Pediatric Tuberculosis

Craig T. Nakamura, M.D.

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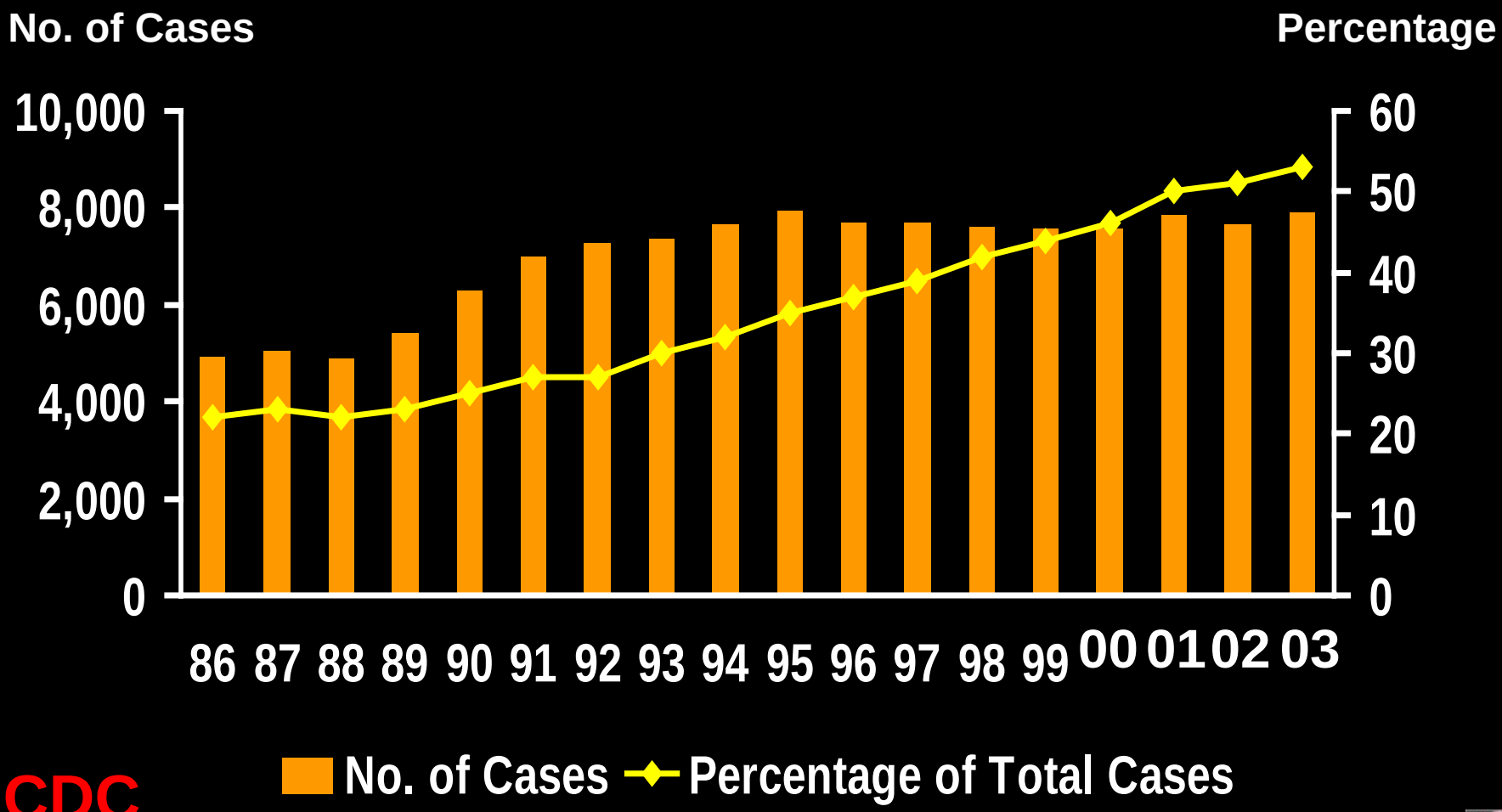
Global Epidemiology of TB

- **TB remains leading infectious disease in world**
  - **>40% of world's population (> 2 billion people) infected with *M. tuberculosis***
  - **In 1990s:**
    - **90 million new cases**
    - **30 million deaths**
  - **Among children < 15 y/o:**
    - **Aprox 13 million cases**
    - **5 million deaths**

Outline

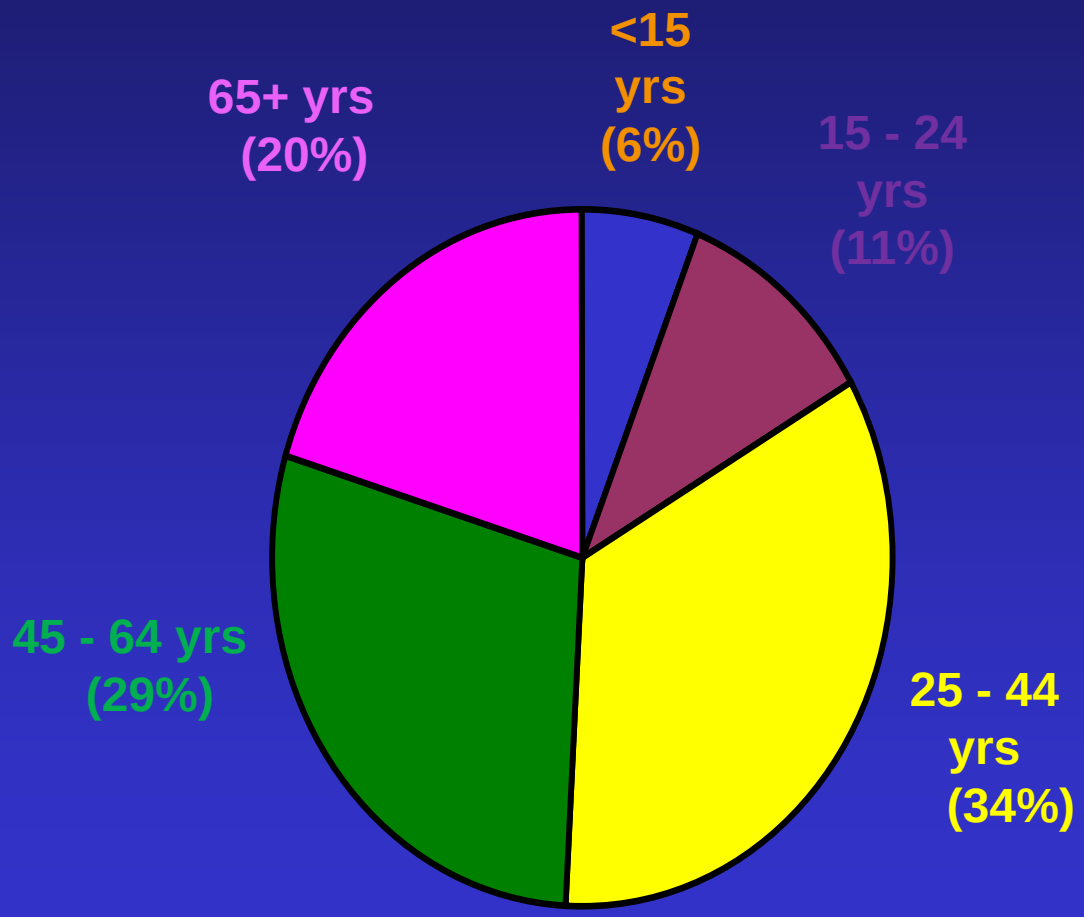
- Epidemiology
- Transmission
- Pathogenesis
- Public Health Aspects & TB Control
- Treatment of Latent TB Infection & TB Disease
- BCG Vaccine

US TB Trends (1986-2003)



CDC

TB Cases by Age (US), 2003



Epidemiology of TB

- Case rates are declining
- Foreign born persons account for > 50% of US cases
- TB in children:
  - Highest risk for disease:
    - < 5 years of age
    - Foreign-born children
      - 60% of cases develop within 18 mo of arrival in US
      - Most common countries of birth: Mexico, Philippines, Vietnam
      - Varies depending on immigration pattern
    - Racial ethnic minorities

Transmission of *M. tuberculosis*

- Spread by airborne route; droplet nuclei
- Transmission affected by:
  - Infectiousness of patient
  - Environmental conditions
  - Duration of exposure
- Most exposed persons don't become infected

TB Pathogenesis:
Latent TB Infection

- Once inhaled, travel to alveoli & establish infection
- After 2 – 12 wks, immune response limits activity; infection detectable
- Some bacteria survive & remain dormant but viable for years = latent TB infection (LTBI)

TB Pathogenesis: LTBI

- **Persons with LTBI are:**
  - **Asymptomatic**
  - **Not infectious**

TB Pathogenesis: Active TB

LTBI progresses to TB disease in:

- **Small number of persons after infection**
- **5% – 10% of persons with untreated LTBI sometime during life**
- **10% in HIV (with untreated LTBI) *per year***

Factors Increasing TB Spread

- Adolescents / Adults
- Cough / Failing to cover cough
- Cough-inducing or aerosol-generating procedure
- Positive sputum AFB smear
- Cavitation on chest radiograph
- Inadequate treatment

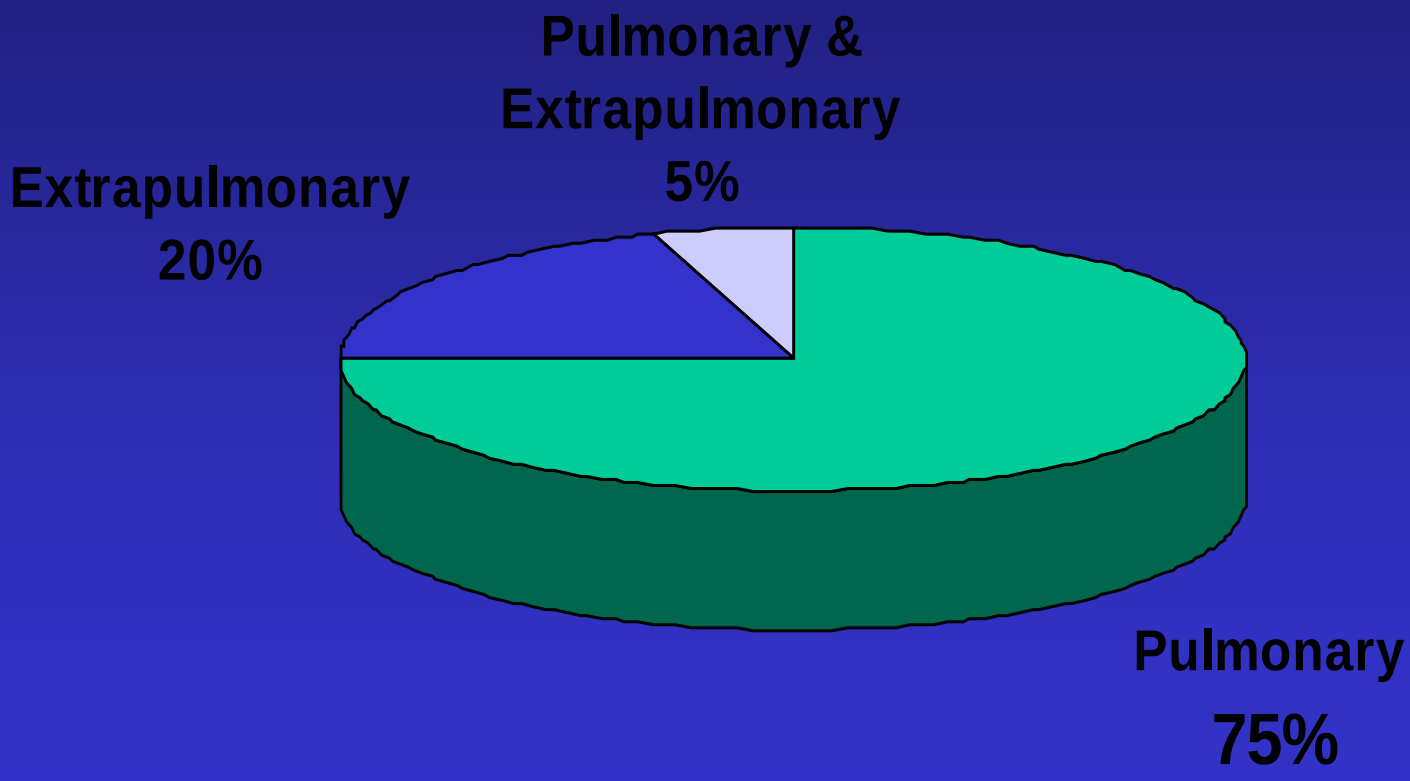
Significance of Pediatric TB

A case of TB in a child is

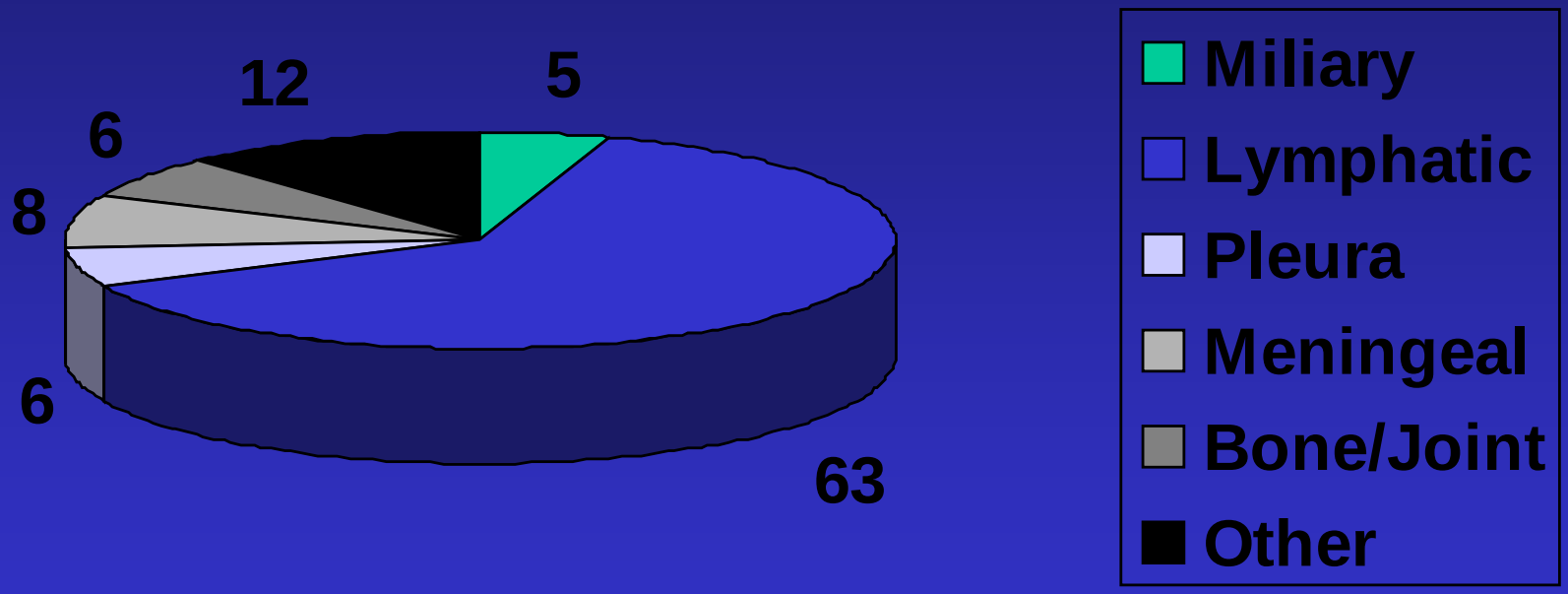
a “sentinel healthcare event”

[represents recent transmission]

TB by site: children (< 15 y/o)



Extrapulmonary TB in Children (< 15)



TB Control in US

- **Identification of new cases TB**
  - Initiate appropriate Rx
  - Directly observed therapy (DOT)
- **Contact Investigations**
  - Identify persons at risk
- **Targeted tuberculin testing**
  - Identifies persons at high risk who would benefit from LTBI Rx
  - Treatment LTBI

AAP Recommendations: Targeted TST

- Exposure risk assessed at clinic visits
- Only children with increased risk considered for testing
- Freq of testing depends on degree of risk
- "Screening" is inefficient way to control TB

Targeted TST Risk-Assessment

- Child born outside US?
  - **Africa, Asia, Eastern Europe, Latin America**
- Child traveled outside US (≥ 1 week)?
- Child exposed to anyone with TB?
  - (TB?; LTBI?; Nature of contact?)
- Close contact with a person with (+) TST?

***Pediatrics* 2004;114:1175, supplement**

Targeted TST Risk-Assessment

- **Depending on local epidemiology other questions:**
  - **Does child spend time with anyone in jail, shelter, uses illegal drugs, or HIV (+)?**
  - **Has child had raw milk or unpasteurized cheese?**
  - **Any household member born outside US?**
  - **Any household member travel outside US?**

***Pediatrics* 2004;114:1175, supplement**

AAP Recommendations: TST

- **Children who should have immediate TST:**
  - Contacts of persons with confirmed / suspected TB (contact investigation)
  - Children with CXR or clinical findings suggesting TB
  - Children from endemic countries
  - Children with histories of travel to endemic countries / contact with persons from those countries

Red Book 2003

AAP Recommendations: TST

- **Children who should have annual TST:**
  - **HIV infection**
  - **Incarcerated adolescents**

***Red Book* 2003**

AAP Recommendations: TST

- **Consider testing children every 2 - 3 years if:**
  - **Exposed to:**
    - **HIV-infected**
    - **Homeless**
    - **Residents of nursing homes**
    - **Institutionalized / incarcerated persons**
    - **Users of illicit drugs**
    - **Migrant farm workers**
  - **Foster children with exposure to adults in high risk groups**

AAP Recommendations: TST

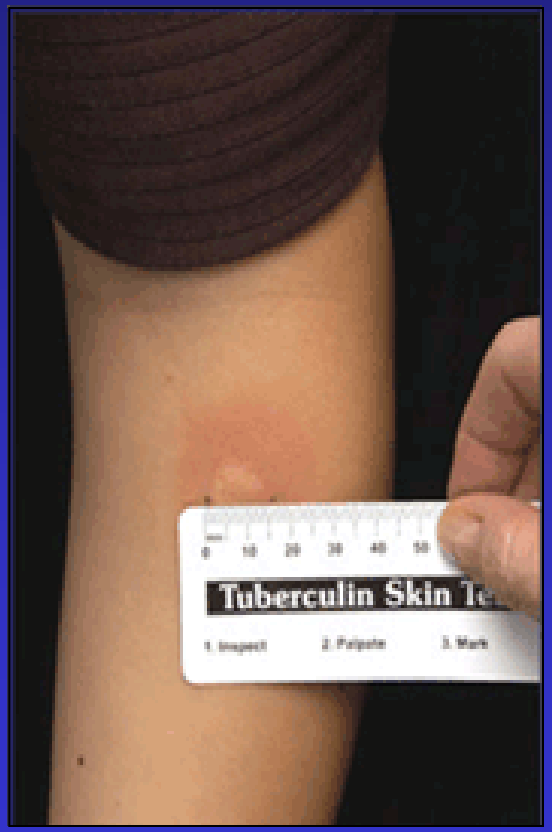
- **Consider TST at 4-6 and 11-16 years of age if:**
  - **Parents immigrated (? TST status) from regions with high prevalence**
  - **Continued exposure by travel to or exposure to contacts from endemic areas (? TST status)**

Administering TST

- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Wheal 6 mm – 10 mm diameter
- Placed & read by experienced health professionals

Reading the TST

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



Parental Reading TST

- **TST was placed; 37 children different families**
  - **Parents were instructed verbally about:**
    - **Importance**
    - **When & how to read induration**
      - **Written instructions**
      - **Date stamped on hands**
  - **Site marked with marker & bracelet with reading date placed on child**
- **Results: 36 / 37 returned for reading**
  - **Only 22% of families (8/36) able to both read & document TST results appropriately**

Cheng TL, *PIDJ* 1996

TST

- **Most used test for *M. tuberculosis* infection in US**
- **Use recommended Mantoux method**
  - **Training materials available from CDC website: http://www.cdc.gov/nchstp/tb/pubs/pem.htm**
  - **Multipuncture (e.g., tine) tests not as reliable**
  - **Contact HD for additional TST resources**

Special Considerations in TST

- Anergy
- Antiretroviral therapy for HIV infection
- Pregnancy
- TST boosting
- Use of two-step TST
- BCG vaccination
- Differences in PPD preparations

Different PPD Preparations

- **Two PPD preparations available in U.S.**
  - **APLISOL®**
  - **Tubersol®**
- **Compared to U.S. standard, no differences***

*** Villarino ME, Burman W, Wang YC, Lundergan L, Catanzaro A, Bock N, Jones C, Nolan C. Comparable specificity of 2 commercial tuberculin reagents in persons at low risk for tuberculosis infection. JAMA 1999:281(2):169-71.**

(+) TST in Children: Definitions

- **Takes into account:**
  - **Risk of infection (exposure)**
  - **Risk of progression to disease**
    - **Immune status**
    - **Age**

Positive TST Results: Infants, Children, & Adolescents

- **TST (+) if ≥ 5 mm induration when:**
  - **Close contact with known / suspected contagious cases TB**
  - **Suspected TB disease:**
    - **CXR consistent with active / previously active TB**
    - **Clinical evidence TB**
  - **Immunosuppressive therapy**
  - **Immunosuppressive conditions**
  - **HIV infection**

Positive TST Results: Infants, Children, & Adolescents

- **TST (+) if ≥ 10 mm induration in children when:**
  - **Increased risk of disseminated disease:**
    - **Young age (< 4 y/o)**
    - **Certain medical conditions (Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition)**
  - **Increased exposure to TB**
    - **Born / parents born or travel to high-prevalence regions**
    - **Frequently exposed to high-risk adults (HIV, homeless, illicit drug users, nursing homes residents, incarcerated/ institutionalized, migrant farm workers)**

Positive TST Results: Infants, Children, and Adolescents

- TST considered (+) when ≥ 15 mm induration
- If TST ≥ 15 mm [even up to 7 days after placement, considered (+)]

Interpreting TST Result

- **Probability of (+) TST accuracy depends on *M. tuberculosis* prevalence in community**

  low prevalence = low probability of accuracy

  high prevalence = high probability of accuracy

Interpreting TST Result

Cut points depend on:

- **Patient's risk for having LTBI**
- **Size of induration**

≥5 mm	highest risk
≥10 mm	other risk factors
≥15 mm	no known risk factors

Evaluating Child with (+) TST

- **Evaluation of children with (+) TST:**
  - **Careful history**
  - **Household investigation**
  - **Physical exam**
  - **CXRs (PA & lateral)**

Treatment LTBI in Children

- **INH 10 mg/kg (max: 300 mg) po qDay x 270 doses**
- **Alternative: Twice weekly directly observed (DOT) INH 20 - 40 mg/kg (max: 900 mg) po x 72 doses**
- **Monitor index case isolate sensitivities**
- **Hepatotoxicity from INH is rare in children:**
  - **Monthly assessment for clinical evidence: decreased appetite or weight, nausea, vomiting, abdominal pain, jaundice**
  - **Routine LFTs NOT indicated**

TB Control in US

- **Contact Investigations**

  "The most reliable TB control program is based upon aggressive & expedient contact investigations, rather than routine screening of large populations with low risk."

  Complex, requires experience, & lots of work.

Work-up Exposure in Children

- History, physical exam, TST, CXR
- Ok if > 4 y/o and:
  - Asymptomatic with normal physical exam
  - TST is neg
  - Chest X-ray normal
- But if < 4 yo, start:

  INH 10 mg/kg (max., 300 mg) po qDay

TB Exposure in Children

- **Why INH if no evidence infection at initial visit?:**
  - **May already be infected**
  - **Infection more likely to progress to disease**
  - **Infants & younger children are more likely to have disseminated disease (or meningitis)**
- **Repeat TST 12 wks after contact broken:**
  - **If TST (-), d/c INH**
  - **If TST (+), re-evaluate child & treat accordingly**

Missed Opportunities

- Failure to find & manage source cases
- Delay in reporting initial dx
- Contact interview failure
- Delay in evaluating exposed children
- Failure to completely evaluate exposed children
- Failure to maintain surveillance
- LTBI diagnosed; Rx not prescribed
- Failure to complete treatment for LTBI (adherence)

Importance of Pediatric Radiologic Expertise

- **Many pitfalls:**
  - **Occasional poor quality films**
  - **Repeat CXR at the same institution, may not address the questions on initial films**
  - **Negative CXRs read positive**
  - **Positive CXRs read as normal**

BCG Vaccine & TST

- **Hx of BCG is NEVER contraindication to TST**
- **Can't distinguish + TSTs of BCG from infection with *M. tuberculosis***
- **Therefore, management of children with a history of BCG & + PPD:**
  - **History**
  - **CXR**
  - **Appropriate Rx**

BCG – Fantasy vs Fact

FANTASY	FACT
• BCG protects against getting TB infection	• BCG will not protect against becoming infected with TB
• BCG provides lifetime protection against developing active TB	• BCG Protects against severe complications of TB disease in young children. Provides little or no protection in adolescents and adults
• BCG causes the tuberculin skin test (TST) to be positive for life	• BCG causes the TST pos for a few years & then TST reaction becomes much weaker. Generally, no reaction is present after 5 years.
• In a BCG-vaccinated person, a pos TST is most likely due to BCG	• There is no way to tell whether a pos TST is due to BCG or TB infection
• A positive TST in a person of any age from any country is most likely due to BCG, not TB infection	• A pos TST in adolescent or adult from a TB high-burden country is almost always due to TB infection, not BCG
• There is no need for a BCG-vaccinated person with a positive TST to be treated	• Persons with pos TST from TB high-burden countries are at high risk of developing active TB & should be treated

QuantiFERON-TB

- **QuantiFERON-TB Gold test (QFT-G)**
- **QFT-G = blood assay for *M. tuberculosis* (BAMT)**
  - **Measures the patient's immune system reaction to *M. tuberculosis***
  - **Must be processed ≤ 12 hours**
  - **Interpretation of results influenced by the patient's risk for infection with *M. tuberculosis***
  - **Alternative to TST**

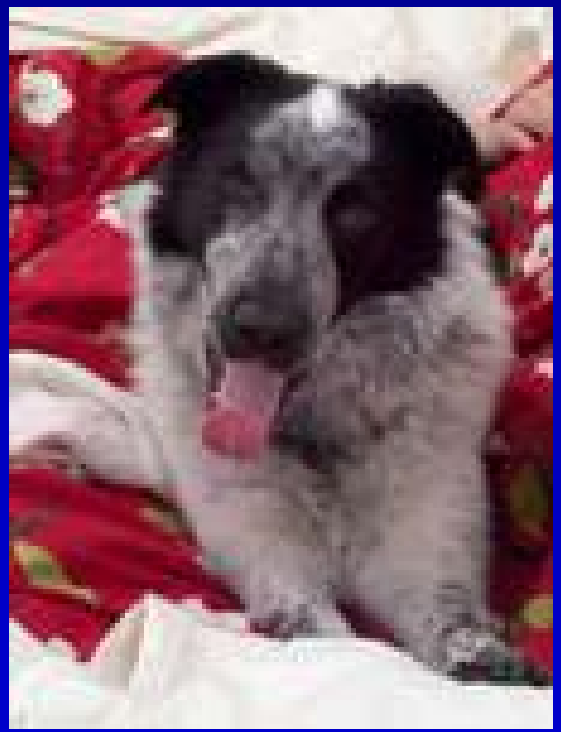
QuantiFERON-TB

- **Measures interferon (IFN)-gamma released in blood when incubated overnight with reagents, including antigens for *M. tuberculosis***
- **Lymphocytes from persons with LTBI react to proteins by releasing IFN-gamma**

Treatment Active TB

- **TB treatment regimens must contain multiple drugs which *M. tuberculosis* is susceptible**
- **Treating with a single drug can lead to resistance**
- **Adding a single drug to a failing regimen can lead to resistance**

QUESTIONS ?

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