



Window Prophylaxis [and other stuff involving tuberculosis infection (TBI) in children]

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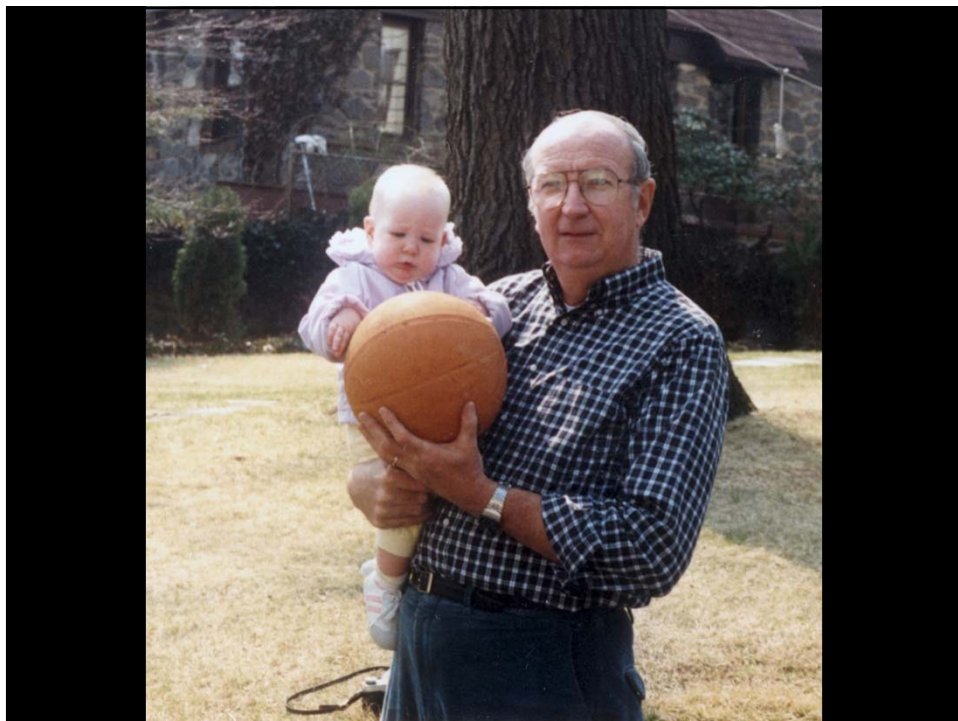
**Pediatric Section
TB Center of Excellence
Rutgers Global Tuberculosis Institute**

**Identify, Test and Treat: Making Strides Toward TB Elimination
Harrisburg, PA
June 19, 2018**



Tuberculosis in Children and Adolescents

- Epidemiology: Global, national, regional
- Transmission of tuberculosis to children and its significance
- Difficulties in the diagnosis and treatment of tuberculosis disease
 - Clinical presentation, mycobacteriology and culture confirmation
- Public Health Aspects of Tuberculosis Control
 - Targeted Tuberculosis Testing: Why and how
 - Use of a Risk Assessment Questionnaire
 - Contact Investigations
 - Management of the TB-exposed child
 - Missed opportunities and their effects
- Tuberculosis Infection (TBI):
 - Diagnosis: The tests (TST, IGRA)
 - Treatment: 3HP, 4R, 9H



Epidemiology

- Tuberculosis remains the leading infectious disease in the world
 - Approximately 1/3 of the world's population (>1.9 billion people) is infected with *M. tuberculosis*
 - In the 2000s:
 - 90 million new cases
 - 30 million deaths
 - Among children <15 years of age:
 - Approximately 13 million cases
 - 5 million deaths
- In 2016: 10.4 million of new TB cases
 - Estimated 1 million of these were in children (about 10% of total cases)
 - Approx. 3% of these cases likely had MDR-TB and 40,000 are HIV-infected
 - In 2016: 250,000 children <15 years old died from TB
 - Account for much of the severe TB morbidity, mortality, and sequelae

WHO Global TB Report

Background: Pediatric Tuberculosis in the U.S.

- **Definition of pediatric tuberculosis (TB):**
 - TB disease in a person < 15 years old
- **In 2016:**
 - 9,272 TB cases were reported among all age groups
 - 387 (4.2%) were pediatric

Age group	N	Percent out of all age groups
0-4 years	224	2.4%
5-14 years	196	1.8%

CDC

Epidemiology: Pennsylvania 2016

- Total cases: 173
- Cases in children by age:
 - <5 years of age: 7 (4%)
 - 5-14 years of age: 2 (1.2%)



Transmission of *M. tuberculosis* to Children

- Children are usually infected by an adult or adolescent in the immediate household
- Casual extra-familial contact is less often the source of infection
- Children rarely infect other children or adults:
 - Tubercle bacilli are relatively sparse in secretions
 - Children with pulmonary TB rarely cough
 - Cough, when present, lacks the tussive force needed to aerosolize bacilli

Significance of Tuberculosis in Children

Public Health: Diagnosis of LTBI or tuberculosis disease in a child is considered a “sentinel public health event” usually representing recent transmission of TB within a community

Personal Health: High rates of morbidity and mortality

Risk of Progression to TB Disease

- Immunocompetent adults: 5-10% lifetime risk of developing disease after infection
- Adults with TB infection and untreated HIV infection: 5-10% annual risk of developing disease
- Children and the risk of TB disease:

Risk of Tuberculosis Disease by Age

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
<1 years	10-20%	30-40%	50%	High rates of morbidity and mortality
1-2 years	2-5%	10-20%	75-80%	High rates of morbidity and mortality
2-5 years	0-5%	5%	95%	..
5-10 years	<0.5%	2%	98%	"Safe school years"
>10 years	<0.5%	10-20%	80-90%	Effusions or adult-type pulmonary disease

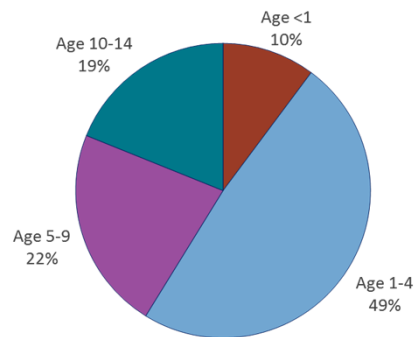
Adapted from reference 30.

Table 1: Risk of pulmonary and extrapulmonary disease in children following infection with *Mycobacterium tuberculosis*

Newton S, et al Lancet ID 2008 after Marais BJ, et al. Int J Tuberc Lung Dis 2004

Percentage of Pediatric TB Cases by Age Group, 1993–2016

N=21,609



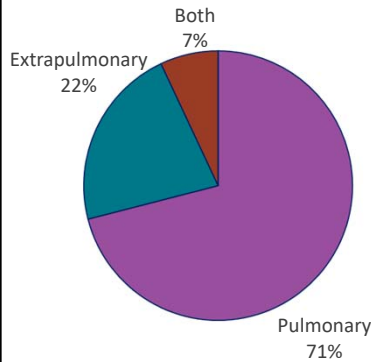
Mycobacteriologic Diagnosis of Tuberculosis

- Adults: 70-90% have a sputum that is (+) for *M. tuberculosis*
- Children:
 - Tubercle bacilli are relatively few in number
 - Sputum generally cannot be obtained from children <10 yrs old
 - Gastric aspirates in children with PTB
 - 30-40 % sensitive in children
 - 60-70% sensitive in infants
 - Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates

Difficulties in the Diagnosis of Tuberculosis in Children

- Children are often asymptomatic or symptoms are nonspecific: Fever, poor appetite, poor weight gain or weight loss
 - Approximately 22-30% of disease is extrapulmonary
 - Meningitis and miliary disease tend to develop soon after infection
 - 70-80% occur in children 0-4 years of age
- Physical examination may be normal
- Epidemiologic link (the adult source case)
 - Crucial to identify the adult source case for the child
 - Provides strong evidence that the child suspected of having TB disease actually has TB
 - May be the only isolate available for susceptibility testing

Pediatric TB Cases by Site of Disease, 1993–2015



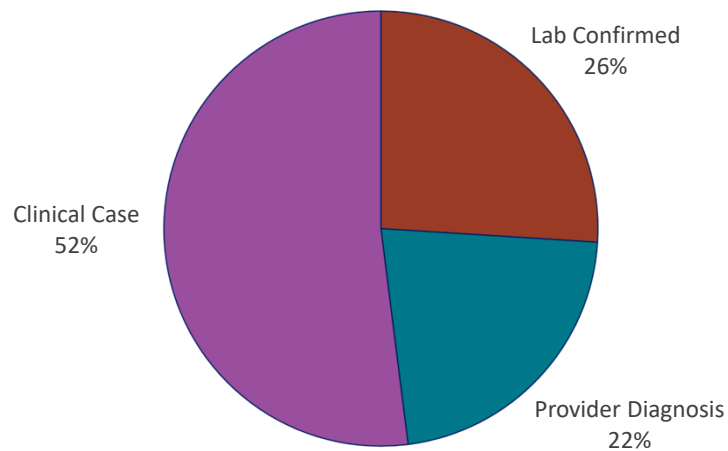
Any extrapulmonary involvement* (totaling 29.5%)

Extrapulmonary site	(%)
Lymphatic	(18.8)
Meningeal	(3.6)
Miliary	(1.3)
Bone & Joint	(1.5)
Other	(4.3)

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both. Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

CDC

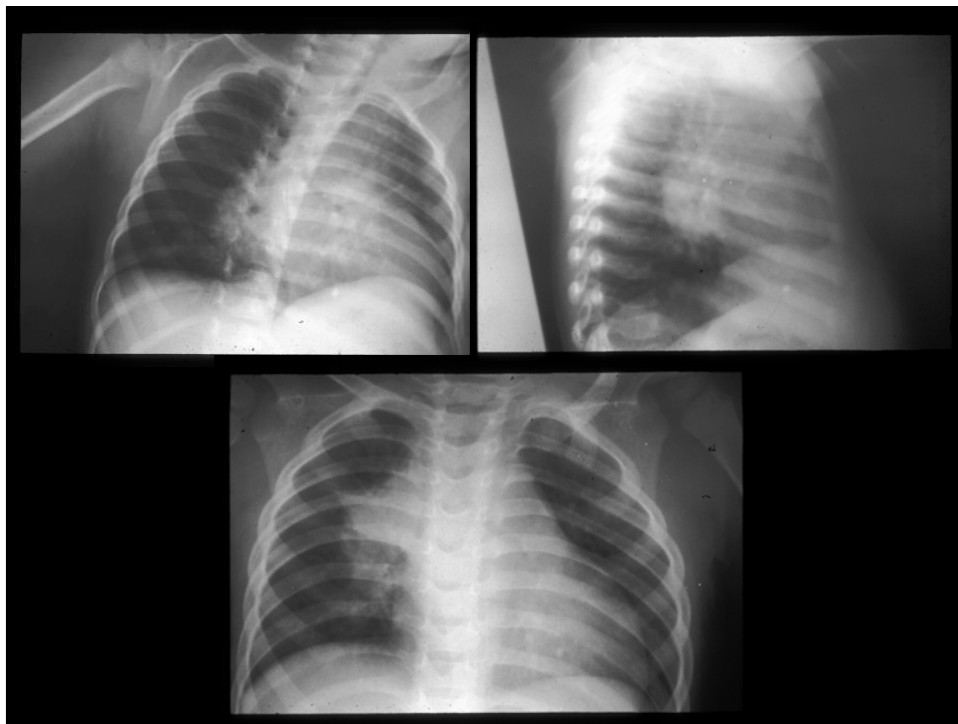
Pediatric TB Cases by Case Verification Criteria*, 1993–2015 N= 21,223

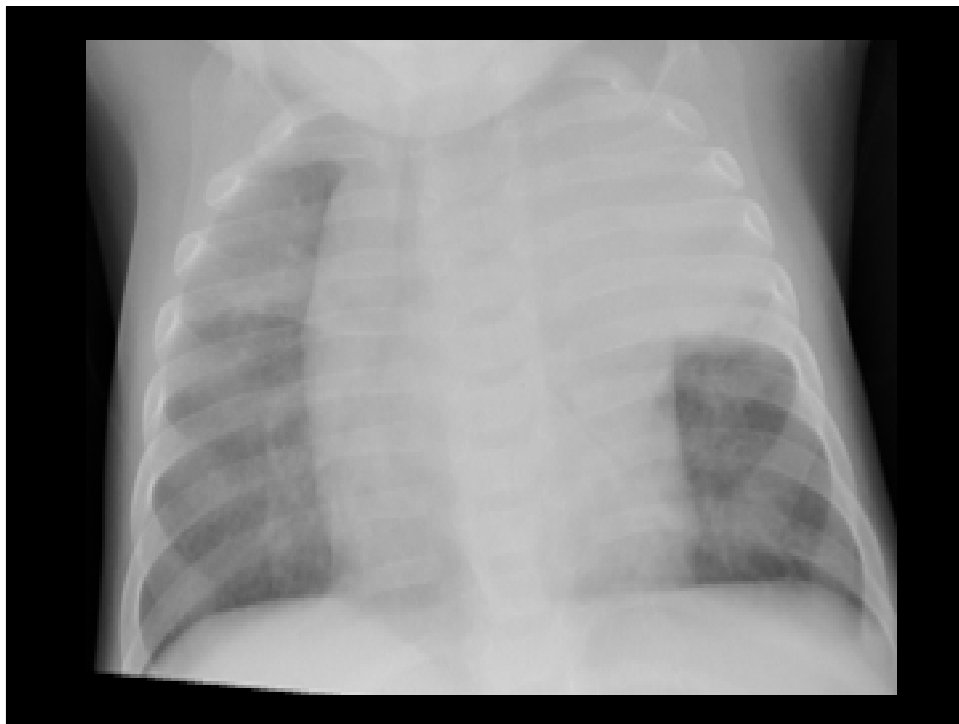
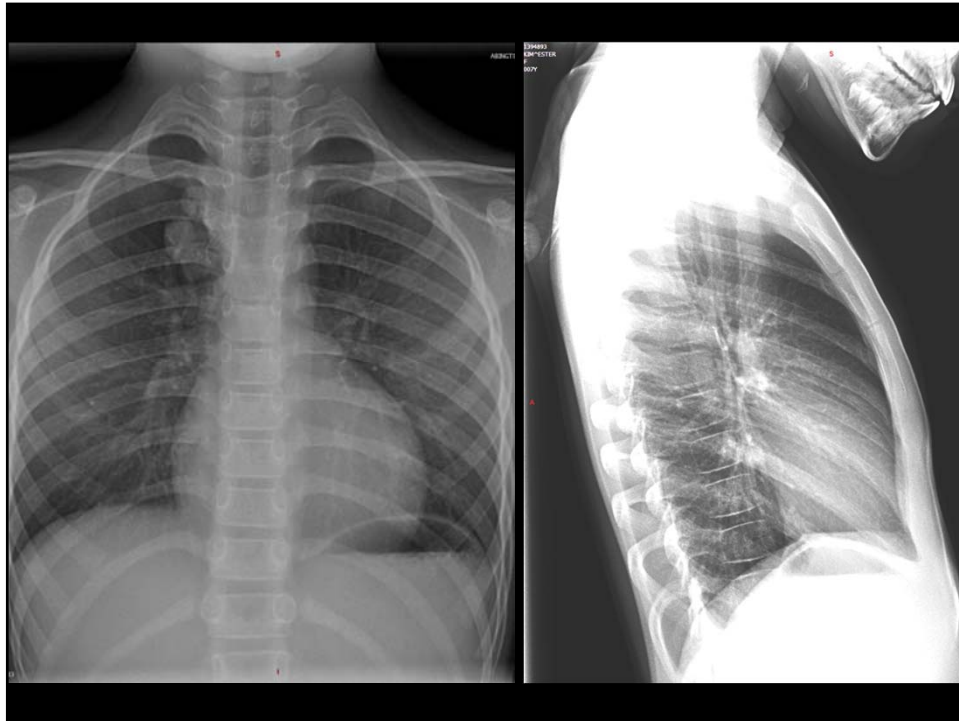


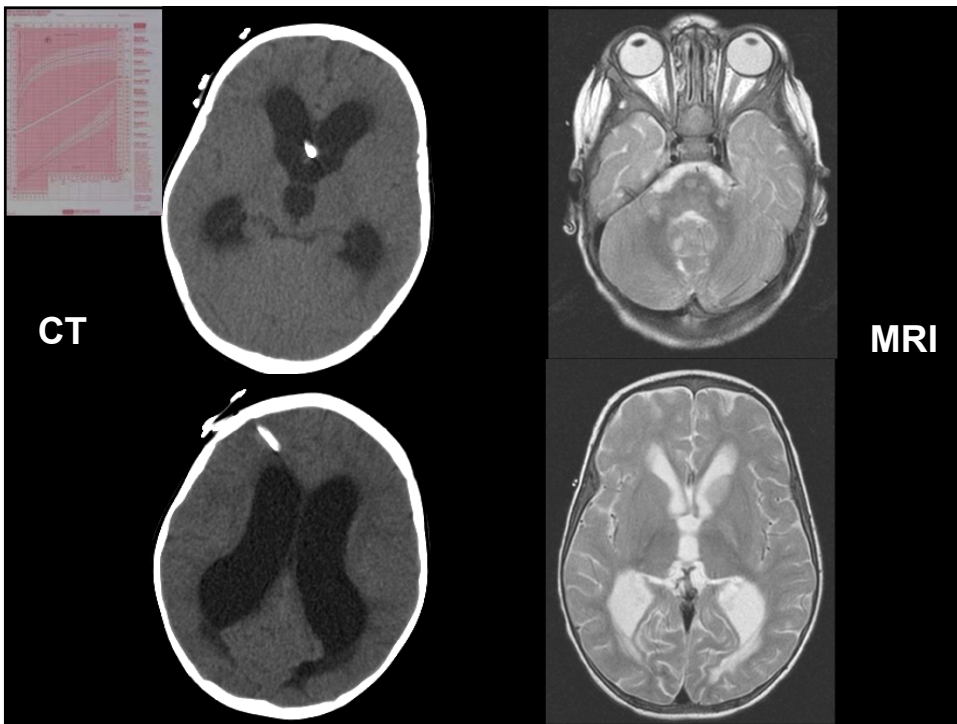
*Based on the public health surveillance definition for TB [MMWR 1997;46(No. RR-10):40-41]

Difficulties in the Diagnosis of Tuberculosis in Children

- TST may be negative (10-40%). IGRA?
- Chest radiograph: Any lobe of the lung may be involved
 - Good technique/experience with children
 - Two views
 - Careful interpretation





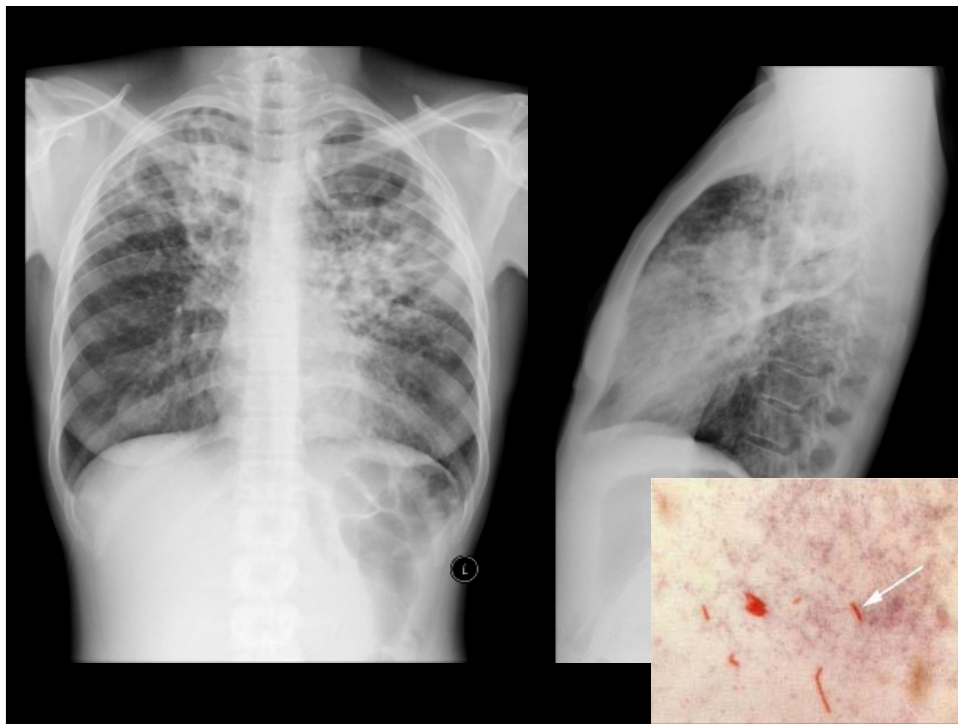




Control of Tuberculosis in the United States

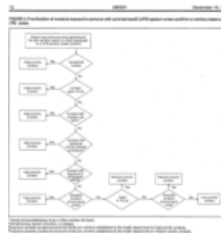
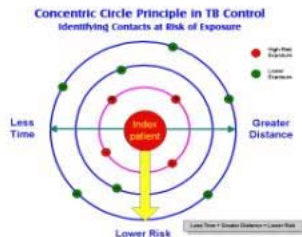
- Case finding and treatment
- Contact investigations
- Targeted testing of persons with risk

Red Book 2012



Control of TB in the United States

- Case finding + treatment -> Contact investigations
 - The most reliable TB control program is based upon aggressive and expedient contact investigations, rather than routine screening of large populations



High priority contact:

- Household
- Age <5 yrs
- Med risk condition
- Procedure
- Congregate, Time

- Can be complex and may require lots of detective work

Red Book 2009

Tuberculosis Exposure in Children <4 years of age and “Window Prophylaxis”

- History, PE, TST/IGRA, CXR are done
 - CXR is done regardless of TST/IGRA result
- IF the child is:
 - Asymptomatic and physical examination is normal
 - TST is negative (<5 mm) or IGRA negative
 - Chest X-ray is normal
- AND IF <4 years of age START: Isoniazid (INH) 10 mg/kg (max., 300 mg) PO once daily



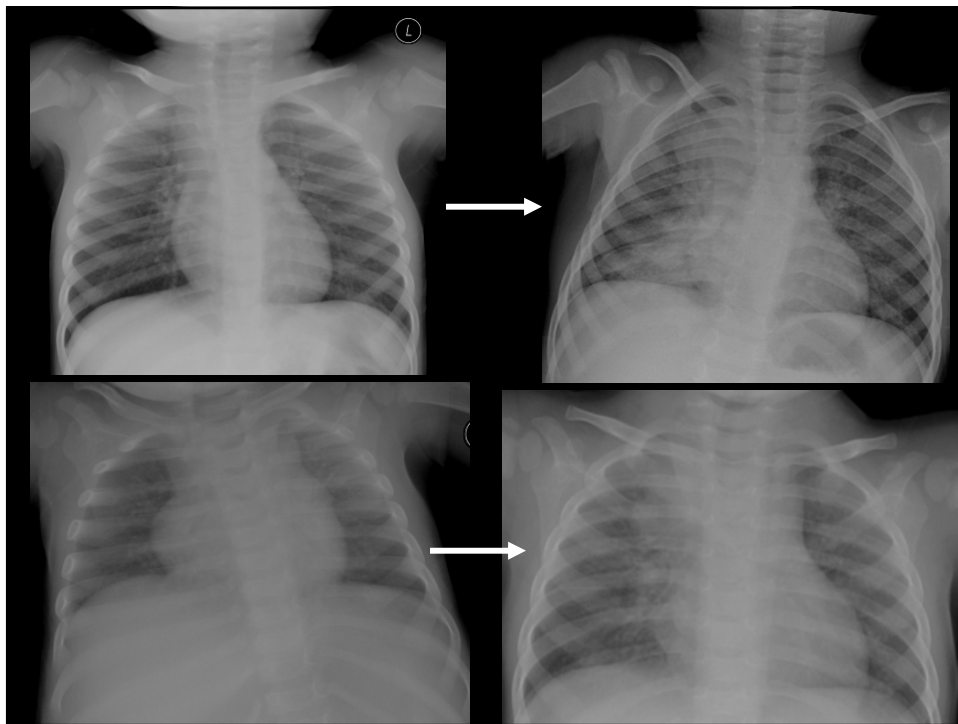
Tuberculosis Exposure in Children

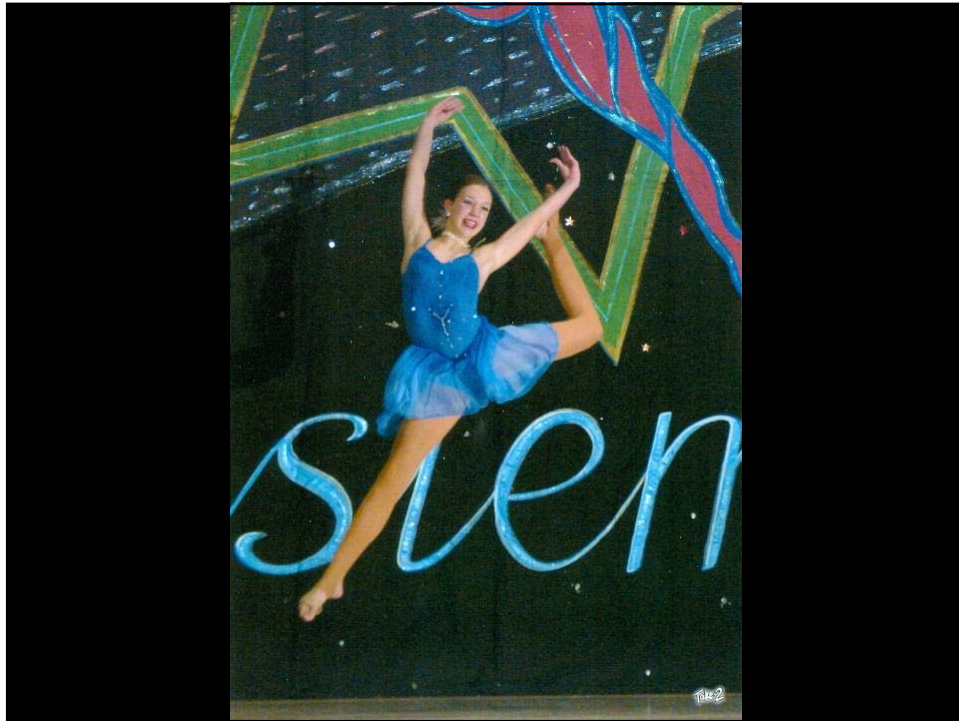
Why is INH given as **“Window Prophylaxis”** even if there is no evidence of TB infection or disease at the initial visit?

- Child may already be infected
- Infection more likely to progress to disease
- Infants and younger children are more likely to develop disseminated disease or meningitis

TST/IGRA repeated 8-10 weeks after contact broken with infectious adult:

- If TST/IGRA (-), discontinue INH
- If TST/IGRA (+), re-evaluate child and treat accordingly





TB Control: Targeted TB Testing

- What is Targeted TB Testing?
 - Identifies persons at high risk of infection with *M. tuberculosis*
 - Identifies persons at high risk of progressing to disease should they be infected
 - Reduces unnecessary testing, evaluations and treatment

Tuberculin Skin Test and IGRA Recommendations for Infants, Children and Adolescents

- Children for whom immediate TST or IGRA is indicated:
 - Contacts of people with confirmed or suspected contagious TB (contact investigation)
 - Children with radiographic or clinical findings suggesting tuberculosis disease
 - Children immigrating from areas with endemic infections (eg, Asia, Middle East, Africa, Latin America, counties of the former Soviet Union)
 - Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population
- Children who should have annual TST or IGRA:
 - Children with HIV infection
- Children at increased risk of progression of TBI to TB disease
 - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists

Red Book 2018

Targeted TB Testing Risk-Assessment Questionnaire

- Has a family member or contact had TB disease?
- Has a family member had a positive TB test?
- Was your child born in a high-risk country (i.e. outside US, Canada, Australia, New Zealand, or Western European countries)
- Has your child traveled to a high-risk country and spent >1 week with the resident population?

Red Book 2012



RUTGERS

Diagnosis of TB infection in children

- Tuberculin skin test (TST)
- Interferon- γ release assays (IGRAs)



Changes in TB Diagnosis in Children: IGRAs and the 2018 “RED BOOK”

- Can use IGRAs in immunocompetent children **≥ 2 years of age** [previously ≥ 5 years of age] in all situations where a TST would be used
 - Some experts may use IGRA down to 1 year of age
- Particularly useful for children who have received BCG vaccination
- Same recommendations as TST for risk factors and frequency of testing
- Use with caution in immunocompromised children
- Neither IGRAs nor the TST are perfect; always need clinical judgement

Red Book 2018 from J. Starke



Interferon gamma release assays: Use in children

- Similar to the TST, IGRAs do not distinguish between TB infection and TB disease
 - Negative IGRA does not rule out either in child with suspicious findings
- No cross reactivity with *M. bovis* (BCG vaccine) nor with *M. avium* complex (MAC)
- Cross reactivity: *M. marinum*, *M. kansasii*, *M. szulgai*, *M. flavescens*

AAP Technical Report. Pediatrics 2014;134(6)e1763.

Interferon gamma release assays (IGRA): Use in children

- TST preferred:
 - Children <2 years of age
 - Positive IGRA likely indicates infection with *M. tuberculosis*
 - Negative IGRA does not rule infection with *M. tuberculosis*
 - Some experts will use an IGRA down to 1 year of age
- IGRA preferred, TST acceptable: Children ≥ 2 years of age
 - Children ≥ 2 years of age who have received BCG vaccine
 - Children ≥ 2 years of age unlikely to return for TST reading

AAP Red Book 2018

Interferon gamma release assays:

- Both TST and IGRA should be considered when:
 - Initial and repeat IGRA are indeterminate
 - Initial test (TST or IGRA) is negative and:
 - Clinical suspicion for TB disease is moderate to high
 - Has TB risk factor and risk of progression and poor outcome is high (especially therapy with immunomodulating biologic agent, such as a TNF-alpha antagonist)
 - Initial TST is positive and:
 - The patient is ≥ 2 years of age and has history of BCG vaccination
 - Child healthy and at low risk
 - Additional evidence needed to increase adherence
- Interpretation of (-) IGRA in child with (+) TST:
 - Child unlikely to have LTBI but negative IGRA cannot be interpreted as universally ruling out TB infection (depends on clinical situation)

Red Book 2018

IGRAs in Children-Some Clinical Issues

- BCG-vaccinated child:
 - Strategy 1: TST: if negative, no further testing; if positive, follow with an IGRA
 - Strategy 2: Do only an IGRA
 - Note: If known TB exposure, child should be considered infected if either test is positive
- Child about to be immune compromised
 - No TB risk factor: do either a TST or an IGRA
 - TB risk factor: do both a TST and an IGRA and evaluate and treat if either test is positive (Risk vs Benefit)

Adapted from J Starke



Treatment of Tuberculosis Infection in Children: 2018 Red Book

- Isoniazid + rifapentine (3HP)*
- Rifampin (4R)
- Isoniazid (9H)

*Red Book does not state a preference but says that some experts think 3HP is the preferred regimen

LTBI treatment: 3HP for children

- Children ≥ 12 years of age: Recommended as equal alternative to 9 months of INH
- Children 2-11 years of age: Recommended as equal alternative to 9 months of INH
- Children < 2 years of age:
 - INH-RPT: Not recommended: Lack of safety and pharmacokinetic data in this age group

Dosing: 3HP

- INH (100 and 300 mg tabs):
 - Children age 2-11 years: 25 mg/kg/dose [900 mg]
 - Children older than 12 years of age: 15 mg/kg/dose [900 mg]
- Rifapentine (150 mg tabs):

Weight (kgs)	Dose (mg)	Maximum (mg)
10-14	300	
14.1-25	450	
25.1-32	600	
32.1-49.9	750	
>50	900	900

3HP: Thoughts

- When compared to 9H:
 - Just as effective
 - Shorter course
 - Better completion rates
 - Less toxicity
- Some parents prefer due to shorter course
- Greater pill burden
- Cannot be used in children under 2 years of age due to lack of safety and pK data for rifapentine



Treatment of Latent Tuberculosis Infection

- Rifampin for 15-20 mg/kg/day (max. 600 mg) po daily for 4 months (prior recommended dose 10-15 mg/kg)
 - First line option
 - INH not tolerated
 - Index patient isolate INH-resistant
- Cruz & Starke, (IJTLD 2014) : Rifampin 10-15 mg/kg/day (max. 600 mg) po daily for 4 months: Safe, completion rates similar to 9INH by DOPT
- Gaensbauer (PIDJ 2018): No treatment failures: 395 children; well-tolerated; high completion rates
- Concern about CNS levels being non protective against TBM

4R dosing: Target serum and CSF levels and Protection against TB meningitis (TBM)

- Standard treatment doses increased to:
 - 15-20 mg/kg/day
- New standard dosing still does not uniformly allow for protective CNS levels which is important in the infants and toddlers at greatest risk of TBM
 - Studies show that to reach target serum and hence target CSF levels in most (but not all) children doses should be at least 30 mg/kg/dose
 - Perhaps higher
- As a result many experts recommend dosing of rifampin at 20-30 mg/kg/dose for infants and toddlers and those with severe disease (TBM and disseminated disease)

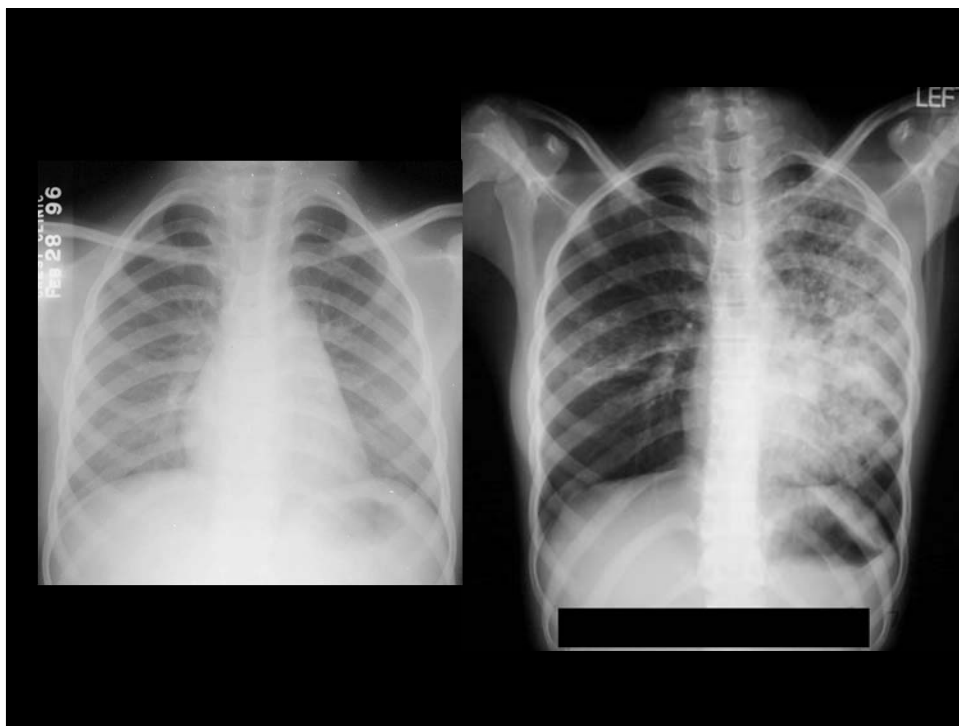
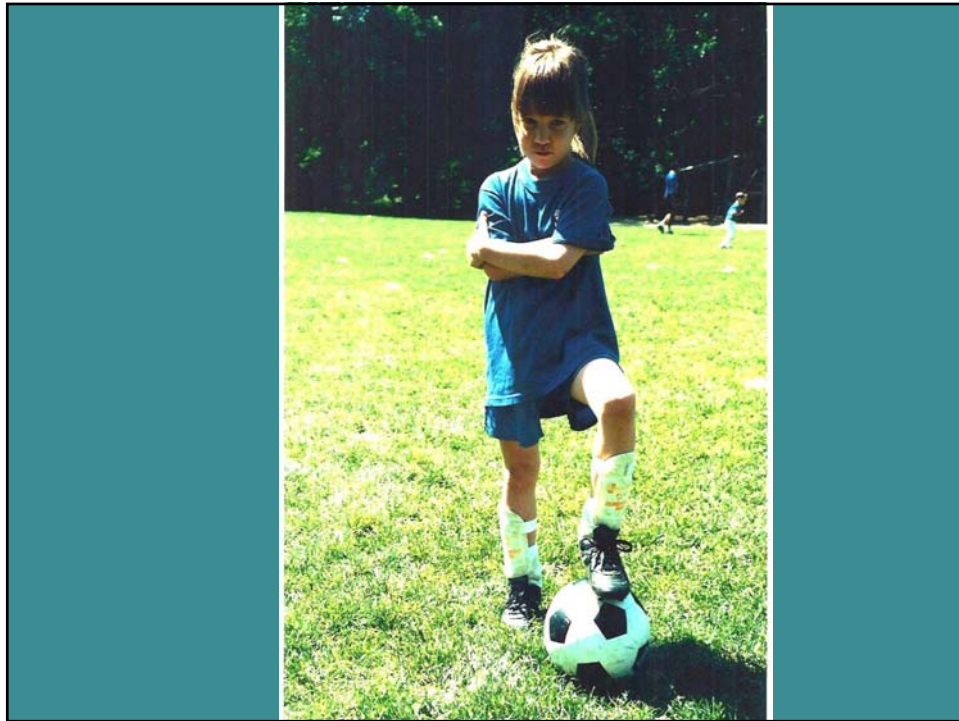
4R for TB Infection: Thoughts

- When compared to 9H:
 - Just as effective
 - Shorter course
 - Better completion rates
 - Less toxicity
- Parents prefer due to short course
- Need higher doses than previously given but these appear safe
- Can involve opening capsules which is difficult and can lead to spillage or a compounded suspension



Treatment of Latent Tuberculosis Infection

- INH 10-15 mg/kg (max., 300 mg) PO daily for 270 doses
 - Efficacy approaches 100%; prevents TB meningitis
 - Poor completion rates
- Alternative: Twice weekly directly observed (DOT) INH 20-40 mg/kg (max., 900 mg) PO for 72 doses
- Monitor index case isolate sensitivities
- Hepatotoxicity from INH is rare in children:
 - Monthly assessment for clinical evidence of hepatotoxicity should be made: malaise, loss of appetite or weight, nausea, vomiting, abdominal pain, jaundice
 - Routine monitoring of LFTs is not indicated, except:
 - Concurrent liver disease
 - Pregnancy or first 12 weeks postpartum
 - Concurrently on other hepatotoxic medications
 - Clinical evidence of hepatotoxic effects



Summary

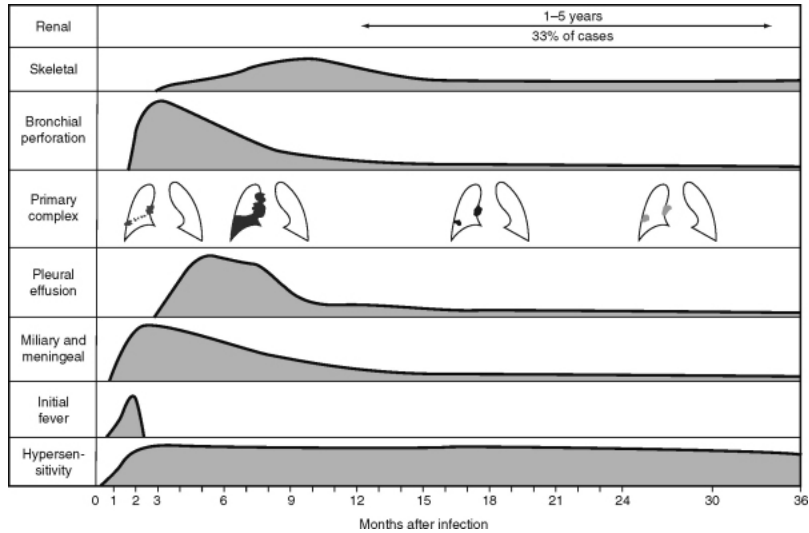
- Reported U.S. pediatric TB cases in 2016: 4.2% of the total
 - Case rates are highest in infants and toddlers
- Children are usually:
 - Infected by adult or adolescent household contacts
 - Not infectious (contagious)
- Tuberculosis or LTBI in a child is a **sentinel public health event**
- Window prophylaxis is indicated in TB-exposed children <4 years of age
- Diagnosis and treatment of TBI is a key to TB control
- IGRAs: test of choice down to 2 years of age
- 3HP [age 2 years and above], 4R and 9H are acceptable regimens
- Rifampin dose increase recommended

TST vs. IGRA

Characteristic	TST	IGRA
Antigens used	Many; PPD	3 (QFT) or 2 (T-SPOT)
Sample	Intradermal injection	Blood draw
Patient visits required	2	1
Distinguish between LTBI and TB disease	No	No
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM	Yes	Only rare species ^a
Differing positive values by risk	Yes (5-10-15)	No
Causes boosting	Yes	No
Subject to boosting by previous TST	Yes	Possible
Durability over time (stays positive with or without treatment)	Yes	Unknown
Difficulties with test reproducibility	Yes	Yes
Relative cost	Lower	Higher
Location of need for trained staff	"Bedside"	Laboratory
Estimated specificity in BCG-unvaccinated children	95% to 100%	90% to 95%
Estimated specificity in BCG-vaccinated children	49% to 65%	89% to 100%
Estimated sensitivity (confirmed TB disease)	75% to 85%	80% to 85%
Estimated sensitivity (clinical TB disease)	50% to 70%	60% to 80%

Starke, Pediatrics 2014

Timetable of TB in Children after Walgren



Tuberculosis. Starke JR, in Feigin, Cherry, Demmler, Kaplan, ed: Textbook of Pediatric ID 2009