

Window Prophylaxis

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Summary

- Epidemiology
- Definitions
- Finding contacts
- Why window prophylaxis needed?
- What do we use?
- When to stop?
- What if child converts?
- Cases and lessons learned
- Key Points

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Summary

- Definitions
- Why we use it?
- Key points (Can't trust: IGRA in less than 2 y/o, TSTs done by PMDs, sputums at hospitals, hx always changes after seeing patient- Length of cough and amt of contact)
- Getting the help you need from: pediatricians, school nurses
- Cases: Priya, Angel, Poppy, Ethan/Ella, Mark/Alex
- Reasons not to start- 1-2 weeks until retest date
- Retest 10-12 weeks instead of 8?
- When Window ppx started? Another name for it to find older studies?
- Use TB clinic resources- name Peds TB docs and clinics in NJ
- Where concentric circle diagram from?
- TBI contacts, late 50s/ 60s
- Starke paper Lincoln last chapter307 dx prophylaxis Pas streptomycin- getting TB meningitis
- COVID

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Latest TB incidence in U.S. (CDC)

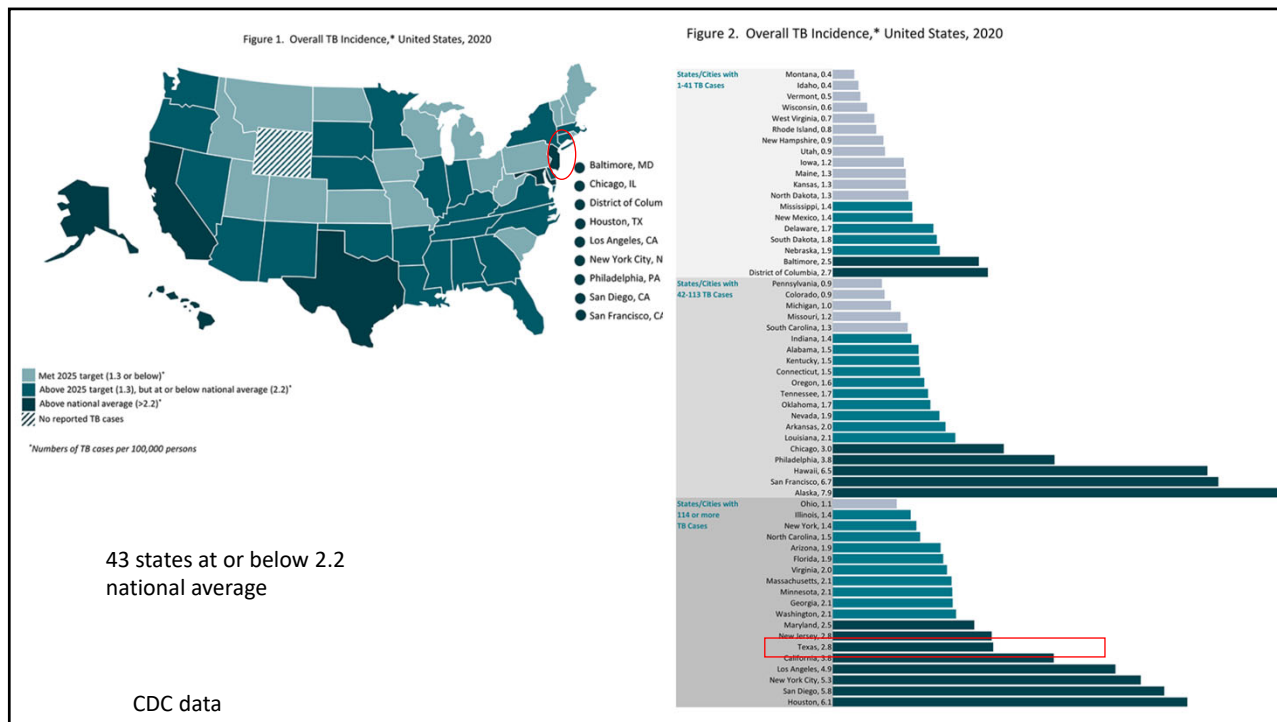
(Updated 10/26/22)

| Year | Number of Cases | Rate (cases/100K) |
|-------------|-----------------|-------------------|
| 2021 (-13%) | 7,860 | 2.4 |
| 2020 (-20%) | 7,174 | 2.2 |
| 2019 | 8,904 | 2.7 |
| 2018 | 9,006 | 2.8 |
| 2017 | 9,071 | 2.8 |
| 2016 | 9,242 | 2.9 |

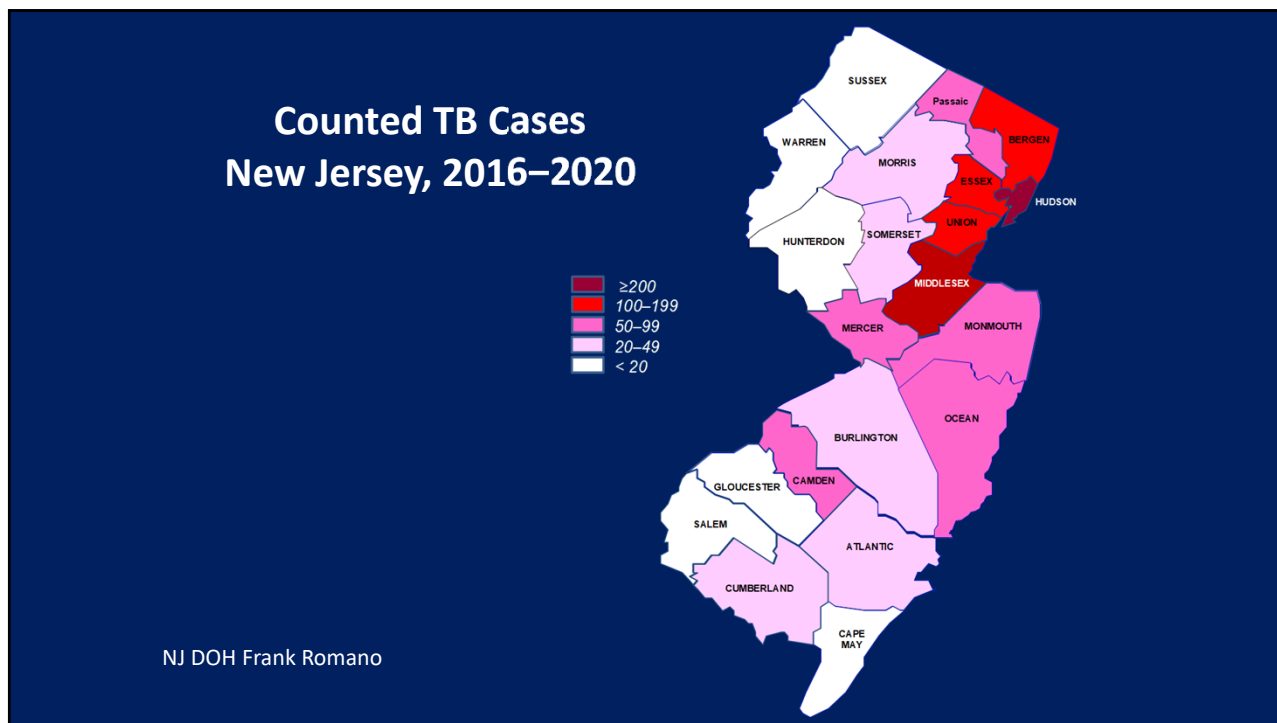
From 60 reporting jurisdictions

- **Up to 13 million:** estimated LTBI cases
- Reduction in TB disease ?
- Missed or delayed diagnosis
- OR combination

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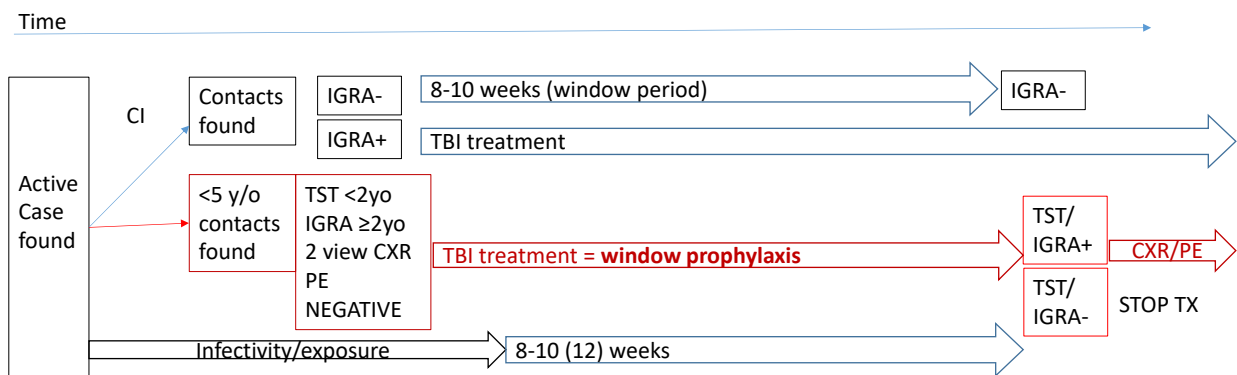
Definitions

| | TST/ IGRA | Physical Exam | CXR |
|----------------------------|-----------|-----------------|----------|
| Exposed | Negative | Normal | Normal |
| TB infection (LTBI) | Positive | Normal | Normal |
| TB disease | Positive | Abnormal/normal | Abnormal |

- **Source case:** adult with active contagious disease
- **Window period:** estimated interval between infection and detectable skin test reactivity/ positive IGRA
- **Window prophylaxis:** treating patients at high risk for progression to active disease for TBI even if evaluation is negative (during window period)
 - Children less than 5 years
 - Immunocompromised

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Window prophylaxis

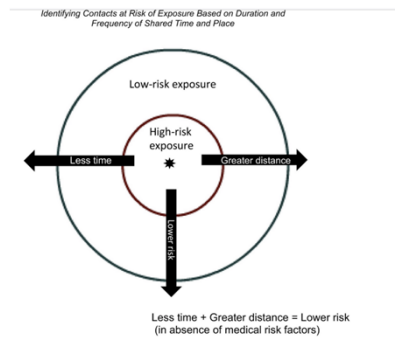


CI: Contact investigation
 PE: physical exam
 CXR: chest x-ray

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Ways of finding TB Contacts

- Contact investigation around a source case
 - Source case: adult with active TB
 - Concentric circle
 - High Priority: Household, Age <5 y, medical risk
 - Multiple rounds of questioning
 - Clues: children's shoes/toys in house
 - multiple families
 - illegal day cares
- Screening child -finding LTBI then screening the family to look for source case



Wolman et al. 2018
J Clin Tuberc Other Mycobact Dis

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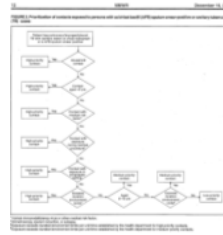
Things I want to know about source cases

- Symptoms for how long?
- Cough for how long?
- Exposure amount?
- Chest imaging: Cavitory vs. non-cavitory? Miliary? Laryngeal?
- Sputums?
 - AFB smear results
 - Where done: Hospital? Non-induced at home? Induced at TB clinic?
- When treatment started?

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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
(Dr. M. Sherry)

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Why do we need window prophylaxis?

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Risk factors for developing disease

- Age < 4 years old
- Recent infection (within past 2 years)
- Medical conditions:
 - Hodgkin disease, lymphoma
 - End-stage renal disease
 - Diabetes mellitus
 - Malnutrition
- Immune suppression
 - HIV
 - Chemotherapy
 - Chronic steroid use
 - Other immune altering conditions (post-transplantation)
 - TNF –alpha antagonists (infliximab, etanercept)

Red Book 2012

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Progression to disease

General population:

- 10% will develop disease during their lifetime
- 5% develop disease in first 2 years

- 43% of infants
- 24% of 1-5 year olds
- 15% of 11-15 year olds

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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 schoolyears" |
| >10 years | <0.5% | 10-20% | 80-90% | Effusions or adult-type pulmonary disease |

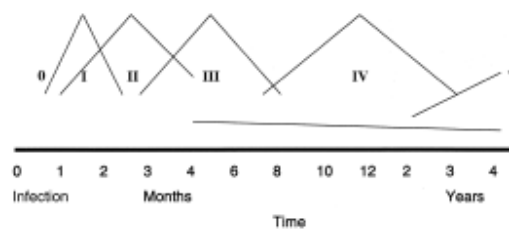
Adapted from reference 30.

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;
Pulmonary TB in adults and children, Miller & Wallgren; T. Nelson & Sons, 1939.

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Schematic Timeline of Primary Tuberculosis

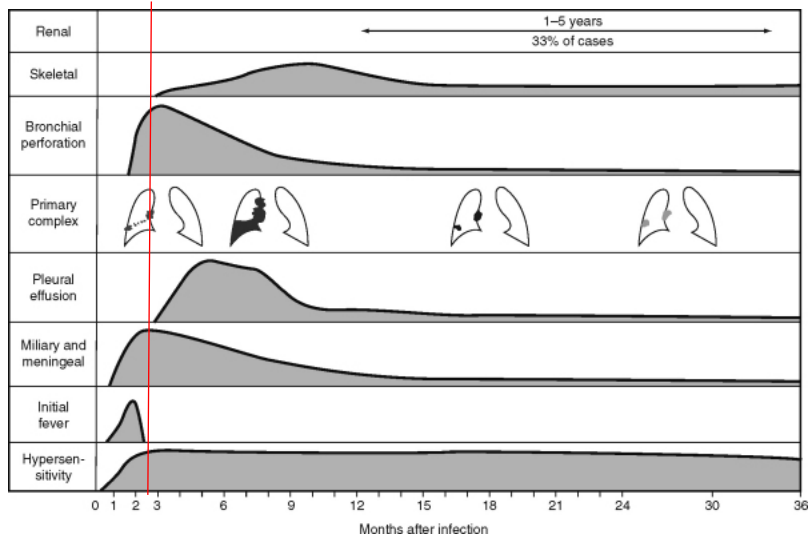


- 0 Incubation phase
- I Hypersensitivity phase
- II Phase of miliary tuberculosis and tuberculous meningitis
- III Phase of segmental lesions in children aged under 5 years and pleural effusion in those aged over 5 years
- IV Phase of osteo-articular tuberculosis in children aged under 5 years and adult-type disease in those aged over 10 years
- V Phase of late manifestations including pulmonary reactivation disease.

Adapted from Wallgren: Time-table of tuberculosis Tubercle 1948

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Timetable of TB in Children after Wallgren



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

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What do we use for window prophylaxis?

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Evolution of the AAP Red Book

- 2012: “For exposed contacts with impaired immunity (eg, HIV infection) and **all contacts younger than 4 years**, **isoniazid therapy** should be initiated, even if the TST result is negative, once TB disease is excluded”
- 2018-2021: For exposed contacts with impaired immunity (eg, HIV) and **all contacts younger than 5 years**, **treatment for presumptive LTBI** should be initiated, even if initial TST/IGRA is negative, once TB disease excluded... if TST/IGRA is still negative in an immunocompetent person, **isoniazid can be discontinued**.
- 2021-2024: For exposed contacts with impaired immunity (eg, HIV) and **all contacts younger than 5 years**, **treatment for presumptive TBI** should be initiated, even if the initial TST or IGRA result is negative, once TB disease is excluded.....If the TST or IGRA result still is negative in an immunocompetent person, **treatment can be discontinued**.

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Which TBI treatment to start?

- ~~Weekly INH and rifapentine → 12 weeks~~
- Daily Rifampin (15-20 mg/kg/day or 20-30 mg/kg/day) → 4 months
 - INH resistance
 - Young infant ? – can’t depend on accuracy of repeat testing
- ~~Daily INH and Rifampin → 3 months~~
- Daily INH (10-15 mg/kg/day) → 9 months

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Evolution of my practice

- INH in < 4 year olds (or Rifampin if INH resistant)



- < 2 year old: INH and finish with INH
- 2-4 year old: INH then switch to RIF (if can dose 15-20 mg/kg/dose with capsules)



- < 2 year old: INH – possibly finish with Rifampin
- 2-4 year old: RIF (unless can't dose Rifampin 15-20 mg/kg/dose)

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How do we know it works?

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Window prophylaxis, Houston 2007-2017 (Cruz and Starke, EID 2019)

- Retrospectively study of safety of INH in 752 TB-exposed children <5 years of age
 - Median age: 2.4 years
 - 41.4% resided in the home of the index patient
 - Index pt. Microbiology:
 - AFB smear positive: 68.2%
 - AFB culture positive: 90.4%
 - Index pt. drug susceptibilities:
 - INH and rifampin susceptible: 93.4%
 - INH resistance: 4.7%
 - INH and rifampin resistance: 1.9%

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Window Prophylaxis: Does it work?

- Window Prophylaxis:
 - INH: 97.1% (DOPT BIW)
 - RIF: 2.7% (DOPT daily)
 - 2 patients: EMB/PZA for MDR TB
- Safety: (AE:7/752= 0.9%): Median time to AE: 5 weeks
 - No hepatotoxicity
 - Vomiting: 2 children
 - Angioedema: 1
 - Weakness: 1
 - Diarrhea: 1
 - Rash: 2

ALL had INH; changed to RIF
- Conversion of TST: 37 children (4.9%)
 - No difference in conversion rate: <2 years of age and >2 years of age
 - Median time between TSTs: 73 days
- 94.6% completed therapy

Cruz AT, Starke, JR. Emerg Infect Dis 2019

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Window Prophylaxis: Does it work? YES

- Accepted by families- know what TB is
- Safe, well-tolerated
- No association between TST conversion (Cruz & Starke)
 - Sputum smear status
 - Some data for highly smear positive cases too weak to cough vigorously
 - Cases not equally contagious over time
 - Cohabitation
 - Don't use strict definition
- Conclusion: safe and effective!

Cruz AT, Starke, JR. Emerg Infect Dis 2019

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When to stop window prophylaxis?

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Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis

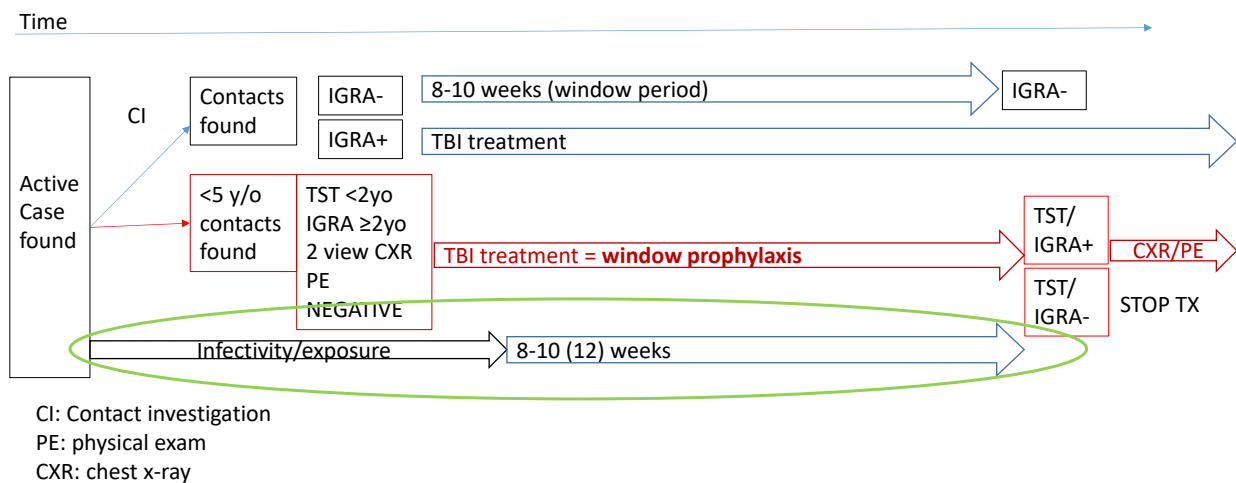
Recommendations from the National Tuberculosis Controllers Association and CDC

MMWR 2005

- Estimated interval between infection and detectable skin test reactivity (window period) is 2--12 weeks
- However, reinterpretation of previous data indicates: 8 weeks is outer limit of window period
- Consequently, NTCA and CDC **recommend that the window period be decreased to 8-10 weeks after exposure ends**

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Window prophylaxis



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What if TST/IGRA converts?

- **Re-evaluate!!**
 - Symptoms, physical exam and repeat CXR
- Complete TBI treatment
 - 9-months of INH or 4 months of RIF
- Cruz AT, Starke, JR. Emerg Infect Dis 2019
 - Changing to full shorter regimen to complete “seems reasonable”
 - No data on shortening 4R of 3HP after INH started- so complete full course

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Lessons Learned

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9 year old girl referred to Peds ID clinic

- 10 mm TST (previously negative)
- Right hilar adenopathy on CXR
- Born in India, 4 y/o: moved to US, last visit to India > 2 yrs ago
- Otherwise healthy
- No symptoms
- Normal physical exam

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9 year old

Mother admitted to OSH with cavitary TB and AFB positive sputum on 4 drugs

- Chronic dry cough for months, failed antibiotics
- Started on 4 drug TB treatment as outpatient by pulmonology
- Vomiting, dehydration, LFT abnormalities- admitted x 1 week

Father denies cough, fever, weight loss, night sweats, or other symptoms

- 10 mm TST
- CXR pending

4 year old brother sitting in office

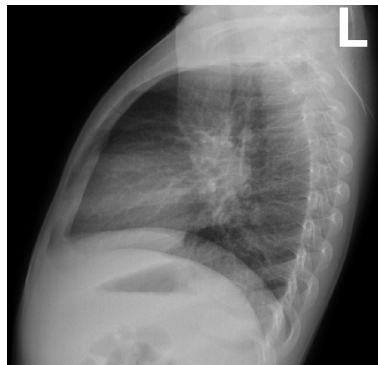
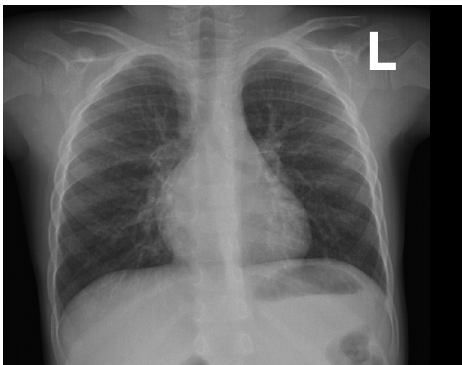
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4 year old brother

- Born in US, visited India > 2 yrs ago
- Completely asymptomatic
- PE completely normal
- TST negative 2-3 months ago

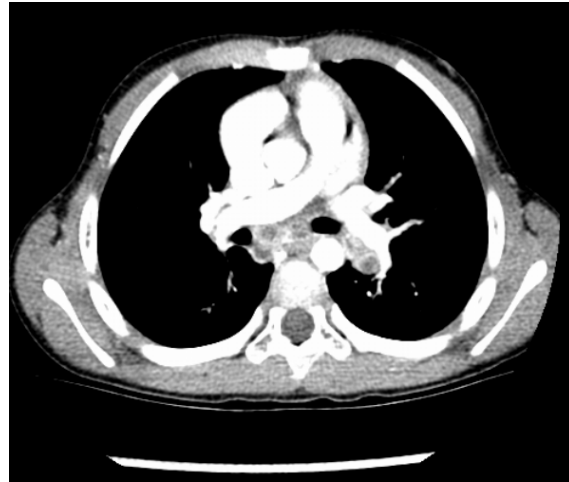
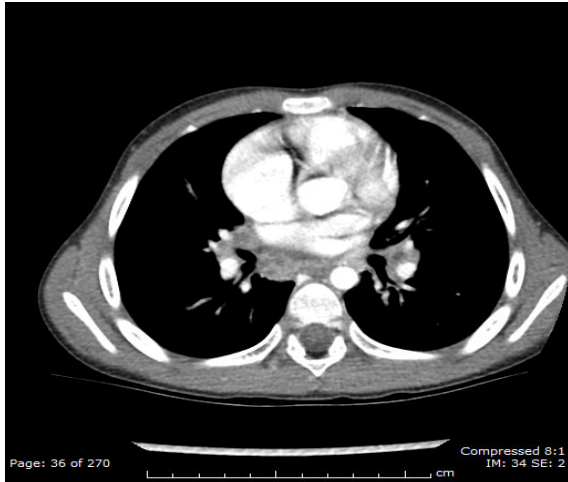
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4 year old



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4 year old



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Follow-up

Sister

- Started on 4 drugs next day
- 1 out of 4 sputum cxs positive
 - Pansensitive MTB
- Completed 6 mos of tx with DOT
- Did very well

Brother

- Started on 4 drugs next day
- Sputum cxs negative
- Completed 6 mos of tx with DOT
- Did very well

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Lessons learned

- Always ask about other siblings or contacts
- Always look for siblings
- Ask about other families living in house

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Jan 2020

- 16 month old contact to father with smear positive active PTB
- CXR normal
- TST 13 mm
- Treated with 9 months of INH
- Mother and 10 yo brother stayed negative

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July 2022

- Mother suspect PTB: + Tspot and abnormal CXR
- 16 mo old now 3 y/o....
- CXR normal, T-spot negative
- Questionable compliance
- No DOT (father took meds at different time)
- Brother now: T-spot positive, CXR negative
 - → Rifampin 4 mos

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Polling Question 1 : What would you do?

- A) Nothing because child got 9 months of INH
- B) Nothing because child is T-spot negative
- C) Start window prophylaxis
- D) I don't know

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We...

- Restarted INH (could not do 15-20 of Rifampin with capsules)
- Mother culture negative, clinical TB
- Will repeat Tspot
- Treat with Rifampin 4 months

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Lessons learned

- ALWAYS USE DOT!!
- Father became sputum positive again
- Mother/Brother tested too early (middle of pandemic, short staffed)
- From father or other source case?

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4/22/21:

- 87 y/o with AFB 1+ smear, RUL reticulonodular density on 3/16 → RIPE 3/17
- 8 mo old and 3 y/o contacts
- “no real contact with the source case”
- “family moved out months ago”

- TB clinic... real story:
- Lived in same house on different floors (used same kitchen and bathroom)
- Sometime coughing, but case “stayed to himself”
- Family moved out 2/25
- 4/3: Children CXR normal and TST/IGRA negative (5 weeks)
- TB clinic visit at 8 weeks – PE normal

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Polling Question 2:
What would you do?

- A) Not a real exposure so would do nothing
- B) Start window prophylaxis now
- B) Repeat testing in 2 weeks
- C) Repeat CXR today
- D) Repeat testing today

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Repeat testing 5/13 (11 weeks)

- Repeat testing done by PMD
- 3 y/o QFN negative
- 8 month old: TST read as 4 mm
- Repeated TST at DOH: 0 mm

- Source case: grew MAC not TB

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Lessons learned

- Get contacts in ASAP regardless of history
- Always get your own history
 - History always changes (length of cough, amount of exposure)
 - Source cases often downplay exposure
 - Parents often downplay exposure
- TST should be done by experienced providers

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4 y/o and 1 month old

- Contact to grandfather with LUL cavitory PTB
 - Cough for 2 weeks
- Smear negative at Pulmonologist (no documentation)
- 8/13: started on RIPE
- 8/17, 8/18, 8/19 at DOH: smear negative
- 1 month old moved out 1 week ago
- 4 y/o still lives in same household

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Started Window

- Started INH on infant
- Started RIF on 4 y/o

- Test negative at 8 weeks for 4 y/o
- Stop window?

- Grandfather's sputums:
 - 7/26 and 7/27: smear positive, culture positive
 - 8/17, 8/18, 8/19: smear negative, culture positive
 - Only 8/18 was induced
 - 10/3: smear negative, culture pending
 - Retested kids at 4 weeks (after treatment started for GF) + 10 weeks

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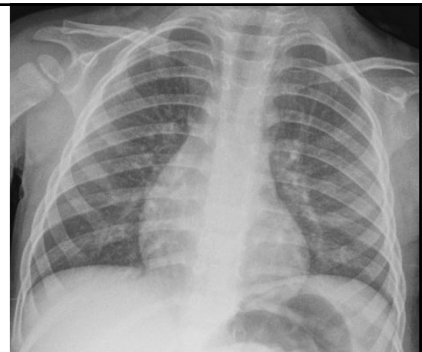
Lessons Learned

- Always get documentation
- Important how and where sputums obtained
 - Don't trust AFB negative sputums from hospitals
 - Home or clinic?
 - Induced or not?

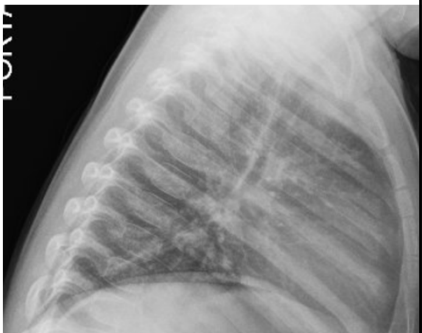
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Monday morning call to TB clinic

- 10/17: "I think I have TB"
- Mom with all classic symptoms
 - coughing since COVID in July
 - 4 previous rounds of TB treatment
- 9 month old and 3 y/o at home
 - 3 y/o has 103 fever, wheezing
- Mom: 4 + sputum, Genexpert +, Rifampin Resistant
- 10/21: TB clinic
 - PE normal
 - Both children CXR negative and TST/IGRA negative
 - Father and maternal grandparents all T-spot negative



10/17: 3 yo: Peribronchial thickening



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Polling Question 3: What Would You Do?

- A) Start INH since Rifampin is Resistant
- B) Start PZA and ethambutol
- C) Start nothing because everyone tested negative in the house
- D) Start nothing because need more information on mother's sensitivities

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MDR contacts

- MDDR results on mother:
 - INH, RIF, EMB resistant, PZA pending
 - Sensitive to Fluoroquinolones/injectables
- WHO guidelines for LTBI: Use Levofloxacin x 6 months “along with other TB medicines, such as EMB (or Ethionamide) if tolerated”
- Newer TB medications ?
 - No data for Bedaquiline in kids under 5 years
 - No data for Pretomanid in kids < 15 years
 - Data for Delamanid for >5 years and possibly (per WHO guidelines) 3-5 year olds (uncertain, how the capsules are absorbed if they need to be broken/crushed)
- New WHO operation handbook on TB (2022)
 - Preliminary dosing down to 3 kgs for both bedaquiline and Delamanid
 - No peds data for Pretomanid

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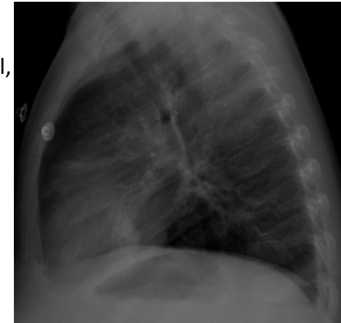
MDR contacts

11/4: TB clinic

- PE is normal, except URI symptoms
- Start Levo 20 mg/kg/day once daily (not 10 mg/kg/dose BID)
- 11/6-11/9: 3 y/o admitted with worsening cough, respiratory distress
 - ER: Solumedrol
 - QFN: positive



11/9: Peribronchial, Thickening; perihilar opacities



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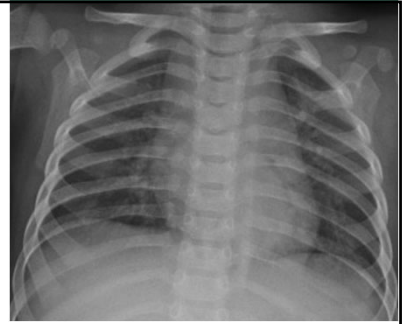
9/24/22

- Mother showed up in ER “worried about 3 year old’s fever because relative is being evaluated for possible TB”
- **MISSED OPPORTUNITY !!!**
- Lesson learned:
- Child with contact to anyone with possible TB → **ALERT ID/DOH!**

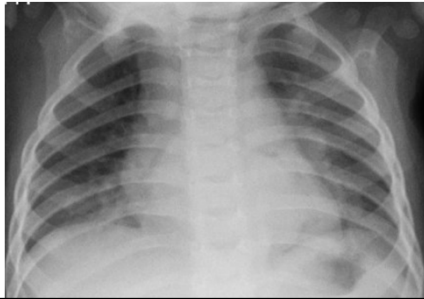
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8 month old

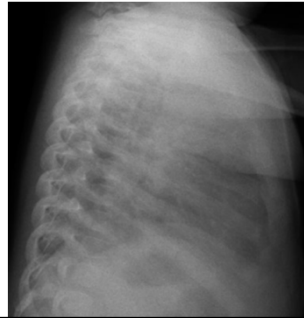
- Contact to father with pansensitive cavitory smear positive TB
- 3/3/21: 2 view CXR negative, QFN negative
- 4/2: ER for 104F, URI symptoms, decreased activity; CXR normal
- 4/7: admitted CXR perihilar opacities



4/2



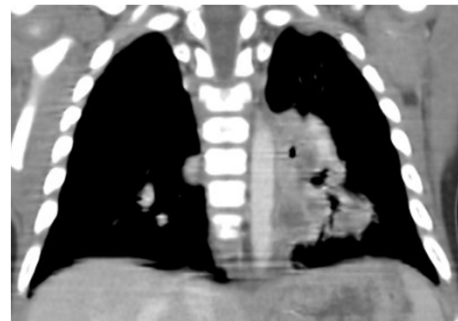
4/11



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8 month old

- 4/9-4/11: Gastric aspirates sent
- 4/15:



- CT necrotic mediastinal LNs, consolidation- started RIPE
- 4/22: home from hospital on RIPE
- 4/23: TB clinic- looking great

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8 month old

- 4/28: wheezing in morning, 100.4F, increased cough, CXR improved
- 4/30: higher fevers, readmitted



4/30



5/3



5/4

- Admitted for 1 month on high doses of steroids and slow taper

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Lessons learned

- Negative IGRA in < 2 year old does not rule out infection
- Window prophylaxis not given **MISSED OPPORTUNITY**
- Preventable disease
- Need to educate all pediatric providers
- Wheezing after start of treatment - think of bronchial obstruction

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Prevention of Tuberculosis in Children: Missed Opportunities

- Failure to find and appropriately manage adult source cases (Case finding)
- Delay in reporting the initial diagnosis of TB
- Contact investigation interview failure
- Delay in evaluation of exposed children
- Failure to completely evaluate exposed children
- **Failure to prescribe prophylaxis INH (WP)**
- Failure to maintain a contact under surveillance
- LTI diagnosed; treatment not prescribed
- Failure to complete treatment for LTI (Adherence)

Nolan RJ. AJPH 1986

Mehta J, Bentley S. Am J Prev Med 1992

Dr. McSherry

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Take home points

- Childhood TB is preventable with window prophylaxis
- Do appropriate testing by the right people
- 2 view CXRs needed in <5 y/o (review with Peds Radiologist)
- Get your own history
- Look for more siblings/contacts
- Look at quality of sputums
- Optimize compliance: DOT, help from pediatricians, school nurses
- Use TB clinic resources

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