

Childhood Tuberculosis: How Children Are Not Just Little Adults

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Epidemiology



- Adults with TB are easy to count
- Children with TB are difficult to count

- Adults get TB because of their own risk factors
- Children get TB because of the risk factors of the adults they hang around with





Tuberculosis in Adults

Pulmonary TB in adults is diagnosed by:

- Sputum microscopy [60 – 70%]
 - Sputum Xpert [75 – 85%]
 - Sputum culture [85 – 95%]
-
- Therefore, the basis for counting adult cases of TB is microbiologic, detection of the organism
 - Only ~10% of cases are extrapulmonary



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Tuberculosis in Children

Pulmonary TB in children is diagnosed by:

- Sputum microscopy [$< 10\%$]
- Sputum Xpert [$\sim 15\%$]
- Sputum culture [$\sim 30\%$]

- Therefore, using microbiology to count cases misses most childhood cases
- Most children with pulmonary TB don't even produce sputum!
- 30% of cases are extrapulmonary!



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DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

Even in developed countries, the “gold standard” for the diagnosis of tuberculosis in children is the triad of:

1. a positive TST 
2. an abnormal CXR and/or physical exam 
3. a history of recent contact to an infectious adult case of TB



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Estimates of Childhood Tuberculosis

WHO: 530,000 annual cases, 74,000 deaths in non-HIV-infected children [no estimate for HIV-infected]

- Actual notifications to WHO were 301,233:
 - AFB smear-positive pulmonary – 46,448
 - AFB smear-negative pulmonary – 163,477
 - Extrapulmonary – 91,308 [30%]



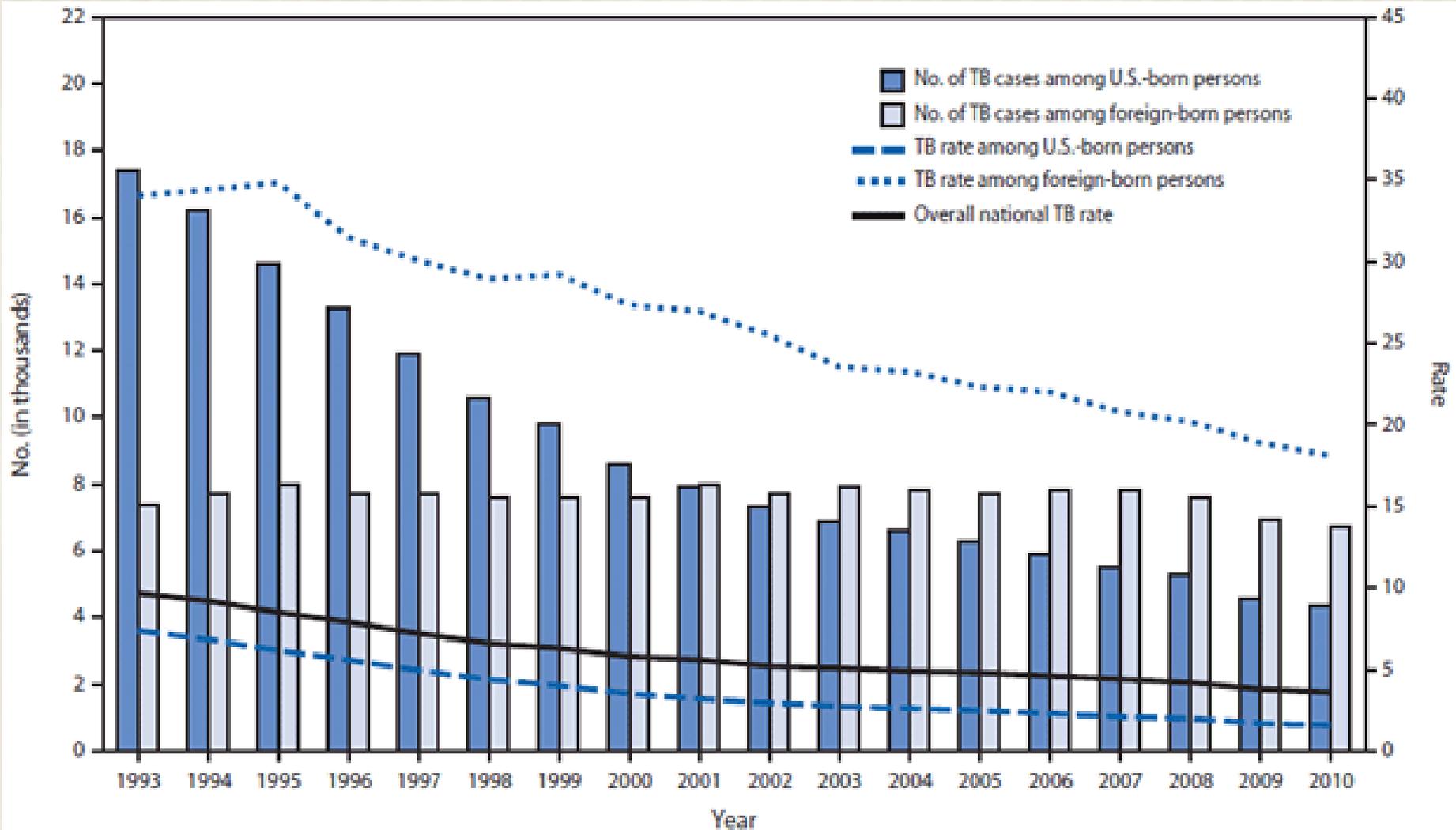
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Jenkins et al.: Modeling study estimate – 999,792 cases

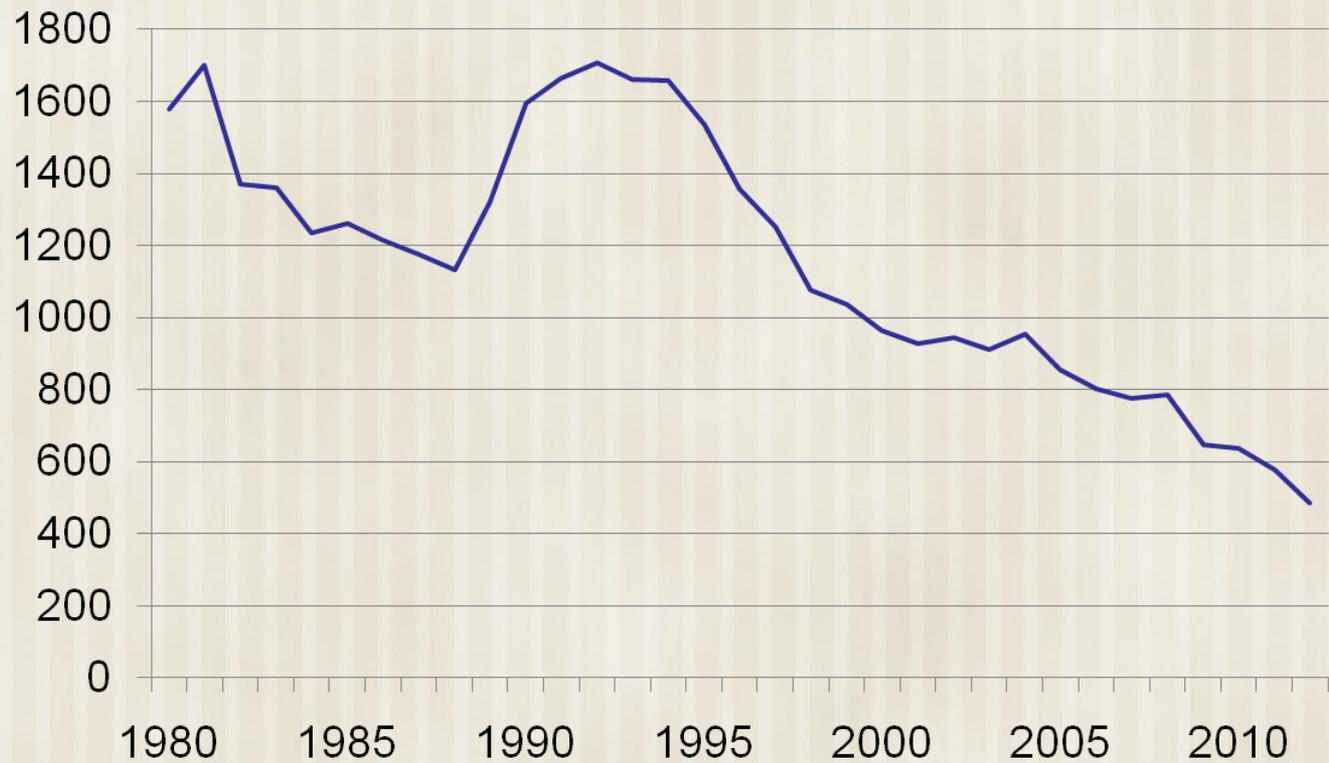
Dodd et al.: Modeling study estimates in 22 high burden countries: 650,977 cases; 7,591,759 children annually infected; 53,234,854 total infected children

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Tuberculosis in the United States



Tuberculosis Cases in Children 0-14 Years of Age, 1980-2012 – United States

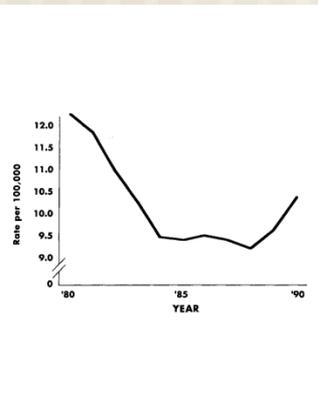


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Why Did TB in Children Resurge in the United States?



1. **HIV/AIDS** – mostly HIV-uninfected children who got TB infection from HIV-infected adults with pulmonary TB
2. **Congregate Settings** – schools, churches
3. **Immigration** – Prior to 2009, no testing for children < 15 yrs of age; now looking only for TB disease, not infection
4. **Poor Tuberculosis Control** – declined budgets, loss of expertise, lack of emphasis on prevention



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LTBI AND RISK OF TUBERCULOSIS DISEASE IN DEVELOPED COUNTRIES

Adults

- Lifetime risk for developing disease after infection – 2% to 10%
- One-half of risk is in the first 2 years after infection

Children

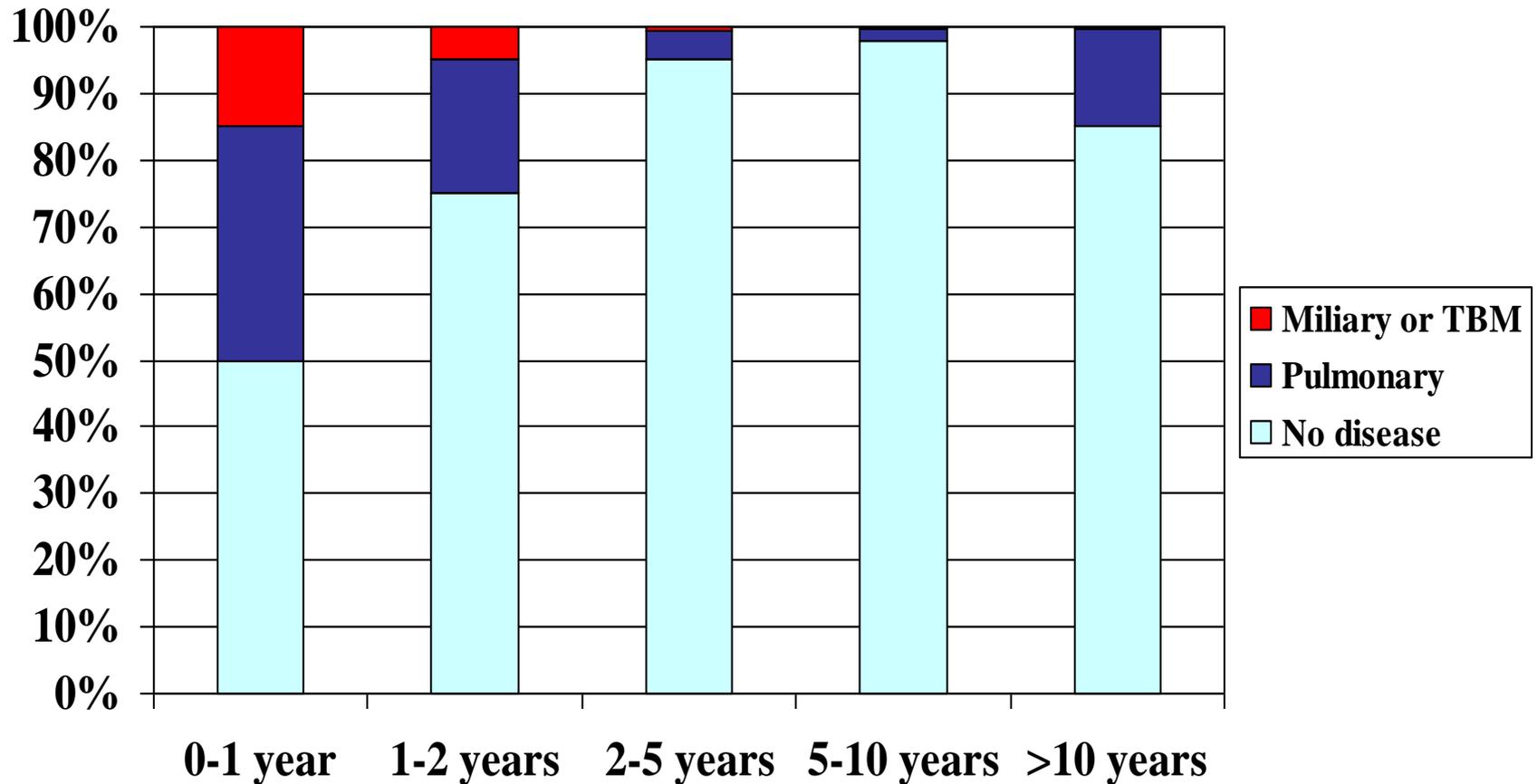
- Risk of disease in infected infants – 40%
- Most disease occurs in 3 to 9 months



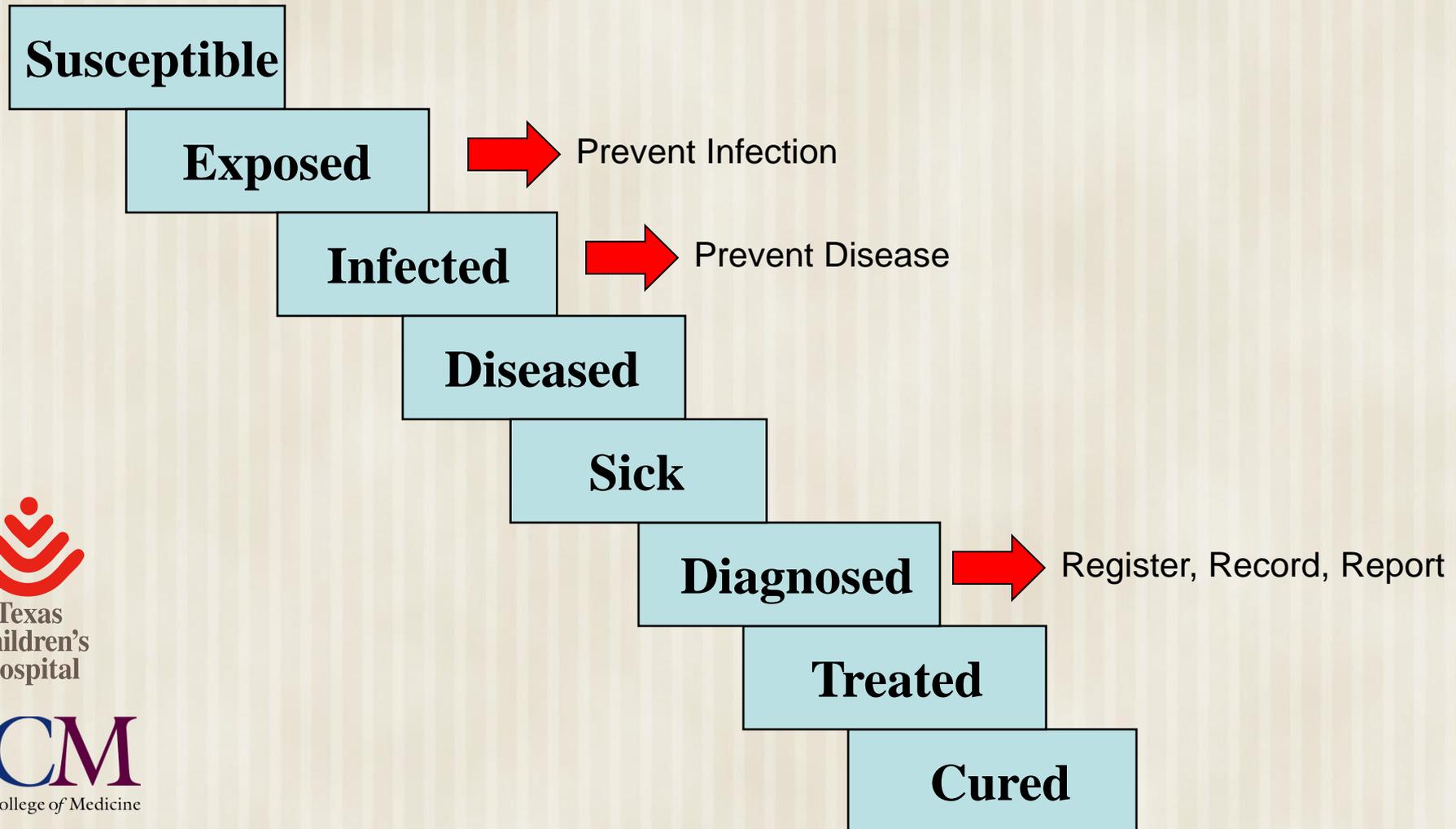
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Average Age Specific Risk for Disease Development Following Primary TB Infection (pre-BCG)



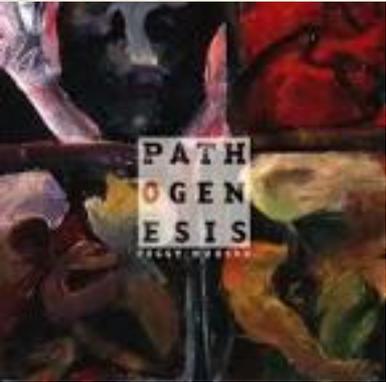
TRANSITIONS IN TUBERCULOSIS



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PATHOGENESIS OF TUBERCULOSIS



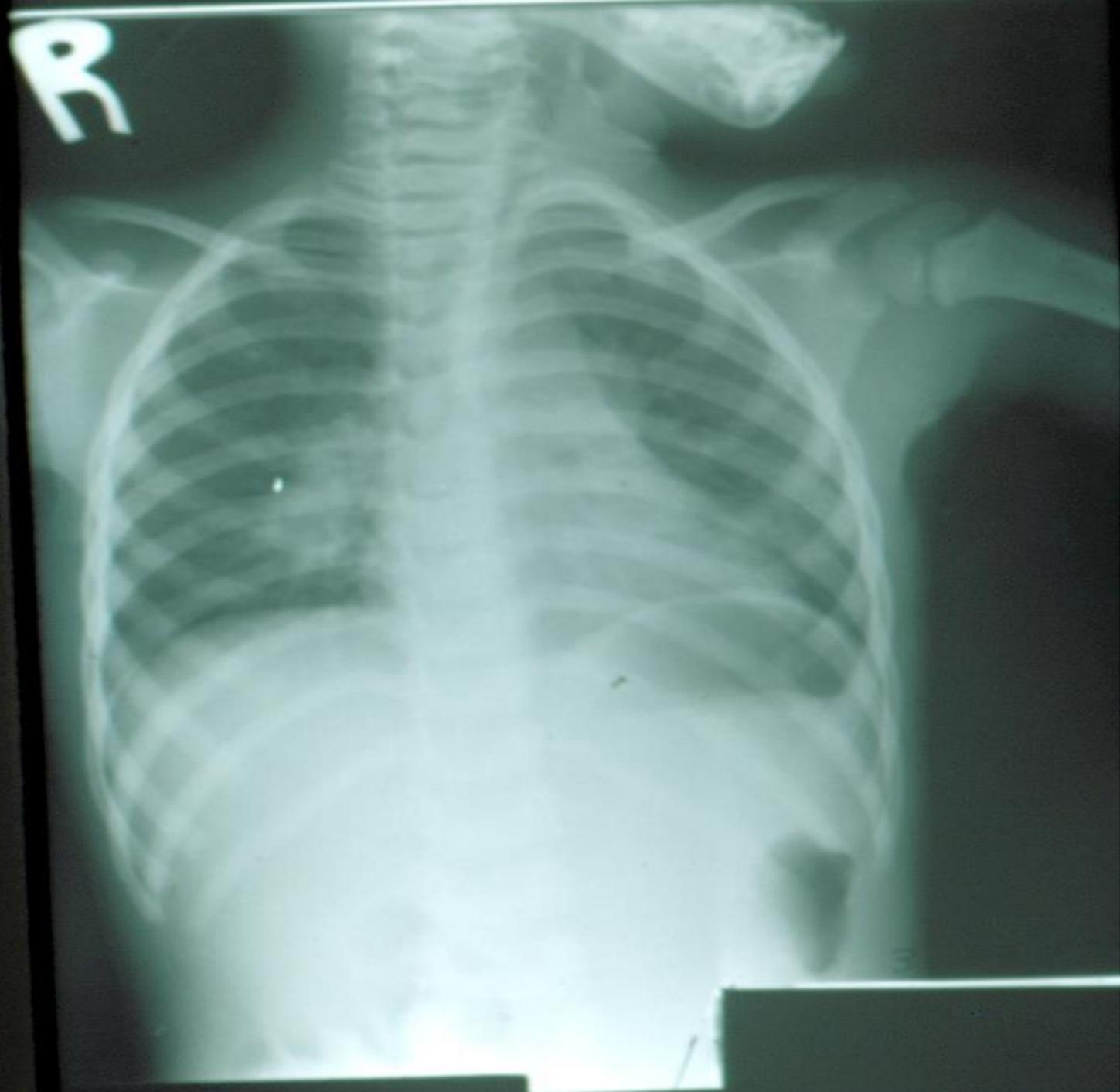
- Organisms contained in droplet nuclei land in the alveoli
- Infectious dose probably < 10 organisms
- Organisms ingested by macrophages, transported to regional [hilar, mediastinal, cervical] lymph nodes
- Lymphohematogenous dissemination of organisms occurs early – meninges, apices of lungs, lymph nodes, other organs



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TIMETABLE OF CHILDHOOD TUBERCULOSIS



Miliary and Meningeal	2 – 6 months
Pulmonary	2 – 12 months
Lymph node	2 – 12 months
Pleural effusion	3 – 12 months
Skeletal	6 months – 2 years
Renal	1 – 5 years



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ARE CHILDREN WITH TUBERCULOSIS EVER CONTAGIOUS?



- **Difficult to answer in the community**
- **Orphanages – caretaker with TB led to transmission; a child with TB did not**
- **Schools – only 2 reported “epidemics” caused by children <13 years old**
- **Children’s Hospitals – rare case reports of transmission, all with special circumstances, none has been patient -to - patient**



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FEATURES OF CONTAGIOUS PEDIATRIC TUBERCULOSIS



- **Cavitary lung lesion**
- **Sputum production**
- **Positive acid-fast stain of sputum smear**
- **Bronchoscopy**
- **Draining lesions or surgical drainage of an abscess**



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Getting Chest X rays on Parents of Children With TB



- Providing rapid chest radiographs for the caregivers of children with suspected tuberculosis remains an important and productive activity
- Overall, 9 of 110 caregivers of children with TB at TCH had pulmonary TB, a case rate of 9,100 per 100,000 [1,300 per 100,000 annual rate]
- Only 39 % of the children with suspected TB actually had TB, and better methods to identify true TB patients need to be developed
- This methodology is protective for healthcare workers, as the rate of TST conversion among them was extremely low, even in contact investigations with suspected exposure



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	# screened	# TSTs	# CXRs	Total cost of eval.	# abn CXR (caregiver) or TST conversion (employee)	Cost per identification of 1 abn CXR or 1 pos TST	# of HCW needed to screen to find an abnormal
Caregiver	254	N/A	254	\$54,705	10	\$5471	25
Employee: Contact investigation	880	498	119	\$88,323	1	\$88,323	880
Employee: Routine screening	19,883	19,841	87	\$1.96M	45	\$22,570	441
Total	21,017	20,339	460	\$2.11M	56	\$37,618	375

Diagnosis of TB Infection



- In adults, prior BCG vaccination has little influence on the TST
- IGRAs can be used on any adult
- In children, BCG can have a large influence on the TST
- So can nontuberculous mycobacteria
- We don't fully trust IGRAs in infants and toddlers



INTERACTION OF BCG VACCINES WITH THE TUBERCULIN SKIN TEST



- 50% of vaccinated infants do not react to a TST; most of the rest stop reacting within 5 years
- most non-infants who get one or more BCG vaccinations will react to a TST (usually < 15 mm), but effect wanes over 5 – 10 years
- outside infancy, “positive” TST more likely to indicate infection with *M. tuberculosis* than be residual from BCG



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INTERACTION OF BCG VACCINES WITH THE TUBERCULIN SKIN TEST

BCG vaccination

- By 5 years post-vaccination, 90% of children will have a negative TST
- Hundreds of millions of children get BCG, so millions have a positive TST from BCG



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Interferon γ tests

- MTB specific antigens:
 - ▣ Genes in region of difference (RD1) on MTB genome
 - ▣ Culture filtrate protein 10 (CFP-10)
 - ▣ Early secretory antigen target 6 (ESAT-6)
 - ▣ TB7.7(p4) in QuantiFERON Gold In-Tube
- Identifies LTBI &/or disease
- Does not cross react with BGC vaccine or most other mycobacteria
- Requires:
 - ▣ single medical visit [for LTBI, not for exposure]
 - ▣ blood collection
 - ▣ laboratory equipment and personnel
- Results in 24-48 hrs



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Comparison For Children

	<u>TST</u>	<u>IGRAs</u>
Estimated specificity BCG-unvaccinated children	90-95%	90-95%
Estimated specificity BCG-vaccinated children	49-65%	89-100%
Estimated sensitivity (confirmed TB disease)	75-85%	80-85%
Estimated sensitivity (clinical TB disease)	50-70%	60-80%



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TST preferred, IGRA acceptable

- Children < 3 years of age when testing for TB infection [Most experts would not use an IGRA in children < 2 years of age because of lack of data for this age group and high risk of progression to disease]

IGRA preferred, TST acceptable

- Children \geq 3 years of age who have had BCG vaccine
- Children \geq 3 years of age who are unlikely to return for TST reading



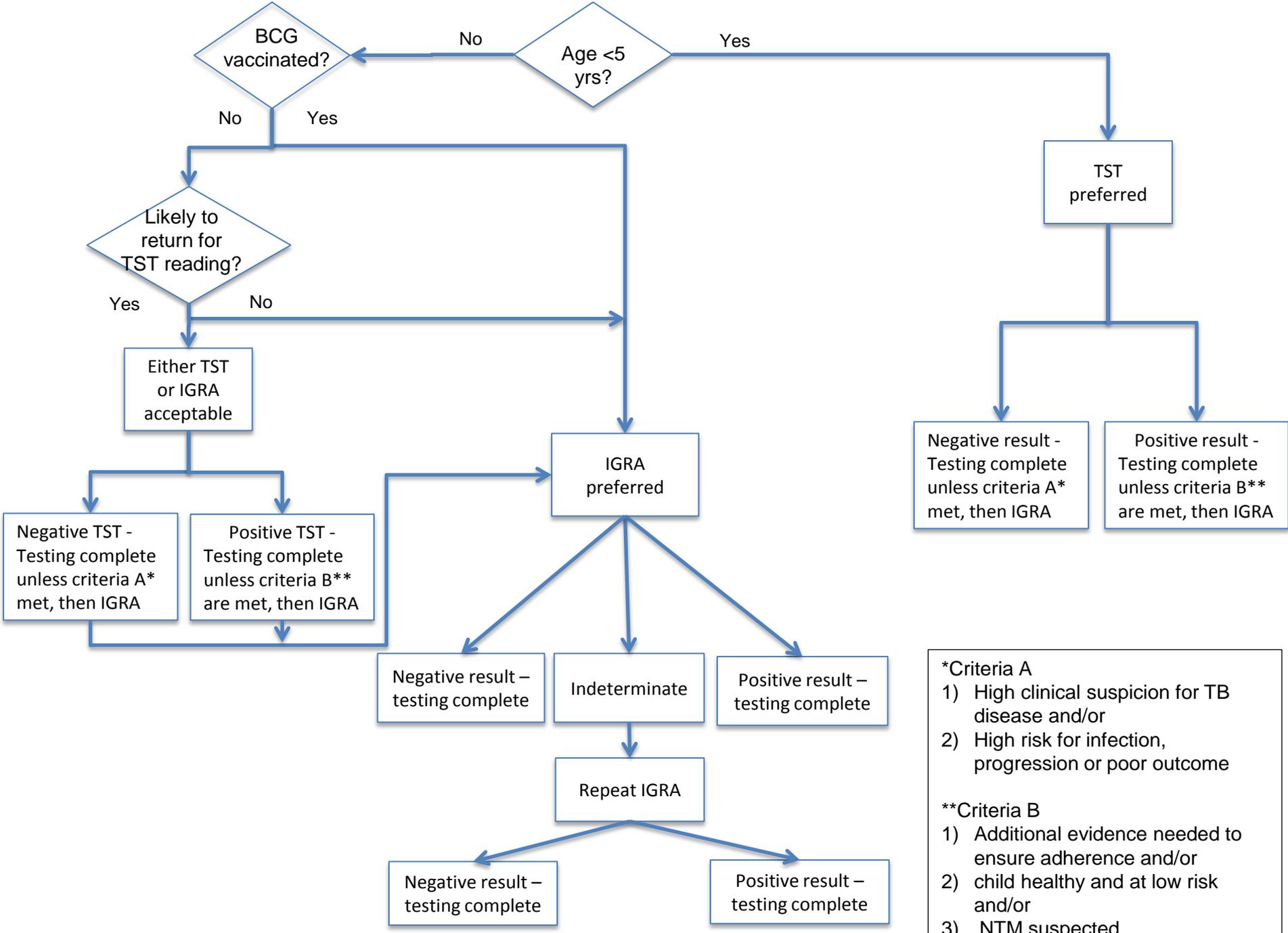
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Consider Both TST and IGRA for Children When:

- The initial and repeat IGRA results are indeterminate
- The initial test (TST or IGRA) is *negative* and:
 - ▣ There exists clinical suspicion for TB disease*
 - ▣ Risk of infection with poor outcome is higher*
- *[Either positive test is considered significant]
- The initial TST is *positive* and:
 - ▣ ≥ 5 years of age and history of BCG vaccination
 - ▣ Need additional evidence to increase compliance
 - ▣ NTM disease is suspected





***Criteria A**

- 1) High clinical suspicion for TB disease and/or
- 2) High risk for infection, progression or poor outcome

****Criteria B**

- 1) Additional evidence needed to ensure adherence and/or
- 2) child healthy and at low risk and/or
- 3) NTM suspected

Case Example

A 5 year old child from Nigeria has a 12 mm reaction to a tuberculin skin test. He received BCG vaccine as an infant and came to the U.S. at age 1 year. He has no known exposure to a TB case. A QuantiFERON test is negative.



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What does this mean? What do I do?



PTB in Adults and Children

Adults

Upper lobe apices
Cough, fever, night sweats
Sputum production common
Weight loss common
Long duration of symptoms
Cavities, infiltrate, nodules
Xray looks like the patient
Presentation by symptoms

Children

Any lobe, anywhere
Dry cough, \pm fever
Sputum production rare
Weight loss uncommon
Short duration of symptoms
Lymph nodes, atelectasis
Xray sicker than the patient
Contact investigation [1/2]



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CLINICAL AND RADIOGRAPHIC MANIFESTATIONS OF CHILDHOOD PULMONARY TB

- Paucity of signs and symptoms relative to chest radiograph findings
- Infants more symptomatic: fever, cough, focal wheezing, respiratory distress
- Predominance of hilar and/or mediastinal adenopathy (not always discernable on plain radiographs)
- Any lobe of lung involved; 25% multilobar
- Local pleural reaction/effusion is common
- Collapse-consolidation or segmental pattern most common
- Obstructive signs/symptoms with endobronchial lesions
- Not contagious



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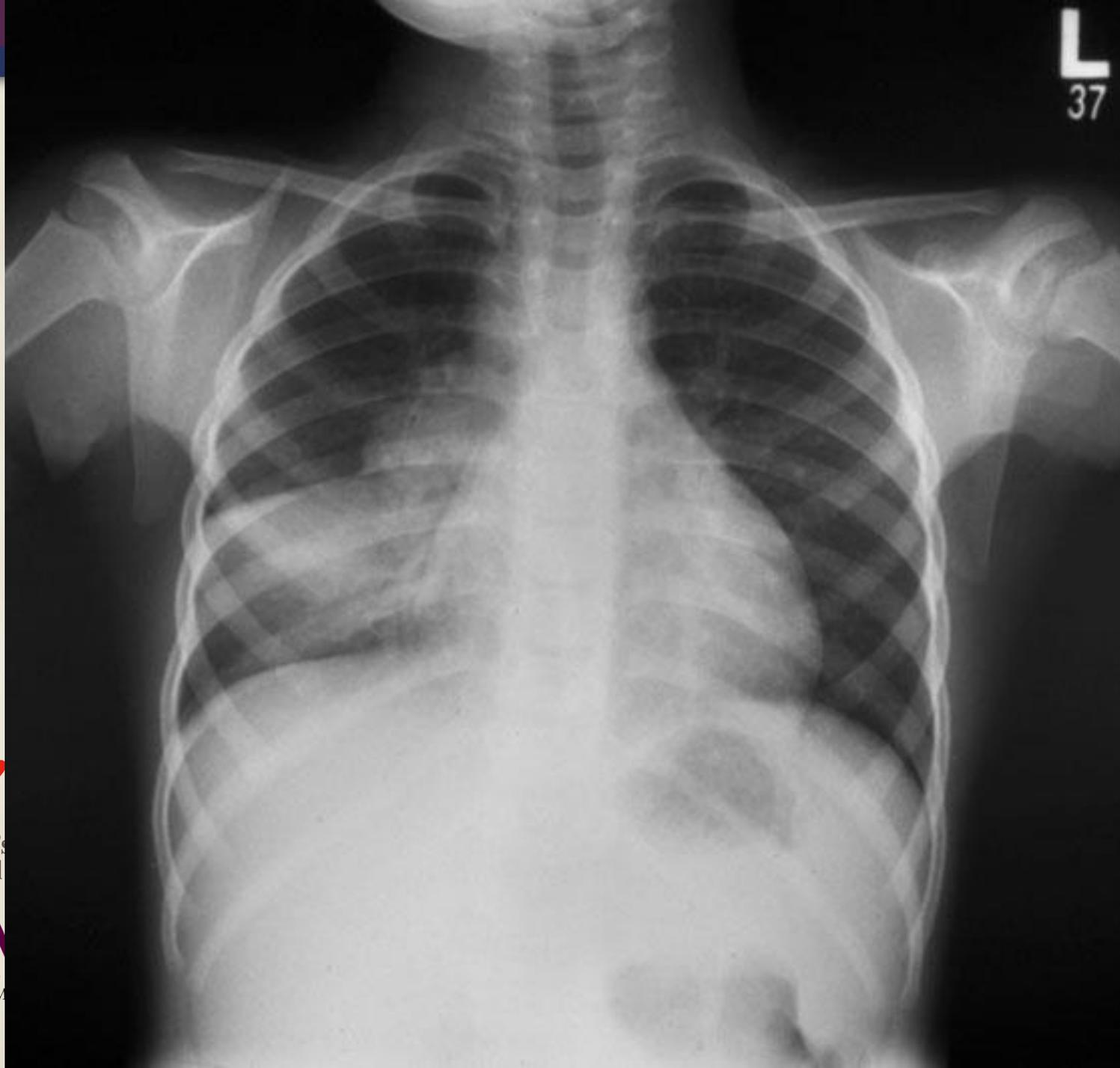
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DISSEMINATED (MILIARY) TUBERCULOSIS IN CHILDHOOD

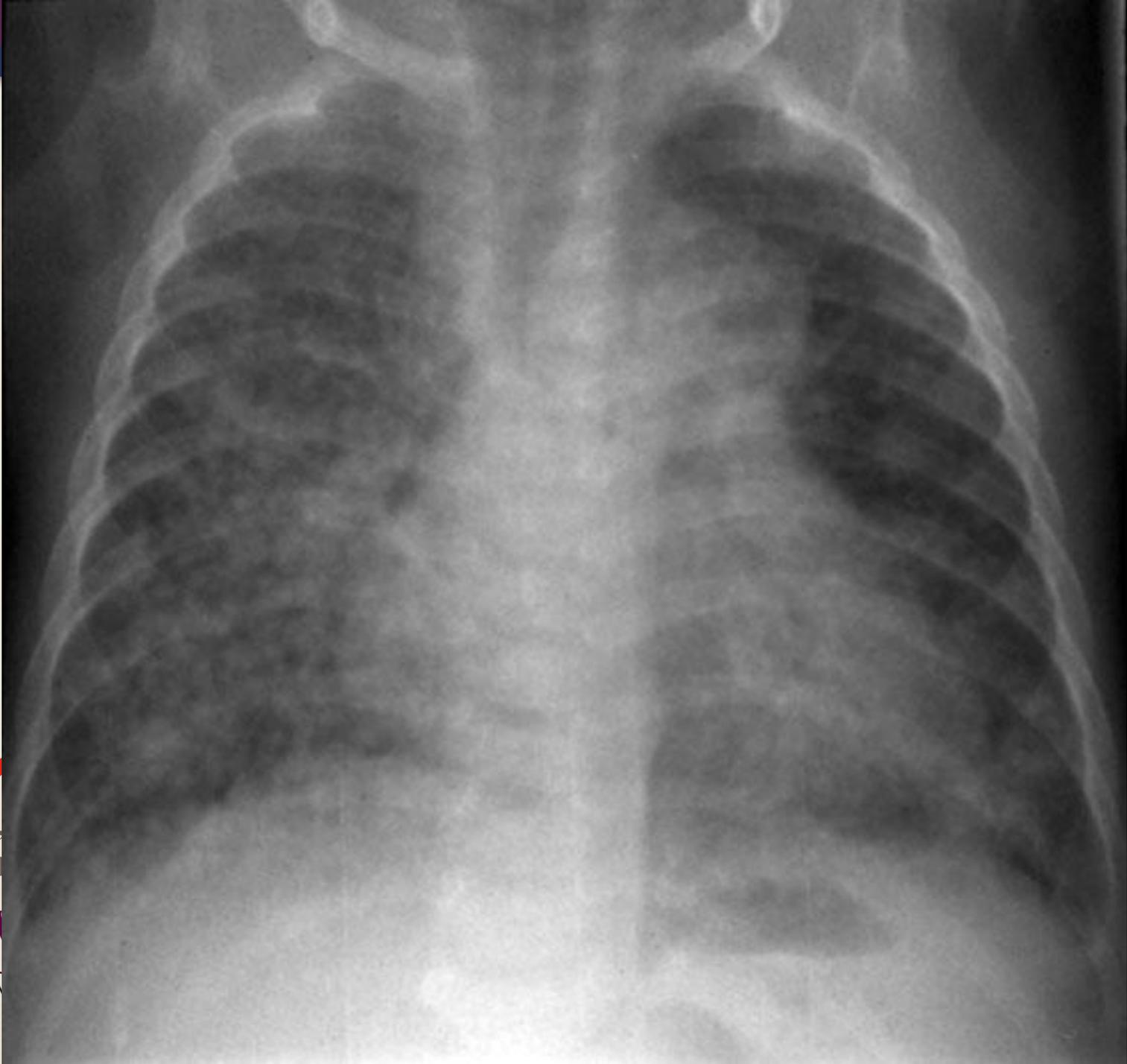
- most common in infants, recent after infection
- protean manifestations at first - FUO common
- usually insidious but may be explosive
- chest radiograph usually normal early, then classic
- other common features: hepatosplenomegaly, lymphadenopathy, cutaneous lesions, choroid tubercles
- TST negative in up to 50% of cases
- Dx: gastric aspirate, bronchoscopy, lung biopsy, liver biopsy, bone marrow, urine culture



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TUBERCULOSIS AND HIV INFECTION IN ADULTS



- If CD4 count is >500 cells/mm³, disease tends to resemble that in normal hosts
- With further immune suppression, disease expression becomes more similar to that in small children: nonapical, adenopathy, no cavities, extrapulmonary
- If infection with *M. tuberculosis* occurs after profound immune suppression, tuberculosis can be aggressive and progress rapidly : 4-6 weeks
- HIV infection can both accelerate and amplify tuberculosis



TUBERCULOSIS IN HIV-INFECTED CHILDREN

Clinical and Radiographic Presentation



- in children with preserved immunocompetence, presentation is indistinguishable from HIV-uninfected children
- most common symptoms remain malnutrition, fever, night sweats, lymphadenopathy and cough
- extrapulmonary disease (meningitis and tuberculoma, abdominal) is more common
- TB meningitis has the same clinical and CSF findings as in HIV-uninfected children except that intracerebral mass lesions are more common
- chest radiograph findings are typical, but more extensive and a broader differential diagnosis



EVALUATION OF A CHILD WITH SUSPECTED TUBERCULOSIS DISEASE



- Evaluate family members, other contacts
- Tuberculin skin test
- Appropriate radiographs
- Sputum (if available) for AFB stain, culture
- 3 early a.m. gastric aspirates (pulmonary)
- LP if < 1 year old
- Bronchoscopy - if anatomy needs to be defined or diagnosis is in doubt
- Report suspicion of disease to health department ASAP



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Gastric Aspirates

- Inpatient procedure
- Overnight fasting
- Lavage with NS if volume < 20cc

- Generally done qAM x3
- Inpatient costs substantial
- AFB smear yield: minimal
- AFB Culture yield: 20-30%



Induced Sputum

- Outpatient procedure
- 2-3h fasting period
- Pretreated with salmeterol; nebulized saline, then CPT given
- Nasopharynx suctioned
- One specimen sufficient
- Minimal costs



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Lancet. 2005;365:130



Treatment

- Adults have lots of bacteria
- Children have many fewer bacteria

- Adults have lots of adverse reactions
- Children have few adverse reactions

- Pills are made for adults
- Pills are not made for children



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DRUG RESISTANCE IN TUBERCULOSIS

The development of drug resistance in *M. tuberculosis* is the result of a **conspiracy** among the organism, the patient, the doctor and the healthcare system!



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Preventing Drug Resistance in TB

Cavity

10^9 organisms

10^3 R-INH

10^2 R-RIF

All organisms R-RIF killed



10^3 organisms R-INH
survive and grow

Cavity

10^9 organisms

All R-INH

10^2 R-RIF

R-INH: 10^{-6}

R-RIF: 10^{-7}

R-INH+RIF: 10^{-13}



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INH

Preventing Drug Resistance in TB

Cavity

10^9 organisms

10^3 R-INH

10^2 R-RIF

RIF kills R-INH organisms



INH kills R-RIF organisms

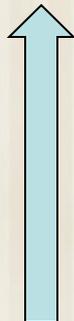
CURE!

R-INH: 10^{-6}

R-RIF: 10^{-7}

R-INH+RIF: 10^{-13}

INH + RIF



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Preventing Drug Resistance in TB

Granulomas

10^{*4-5} organisms

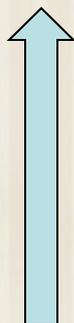
? any R-INH

? any R-RIF



Granulomas

? Cure



INH

R-INH: 10^{*-6}

R-RIF: 10^{*-7}

R-INH+RIF: 10^{*-13}

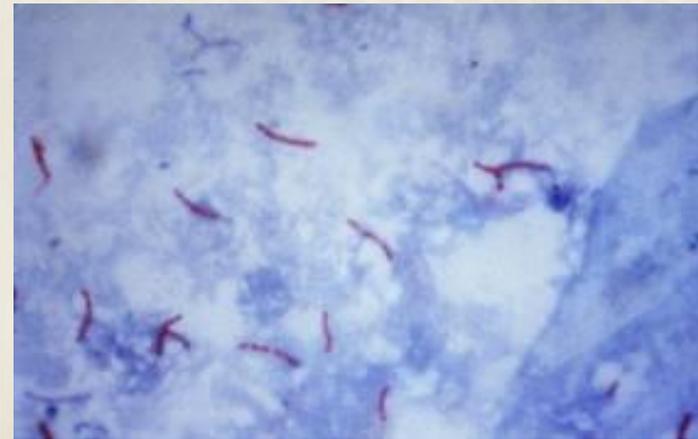


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Treatment of Tuberculosis

“More bugs More drugs!”



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Points To Ponder

What is the real difference between TB infection and TB disease in children?

- The organism is present in both cases
- We can sometimes culture the organism from children with recent infection but no clinical disease
- We treat infection with 1 drug, disease with 3-4 drugs
- The functional difference is the burden of organisms
- Infection and disease are on a continuum – when does “infection” turn into “disease”?
- The convention is that it is disease when “we can see it with our eyes or feel it with our fingers”



Considerations for Pediatric TB Treatment Regimens

- Very few true RCTs have been performed for intrathoracic TB, almost none for extrapulmonary TB
- Regimens that work in adults tend to work in children; may define the *maximum* treatment children require
- However, adult data do not necessarily define the *minimum* treatment required by children
- Children generally tolerate existing drugs and drug regimens better than adults



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Therapy for TB Disease

- Start 4-drug therapy - RIPE
 - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
- Use PZA only during 1st 2 months for susceptible TB
 - This is your 'shortening agent': consolidate from 9 to 6 months of therapy
- Stop EMB once culture results known, if have pan-susceptible TB
 - This is your insurance in case you have drug-resistant TB
- Anticipate minimum 6 month therapy, and we often extend it to longer periods, especially for extrapulmonary disease
- **Always** administered by directly observed therapy (DOT)



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FOLLOW-UP EVALUATIONS FOR CHILDREN WITH TUBERCULOSIS

- skin test stays positive “forever”
- frequent chest xrays unnecessary - at diagnosis, 1-2 months, end of therapy
- follow growth & development closely
- adequate nutrition
- routine liver enzyme monitoring not necessary
- routine vitamin B₆ not necessary except breast-feeding, pregnant adolescents, poor diet



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TUBERCULOSIS IN CHILDREN

IMPACT OF DRUG-RESISTANCE



- Usually must link the child with an adult case to identify it
- Adults with drug-resistant TB are as contagious as those with susceptible disease
- Disease expression in children the same as with susceptible strains
- Children tolerate and respond well to second-line drugs



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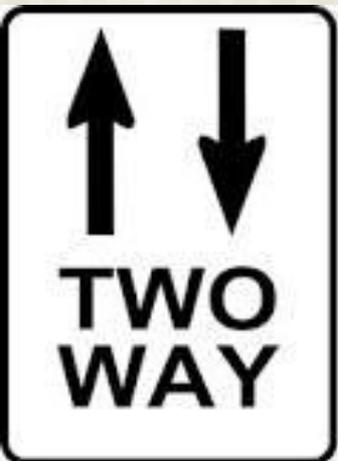
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Prevention of TB

- For adults, the emphasis is usually on determining specific risk factors for infection and then treating
- For children, the family-centered contact investigation is critical
- Prevention centers on both exposure and infection



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There are only two ways a child in a community can come to have TB infection:

1. Acquired within the community
[Contact Tracing]
2. Acquired elsewhere and brought into a community
[Screening for Risk]



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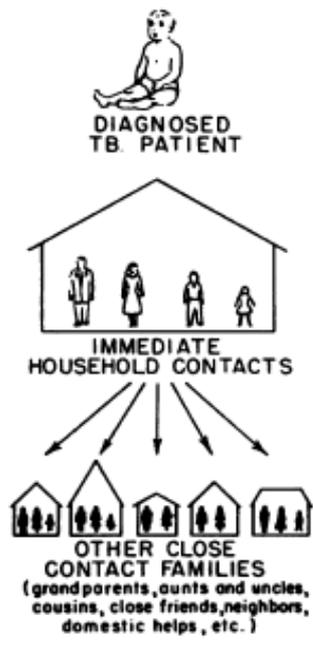
Katherine HK Hsu, M.D.



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SCHEME OF APPROACH



AGENCIES CO-OPERATING IN SCHEME

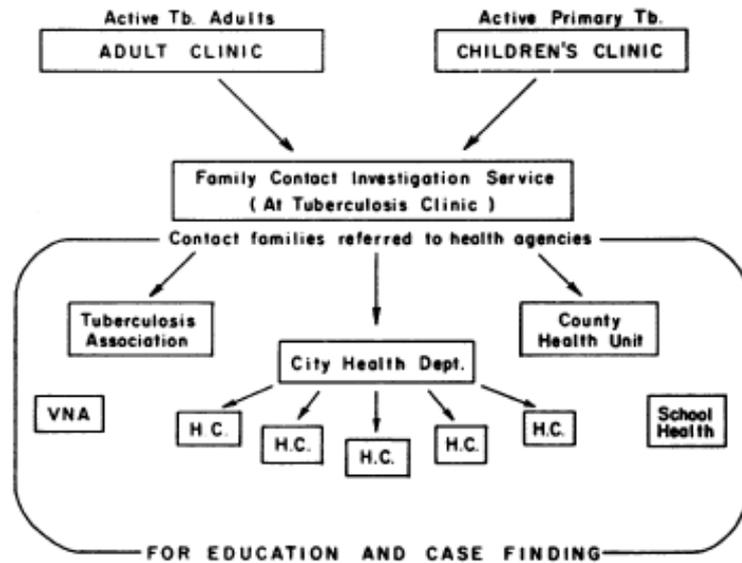


Figure 1—The Scheme for Tuberculosis Contact Investigation

Hsu KHK: Contact investigation: A practical approach to tuberculosis eradication. *AJPH* 53;1751, 1963.

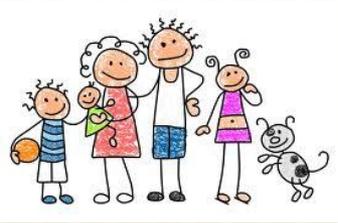


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The findings of a study of 205 family groups for tuberculosis and tuberculosis contacts are reported. These show that tuberculosis exists in "pools" involving large numbers of cases. Public health efforts should be directed to these pools of infection, and contact investigation has proved very efficient in finding pools. Intensive contact investigation will permit wide chemoprophylaxis amid children and young adults.

What Does Family Centered Contact Tracing Do?



- Identifies recently exposed and infected children
 - 1) Opportunity to prevent establishment of infection
 - 2) Prevent infection from progressing to disease
 - 3) Detect early disease – easier to treat & cure
 - 4) Prevent dissemination, hospitalization

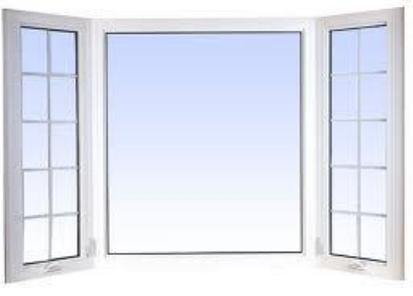
- Only opportunity to determine drug susceptibility for:
 - 1) 50% to 70% of children with disease
 - 2) 100% of children with infection



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TUBERCULOSIS IN CHILDREN TREATING EXPOSED CHILDREN

- So-called “window prophylaxis”
- Very high rate of infection w/o treatment
- Takes up to 3 months for the skin test to turn positive
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household receive isoniazid
- WHO standards – children <5 years old in a TB household should be treated



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Major Issues With Current Treatment Regimens for LTBI

- Acceptance
- Adherence and completion
Self: 49% ESAT: 75% DOT: 98%
- Duration – even 3 months is long
- Adverse events – hepatotoxicity, hypersensitivity reactions
- Cost [beyond isoniazid]
- Drug-Drug interactions [esp. rifamycins]
- Misdiagnosis – early TB disease



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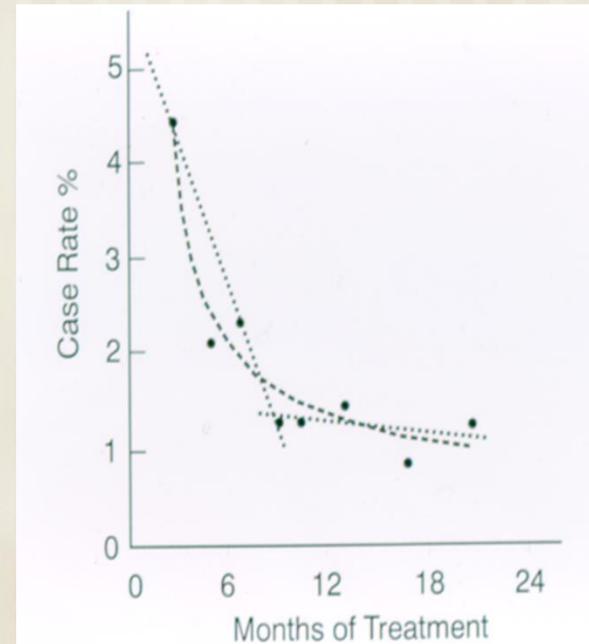
Treatment of [Latent] Tuberculosis Infection

Established therapies include:

- Isoniazid for 9 months
- Isoniazid for 6 months
- Rifampin for 4 months
- Isoniazid and rifampin for 3 months

- RIPE for 2 months [2 RZ]

- **Isoniazid and rifapentine once weekly for 12 weeks [under directly observed therapy]**



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PEARLS OF WISDOM FOR TREATING LTBI IN CHILDREN



- Use INH suspension only in children ≤ 5 kg
- Use DOPT for: recent contacts, infants, immune compromised
- When children aren't tolerating INH, the problem is more often with the parent than the child
- Route LFTs only for: other liver toxic drugs, liver disease, signs or symptoms of hepatitis
- Pyridoxine needed only for breast-feeding infants, pregnancy, poor diets



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SOME REASONS WHY CHILDHOOD TUBERCULOSIS HAS BEEN NEGLECTED



- Inadequate data
- Difficulty confirming the diagnosis
- Children are rarely contagious
[public health “dead end”]
- Perception from TB policy makers that treating adults is enough
- Government programs fail to address children
- Lack of family centered contact tracing
- Perceived lack of scientific study and scrutiny
- Misplaced faith in the BCG vaccines
- Lack of industry support
- Inadequate advocacy by pediatricians

