

Pediatric Tuberculosis Transmission and Pathogenesis/ Testing and Evaluation of Child Contacts

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Disclosures

- I have no relevant financial conflicts of interest

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Agenda

Part I –

- Epidemiology
- Significance of pediatric TB
- Pathogenesis

Dr. Campbell – TB testing, TB infection

Part II –

- **Diagnostic challenges**
- TB infection therapy, special considerations
- TB disease therapy
- Pandemic challenges
- Role of telehealth

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Diagnostic Challenges

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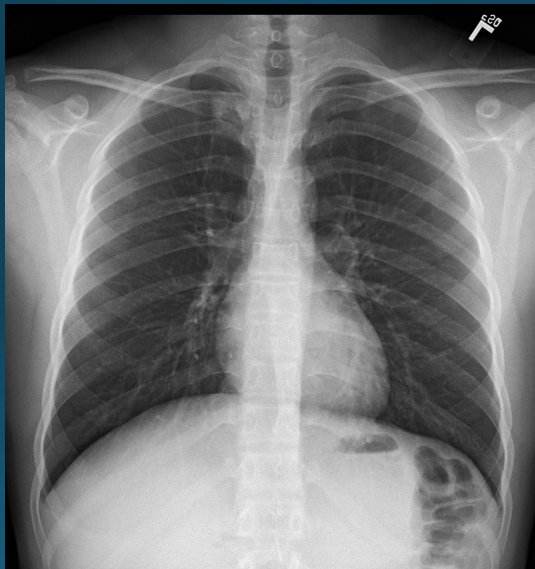
Imaging Pearls

- PA/lateral CXR
 - Children <5
 - Symptomatic
 - Household contact
 - Previously concerning portable or single-view
 - Any other concerns
- Low threshold for low-dose chest CT
 - Need contrast for **lymphadenopathy**
 - Better for subtle findings
 - Younger children without microbiology data – imaging may be only concrete information to follow

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17y0



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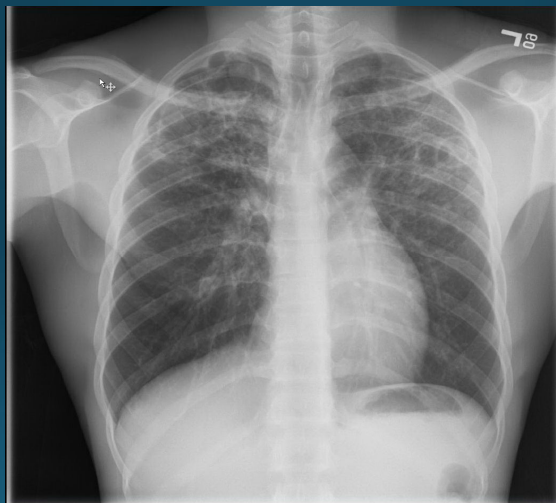
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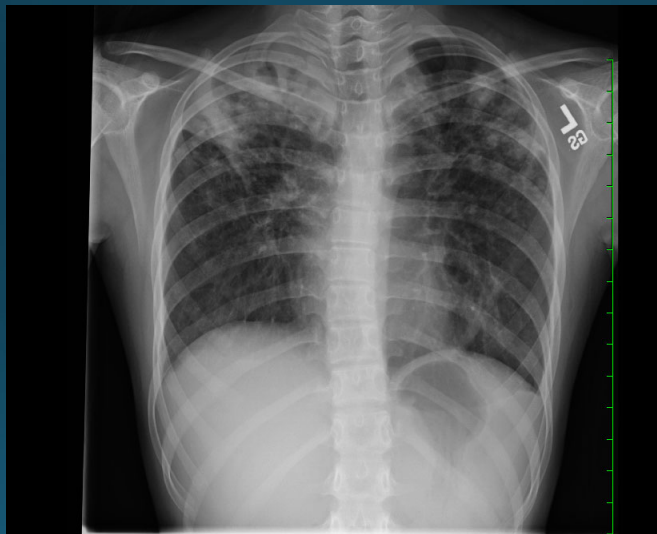
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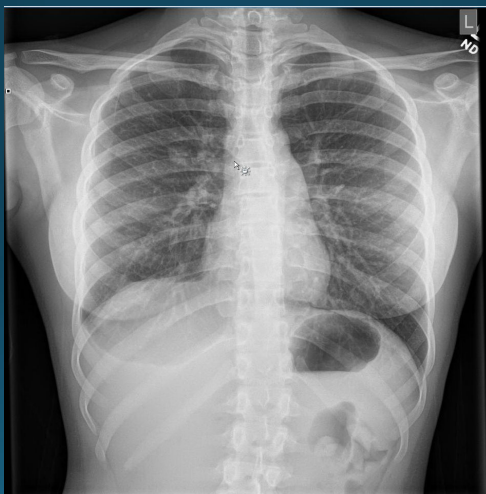
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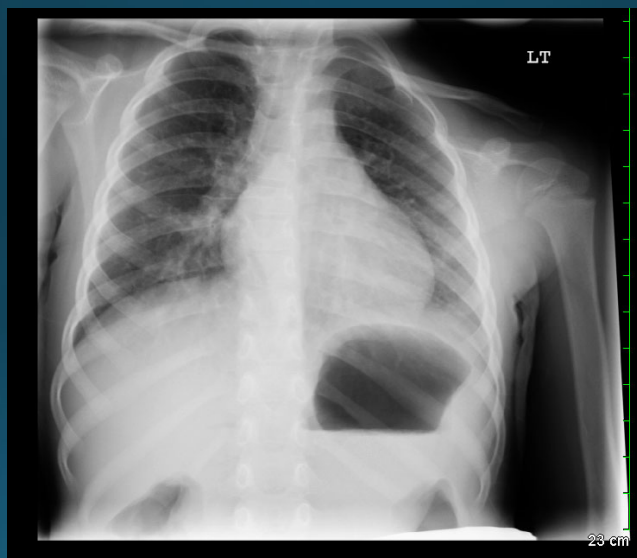
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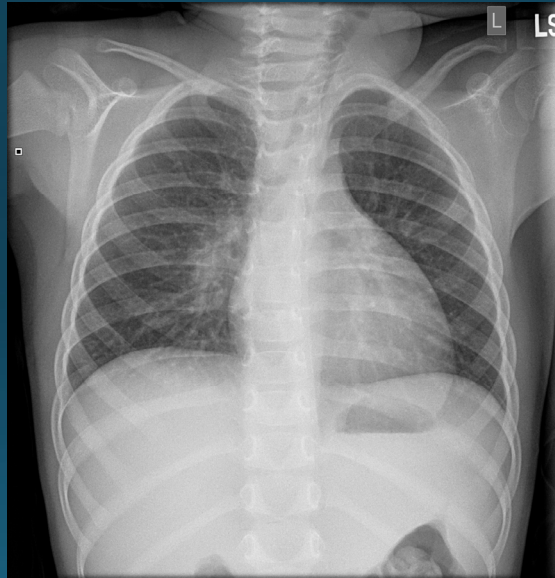
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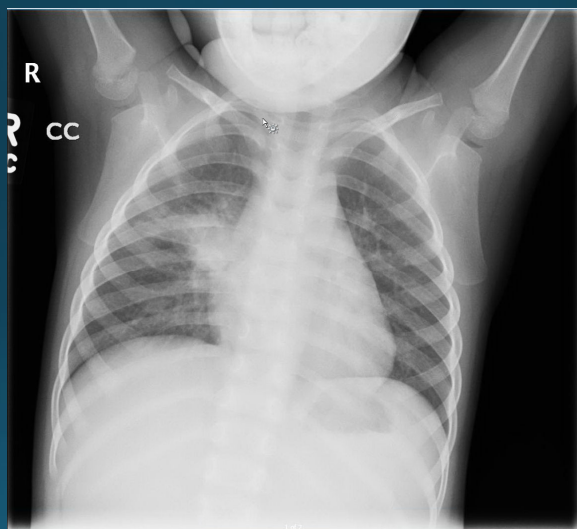
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33mo



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21mo



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13mo



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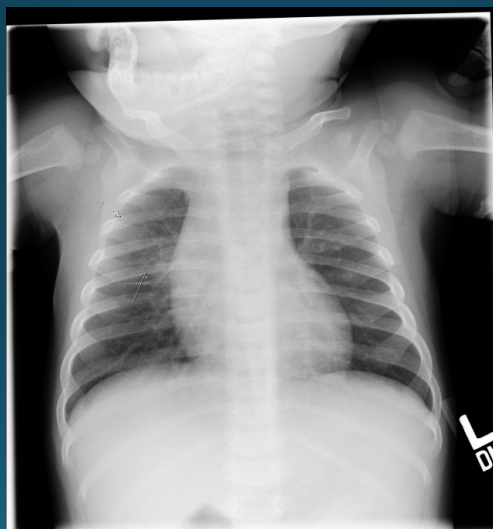
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6mo



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Confirmed TB Infection

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Summary of TB Infection Recommendations

Name	Medication(s)	Details
9H	Isoniazid QD x 9 months	May need B6
4R	Rifampin QD x 4 months	Counseling re: other Rx
3HP	Isoniazid/Rifapentine QW x 3 months (12 weeks)	Weekly DOT, higher doses

- Isoniazid has historically been first-line medication choice in children
- Rifampin increasingly used given equivalent efficacy
- Ideal list for pediatric TB infection regimens:
 - 3HP
 - 4R
 - 9H
- Alternative regimens are recommended by AAP/CDC for patients who are not able to tolerate above regimens

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Treatment of TB Infection

- 12 weeks of isoniazid (15 mg/kg, max. 900mg) + rifapentine
 - 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 maximum
- Recommended as option for ≥5 years (“most experts”)
 - Pros: Done in 12 weeks, no home Rx
 - Cons: Need to adhere to weekly visits w/in 24-hour window, increased side effects
 - Role for telemedicine? Need to make sure medications delivered, etc.
- Children 2-5 years of age
 - Increasing CDC safety and efficacy data to support use (“some experts”)
- Children <2 years of age
 - Not recommended - lack of safety and pharmacokinetic data

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Treatment of TB Infection

- Rifampin 15-20 mg/kg (max. 600 mg) PO daily for 4 months
 - 4-month course ~ 9-month course of INH (Cruz & Starke, IJTL 2014)
 - INH not tolerated
 - Index patient isolate INH-resistant
 - Counseling re: tears/urine, increased/decreased metabolism of other medications (esp. OCP)
 - Nitrosamine contamination*
 - Capsules (150mg and 300mg) – can be opened and mixed with small amount of (non-dairy) food/liquid – juice, honey (if >1), jam/jelly, non-dairy pudding, chocolate syrup (great for masking bitter tastes)
 - Suspension – can stain teeth (try straw if old enough), needs to be refilled every 3 weeks
 - Night-time administration to minimize nausea

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Nitrosamines

- In 2020, FDA notified providers about discovery of excess **nitrosamine impurities** in rifampin and rifapentine
 - Common compounds found in many foods and beverages...with carcinogenic potential
 - Risk is believed to be extremely low, requiring long-term exposure
- In order to maintain the supply of these drugs for treatment of TB disease, FDA raised the maximum acceptable limits for these contaminants in these drugs
 - 31x for rifampin, 200x for rifapentine*
- National TB Controllers Association (NTCA) and CDC are in dialog with FDA and manufacturers

* 10/2020

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Nitrosamines and Rifamycins: Recommendations (MDPH*)

- **Treatment of latent TB infection:**
 - **Currently receiving rifampin or rifapentine:** continue this treatment, although a change to isoniazid (INH) is acceptable *if preferred by the patient/family*
 - **Newly diagnosed LTBI:** Until more information becomes available, consider alternative treatment strategies *in discussion with the patient/family*
- **Treatment of TB disease:**
 - Continue use of rifampin *if acceptable to the patient*, as the risk of not taking rifampin likely outweighs any potential risk from nitrosamine impurities

* 12/2020

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Treatment of TB Infection

- INH 10-15 (20) mg/kg (max. 300 mg) PO daily for 270 doses
 - Efficacy approaches 100%
 - Adherence low (<75%)
 - Alternative: Twice-weekly directly observed (DOT) INH 20-40 mg/kg (max. 900 mg) PO for 72 doses
- Counseling re: avoidance of acetaminophen and alcohol, side effects/toxicity (mostly minor)
- Pyridoxine supplementation for breastfeeding infants, malnutrition, (picky toddlers), pregnancy
- Tablets (100mg and 300mg) can be crushed and mixed with small amount of breast milk, formula, milk, food (similar suggestions to RIF but can be dairy)
- Suspension contains sorbitol and can cause diarrhea
- Night-time administration to minimize nausea

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Treatment of TB Infection

- Monitoring while on isoniazid (or rifampin) monotherapy:
 - Isolate sensitivities from contact (if available)
 - Monthly assessment for clinical evidence of hepatotoxicity malaise, loss of appetite/weight, nausea, vomiting, abdominal pain, jaundice
 - No baseline/routine LFTs unless:
 - Concurrent liver disease
 - Concurrent use of hepatotoxic medications
 - Clinical evidence of hepatotoxicity
 - Pregnancy or first 12 weeks postpartum

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Special Considerations

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“Window Prophylaxis”

- Children who are household/close contacts of known/suspected TB cases
 - Symptom analysis, PE, TST (or IGRA)
 - PLUS CXR (2 views) regardless of TST/IGRA result
- If also ≤ 4 years of age AND
 - asymptomatic/NL PE/ negative TST ($< 5\text{mm}$) OR negative IGRA/NL CXR
 - START isoniazid (or rifampin)
 - 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

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“Window Prophylaxis”

- TST/IGRA repeated 8-10 weeks after last known/suspected contact with index case
 - If TST/IGRA (-), discontinue INH [or RIF]
 - If TST/IGRA (+), re-evaluate child and treat accordingly
 - Exceptions: neonates
 - TST likely not reliable until 4-6 months
 - Could continue RIF x 4 full months or INH x full 9 months, if concerned enough

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TB Disease –
Back to Diagnostic Challenges

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TB Disease

- Important to diagnose, monitor, and treat in consultation with pediatric subspecialist with TB expertise (ID or pulmonology)

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Mycobacteriologic Diagnosis of TB

- Adults: 70-90% have a sputum that is (+) for *M. tuberculosis*
- Children:
 - Paucibacillary disease
 - Sputum difficult/impossible to obtain from younger children (but beneficial with respect to contagiousness)
 - Gastric aspirates in children with pulmonary TB
 - 30-40 % sensitive in children
 - 60-70% sensitive in infants
 - Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates

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Pediatric TB: Diagnostic Challenges

- Asymptomatic or non-specific symptoms
 - 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
 - Low threshold for LP, ophthalmologic evaluation, other imaging
- Physical examination may be normal

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Pediatric TB: Diagnostic Challenges

- TST or IGRA negative early in disease
- CXR challenges (remember quiz)
- Index 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

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Pediatric TB: Other Considerations

- Need for admission (gastric aspirates) vs. home isolation (induced sputum in clinic setting)
- Availability of negative pressure rooms
- Need for family screening (esp. re: visitation)
- HIV testing

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TB Disease Treatment

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Treatment of TB Disease in Children & Adolescents

- If INH resistance rate >4% or if other risk for resistance:
 - Isoniazid (10 mg/kg/day, range 10-20, max. 300)
 - Rifampin (15 mg/kg/day, range 10-20, max. 600)
 - Pyrazinamide (20-30 mg/kg/day)
 - Ethambutol (15-25 mg/kg/day)
 - Pyridoxine
- Medication considerations
 - Toxicity monitoring: clinical side effects, LFTs, uric acid (PZA), ophthalmologic exams (if patient too young for color/vision screening)
 - Formulations: INH crushed tablets, RIF open capsules
- Monthly MD visits

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Treatment of TB in Children & Adolescents

- Directly observed therapy (DOT)
 - 5 days/week + self-administered on weekends
 - BOH RN in house vs. school RN – remember to think about holidays/vacations
- Typical course (pan-susceptible isolate):
 - RIF/INH/PZA/ETH + B6 as initial regimen
 - Discontinue ETH once susceptibility data available
 - Discontinue PZA after 2 months (60 doses)
 - Continue RIF/INH + B6 to complete 6-month course
- Follow laboratory and radiographic data
- Sensitivities very important, if none available, decisions regarding therapy made on combination of clinical and radiographic improvement
- Newer and shorter regimens (e.g., moxifloxacin-based x 4 months) for older children

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Newer TB disease treatment regimens

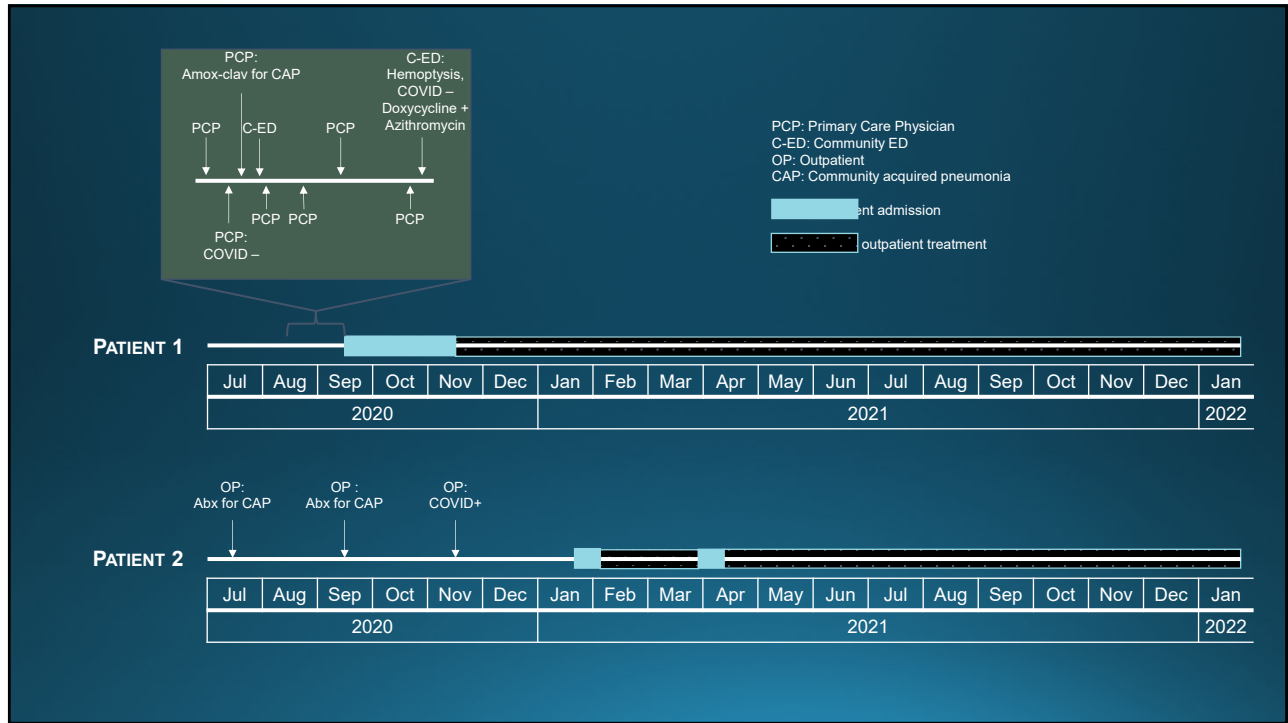
- Newer and shorter regimens for older children
 - 4 months:
 - 8 weeks x rifapentine/isoniazid/pyrazinamide/moxifloxacin
 - + 9 weeks x rifapentine/isoniazid/moxifloxacin
 - ≥ 12 yo, drug-susceptible tuberculosis
 - Non-inferior to traditional regimen

Dorman et al. N Engl J Med 2021; 384:1705-1718. DOI:
10.1056/NEJMoa2033400

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Challenges During the Pandemic

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Telehealth

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Telehealth

- MA DPH clinic experience during COVID-19 pandemic –
 - Deferral of new patients with negative CXR with advocacy for younger patients
 - Phone or car visits for LTBI and some TB disease patients (e.g., COVID-positive parents, stable toxicity monitoring allowing increased interval)
 - Advocacy for pediatric considerations (siblings, need to have parent regardless, etc.)
 - Fewer LTBI referrals – kids are traveling less, school nurses are more focused on COVID
 - Delayed diagnosis of active TB...?

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Telehealth

- MGH Pediatric ID experience –
 - VV for follow-up patients since December 2016
 - Ramped up during pandemic (MD participation, patient volume, new consultations as well)
 - TB infection initial evaluations and follow-up – some all virtual
 - older children seen by PCP
 - not part of contact investigation
 - no need for laboratory monitoring
 - no infants/toddlers needing weight-based dose adjustments
 - Increased use of asynchronous eConsults to guide PCPs in testing/interpretation
- MGH Pediatric Hospital Medicine
 - VV for complicated post-discharge coordination since June 2018
 - Some visits with pharmacist to observe medication administration
- Many potential roles in TB care

Madhavan, VL and El Saleeby, CM. So You Want to Start an Infectious Diseases Telemedicine Service? *JPIDS*. April 29 2020. <https://doi.org/10.1093/jpids/piaa032>
Madhavan, VL et al. Ensuring Quality Transitions of Care from the Hospital to the Home Setting by Utilizing Virtual Visits: A Novel Pilot Study. Meeting Abstract. *Pediatrics*. July 2020. <https://doi.org/10.1542/peds.146.3.MeetingAbstract.234-a>

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Take-home points

- Pediatric TB case rates highest in infants and post-pubertal adolescents
- Children are usually:
 - Infected by adult/adolescent household contacts
 - Not infectious (contagious)
- Tuberculosis infection or disease in a child is a **sentinel public health event**
- TB control in US:
 - Targeted testing – TST vs. IGRA (latter preferred down to age 2)
 - Contact investigations
 - Evaluation of TB-exposed child - TST/IGRA, CXR, “window prophylaxis”
 - Importance of TBI identification and treatment (changing Rx recommendations)
- **Always have a high index of suspicion for TB in children – diagnostic challenges**
- Medication challenges in children and importance of DOT

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Thank you – Questions?
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