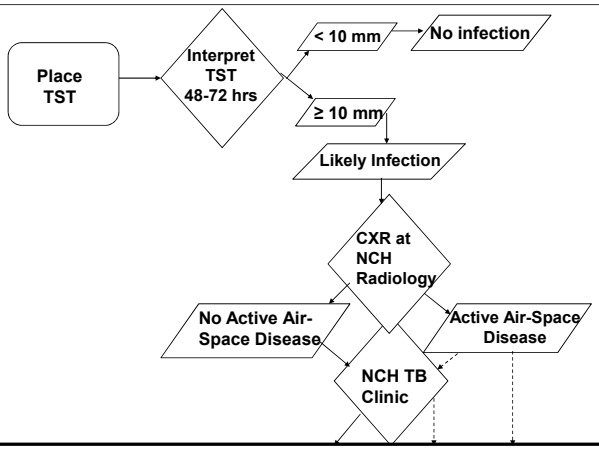
Tuberculosis Complex	ESAT	CFP 10
M. tuberculosis	+	+
M. africanum	+	+
M. bovis	+	+
BCG substrains	-	-

Non-tuberculous Mycobacteria	ESAT	CFP 10
M. kansasii	+	+
M. marinum	+	+
M. szulgai	+	+



Tuberculosis Testing and Treatment



Approach to Diagnosis of TB in Children

- **Child ≥ 5 yrs old with known exposure to TB: IGRA and TST**
- **Child < 5 yrs old with known exposure to TB: use TST**
- **Child of any age with suspected TB: TST and IGRA, and aggressively seek TB isolate and epidemiology of exposure**
- **Child < 5 yrs old immigrating from high risk country without known TB exposure: use TST as screen – follow Redbook guidelines for interpretation**
- **Child ≥ 5 yrs old immigrating from high risk country without known TB exposure: use TST as screen:**
  - **If TST ≥ 15 mm, assume TB infection**
  - **If TST 10-14 mm, obtain IGRA to confirm or refute TB infection**

Powell DA. Pediatr Infect Dis J 2009;28:676

Question

Which of the regimen(s) would you prescribe for LTBI therapy in a child?

a. 2 months of pyrazinamide and rifampin
b. 3 months of isoniazid and rifapentine (12 weekly doses)
c. 4 months of rifampin
d. 6 months of rifampin
e. 9 months of Isoniazid

Treatment of LTBI in Children

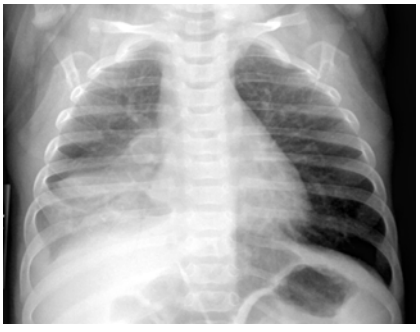
Drug	Duration	Daily Dose	Comment
Isoniazid	9	10-15 mg/kg (max 300 mg)	270 doses
Rifampin	6	10-20 mg/kg (max 600 mg)	180 doses INH resistant TB
Isoniazid/ Rifapentine	3	H – 15 mg/kg (max 900 mg) P - 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg max	12 weeks ≥ 12 years old

Answers – b, d, or e

- Recommend 9 months of INH
- Acceptable alternatives
  - 6 months of Rifampin
  - 12 doses of INH and Rifapentine*
    - Directly Observed Therapy (DOT) only
    - Enrollment 6/01-2/08, follow-up ended 9/30/10
    - 9H, 15/3745 (0.43%) – 69% completion, discontinuation 3.6%
    - 3HP, 7/3986 (0.19%) – 82% completion, discontinuation 4.7%
    - Otherwise healthy patients ≥ 12 years of age
- PZA and RIF combination therapy is no longer recommended due to hepatotoxicity and deaths

**MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection*
N Engl J Med 2011;365:2155-66

Progressive Primary Pulmonary TB in Children



4-month-old female with RLL consolidation and R hilar lymphadenopathy

Diagnosis of Pulmonary TB

Gastric lavage (GL) is better than bronchoaleolar lavage (BL) for isolation of *Mycobacterium tuberculosis* in childhood tuberculosis Abadco and Steiner, PIDJ 1992;11:735-738

- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY

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- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY
- GL: 10 (50%) cx + and 0 smear +, BL: 2 (10%) cx + and 0 smear +

Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study Zar et al, Lancet 2005;365:130-134

- 250 children, 1 mo – 5 y/o, admitted 2000-2002 for suspected pulmonary tuberculosis in Cape Town, South Africa; 58 (23%) cx + and 29 (12%) smear +

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- 1 induced sputum, smear or cx + = 41/62 (66%)
- 3 gastric aspirates, smear or cx + = 40/62 (64%)

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- 3 gastric aspirates, smear or cx + = 40/62 (64%)
- *3 induced sputa, smear or cx + = 54/62 (87%) yield, youngest 3 mo*

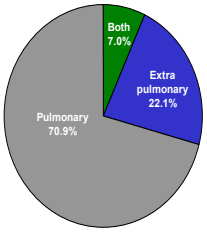
Percent of Pediatric TB Cases with Extrapulmonary Involvement* by Age Group & Sites of Disease, 1993–2008 (N=17,502)

Site of Disease	Age < 1 (n=1,697)	Age 1-4 (n=8,616)	Age 5-9 (n=3,991)	Age 10-14 (n=3,198)
Lymphatic	7.8	19.3	22.2	19.4
Meningeal	7.6	3.6	1.5	1.8
Miliary	5.5	1.2	0.6	1.1
Bone & Joint	0.4	1.3	1.6	2.4
Other	3.5	2.7	4.2	8.4
Total	24.8	28.1	30.1	33.1

*Any extrapulmonary involvement includes extrapulmonary only and both

CDC

Pediatric TB Cases by Site of Disease, 1993–2008



Any extrapulmonary involvement* (totaling 29.1%)

Lymphatic	18.9%
Meningeal	3.1%
Miliary	1.5%
Bone & Joint	1.5%
Other	4.1%

*Any extrapulmonary involvement, with or without pulmonary involvement (patients may have > 1 disease site but are counted in mutually exclusive categories for surveillance purposes)

CDC

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CDC

Symptoms in Children with Tuberculosis

Symptom	Frequency (%)	
	Study A*	Study B^
	(47 infants < 1 Yr old)	(156 children < 20 yrs)
Cough	79	62
Fever	64	55
Loss of Appetite	43	NR
Diarrhea/vomiting	17	NR
Weight Loss	15	32
Night Sweats	NR	26
Hemoptysis	NR	12
Seizures	11	NR

*Vallejo et al. Pediatr 94:1, 1994 ^ Burroughs et al. PIDJ 18:440, 1999

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Conclusions

- A major focus of TB eradication in the US has been to identify and treat patients with LTBI – treatment is prolonged and compliance is difficult
- Childhood TB is most often pulmonary and may appear like many other forms of pneumonia
- In the U.S., interferon-γ release assays have already replaced TSTs for targeted screening in adults, but their use in children, < 5 years of age in particular, continues to be defined
- Pediatric LTBI and TB disease treatment mirrors that in adults - a weekly 12-dose regimen of INH and rifapentine has been approved recently by the CDC for LTBI