Using the SHINE Trial Data and Other Updates from the AAP

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New Directions in TB
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Jeffrey R. Starke, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

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Disclosures

I have no conflicts of interest to declare.

I will not discuss off-label uses of diagnostic procedures and medications [lack of FDA-approval 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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DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS*

- genetic loci for resistance on chromosome, unlinked
- resistance of drugs independent
- frequency of mutations at loci is known
- more likely to have mutations when mycobacterial population is larger : infection vs. disease

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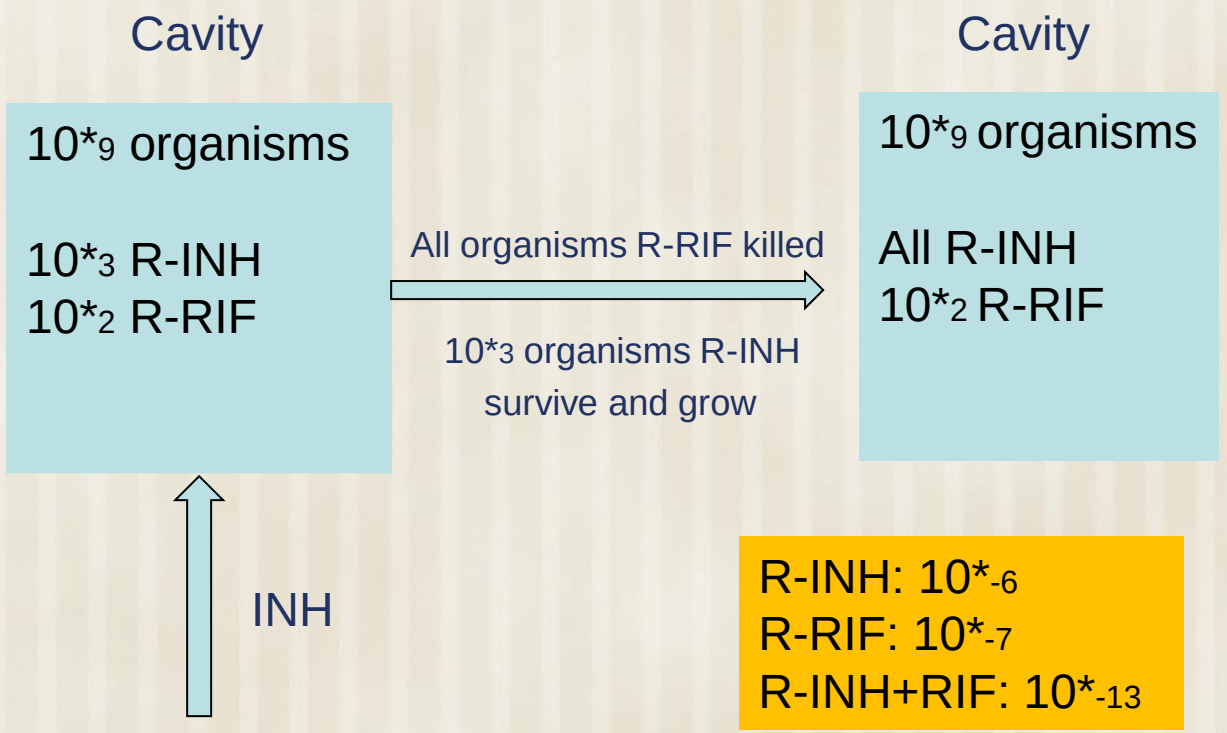
Preventing Drug Resistance in TB



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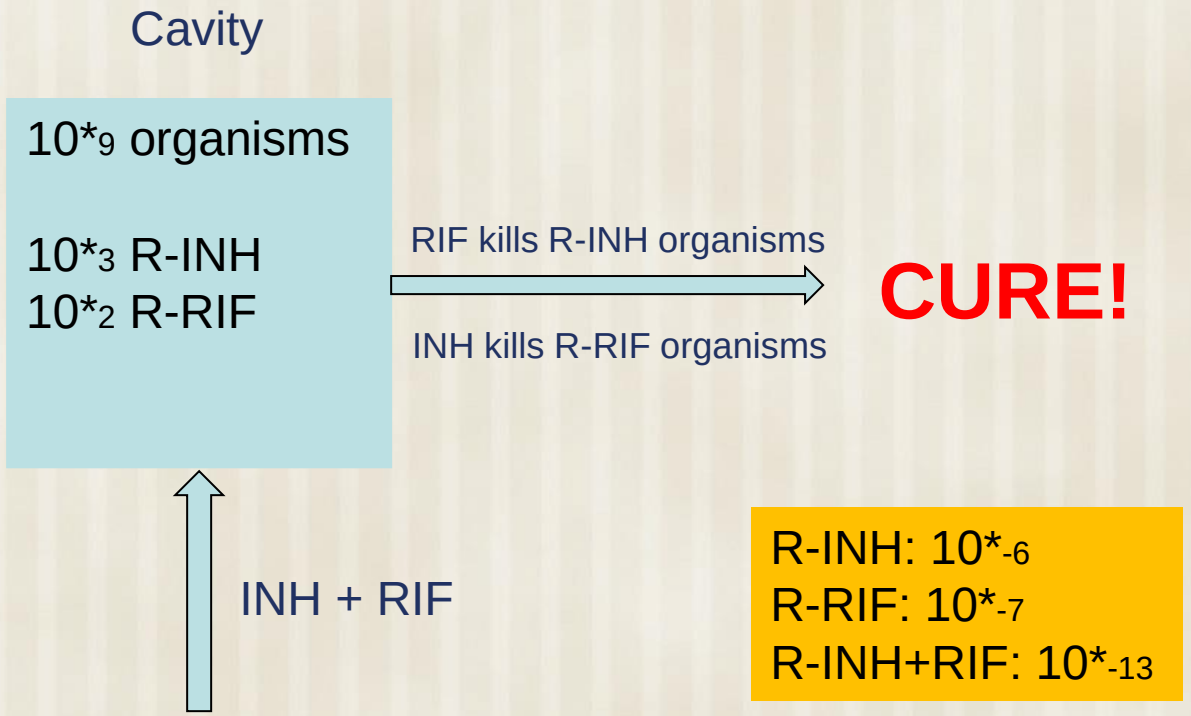

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So, Where Does Childhood TB Disease Fit Into All This

- The burden of organisms is likely much lower than in adults, but this has never been measured – is it closer to TB disease in adults, or closer to TB infection?
- And when does TB infection turn into TB disease:

  Symptoms? Chest X-ray findings?

  Burden of organisms?
- Much of what we see on the chest X-ray – and likely some of the symptoms - comes from the immunological response to the organism, not the burden of organisms

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Roles of Specific TB Drugs in Regimens

Isoniazid

- Bactericidal
- Prevents emergence of resistance to other drugs

Rifampin

- Bactericidal
- Prevents emergence of resistance to other drugs

Ethambutol

- Bacteriostatic at lower doses
- Prevents emergence of resistance to other drugs

Pyrazinamide

- Allows for shorter durations of therapy

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What Do Anti-Tuberculosis Drugs Do?

They kill TB germs – that's it!

They do NOT:

- Reduce inflammation
- Shrink lymph nodes
- Absorb pleural fluid
- Close cavities

****Remember: many children successfully treated for pulmonary TB with a 6-month regimen have radiographic abnormalities at the end of therapy. We would expect the same with the 4-month regimen.**

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The SHINE Trial

4 month regimen for non-severe DS-TB Disease

Turkova et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med 2022;386:911-922.

- phase 3 randomized-controlled open label trial of 4 versus 6 months for children with symptomatic, non-severe, presumed drug-susceptible, smear-negative TB disease
- 1,204 children <16 years [median age: 3.5 yrs] were randomized to 2HRZE/2HR vs. 2HRZE/4HR
- All drugs were dosed at the standard WHO pre-qualified pediatric fixed-dose combination formulations
- 11% of subjects were living with HIV
- *****Decision to choose a regimen made at diagnosis, NOT at the 4-month mark – patients in the 6-month control group got the full course regardless of clinical/radiographic evaluation at 4 months of treatment**

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The SHINE Trial Inclusion Criteria

- **Main inclusion criteria:**
  - Age 0-16 years, weight ≥3kg
  - No known drug resistance
  - Clinical decision to treat TB
  - Symptomatic but non-severe TB
  - Smear-negative on respiratory samples
    - GeneXpert positive allowed
  - Not treated for TB in previous 2 years
  - Known HIV status (positive or negative)

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Definition of Non-Severe TB

Non-severe TB

- **Respiratory TB**
  - **confined to < one lobe***
  - **no cavities**
  - **no significant airway obstruction**
  - no complicated pleural effusion
  - no miliary TB
- **Peripheral lymph node TB**

*Expansile pneumonia (involving ≥ 1lobe) was considered as severe TB

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Caveats

- No standardized case definition – encouraged use of NIH criteria
- ~50% of the subjects were contacts to known cases
- TST/IGRA results not part of the case definition
- 3 blinded reviewers [retrospective]: 85% of cases likely TB; non-TB evenly distributed between the 2 regimens
- Positive AFB smear of the sputum was exclusionary but not a positive Xpert result
- Used pediatric fixed dose combination dispersible medications – not available in the U.S.
- Ethambutol use at the discretion of the local physician
- No DOT – all self-supervised therapy with pill counts at each visit

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The SHINE Trial

4 month regimen for non-severe DS-TB Disease

- **The primary finding was that four months of treatment was non-inferior to six months in respect to unfavorable outcomes (failure, recurrence, death, or loss to follow up)**
- *Non-inferiority was consistent across all key analyses (including age groups, HIV status, type of TB, microbiologic status, geographic region, and adherence)*
- Adverse events ≥ Grade 3 were uncommon in both arms.
- The 2022 WHO Child and Adolescent Treatment Guideline has incorporated these trial results with the recommendation that children <16 with non-severe TB disease should be treated with 4 months of therapy.

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Outcomes among children with ‘severe TB’ as adjudicated by central radiology expert review

- All children enrolled in the trial had non severe TB as judged by local site clinicians
- Overall, 71 children were adjudicated to have severe TB at the Central CXR review
- Of these, 16 (23%) were microbiologically confirmed (GeneXpert or Culture)
- 94% had favourable outcomes
  - ITT population in the whole trial – 93% had favourable outcomes

	4 Months N=34	6 Months N=37
Total number of unfavourable outcomes	**2**	**2**
Suspected TB	1	1
Death	1*	1**
	*Solid tumour Week 28	**Pneumonia Week 67

Question

If the patient did not fit the SHINE criteria for 4-month therapy **at diagnosis**, but symptoms and radiographic findings have resolved at 4 months of therapy, can we stop the treatment?

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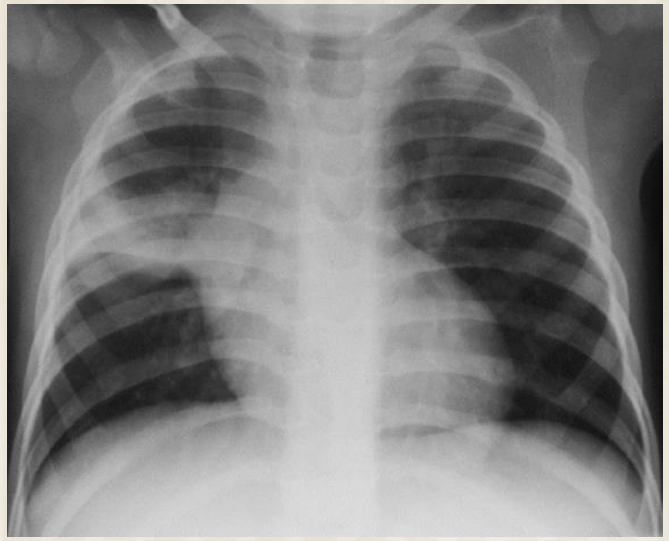
Clinical Scenario

Eligible for 4-month therapy?

- 3 year old child who is a household contact of a case with AFB sputum smear positive, Xpert-negative pulmonary TB
- Child is asymptomatic
- CXR shows right middle lobe infiltrate with possible hilar nodes



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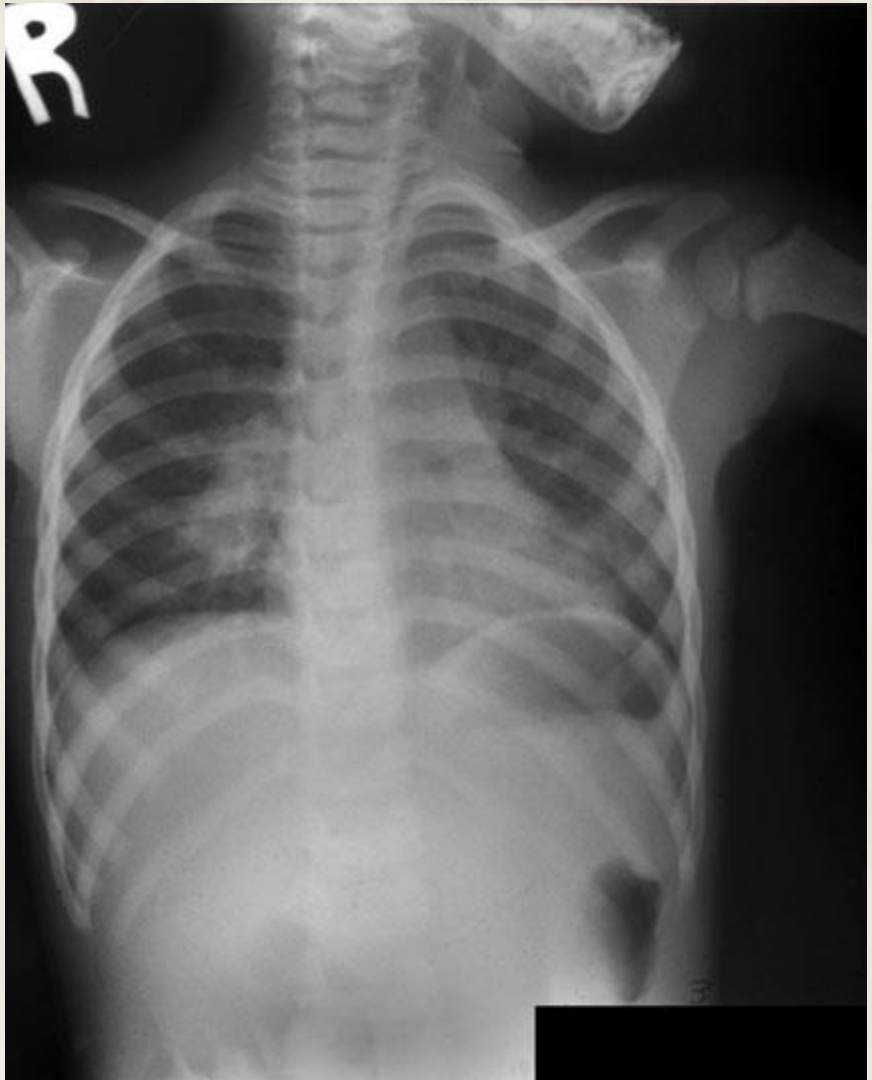
Let’s Look At Some Chest X-rays

Eligible for 4-month therapy?



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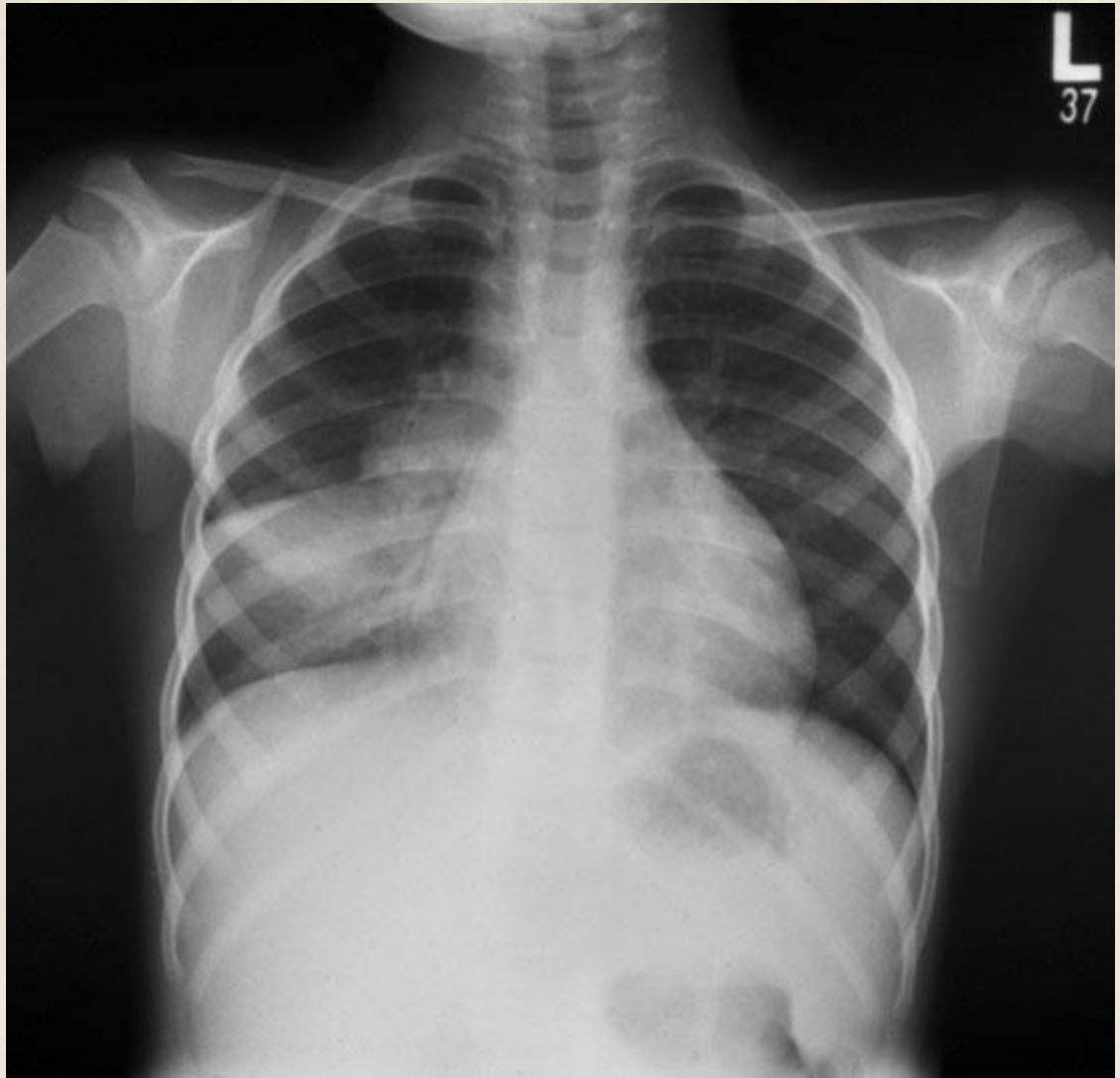

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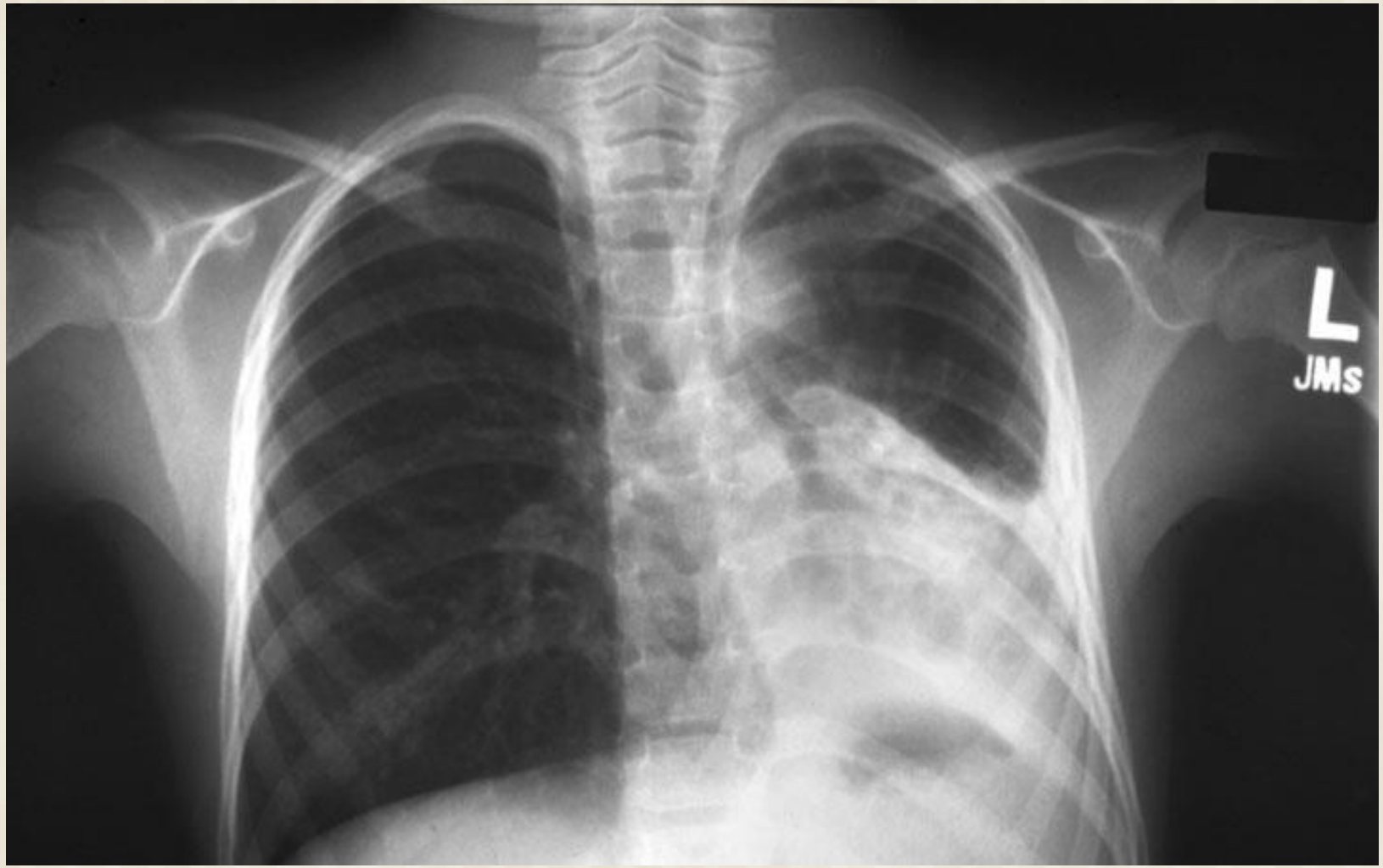

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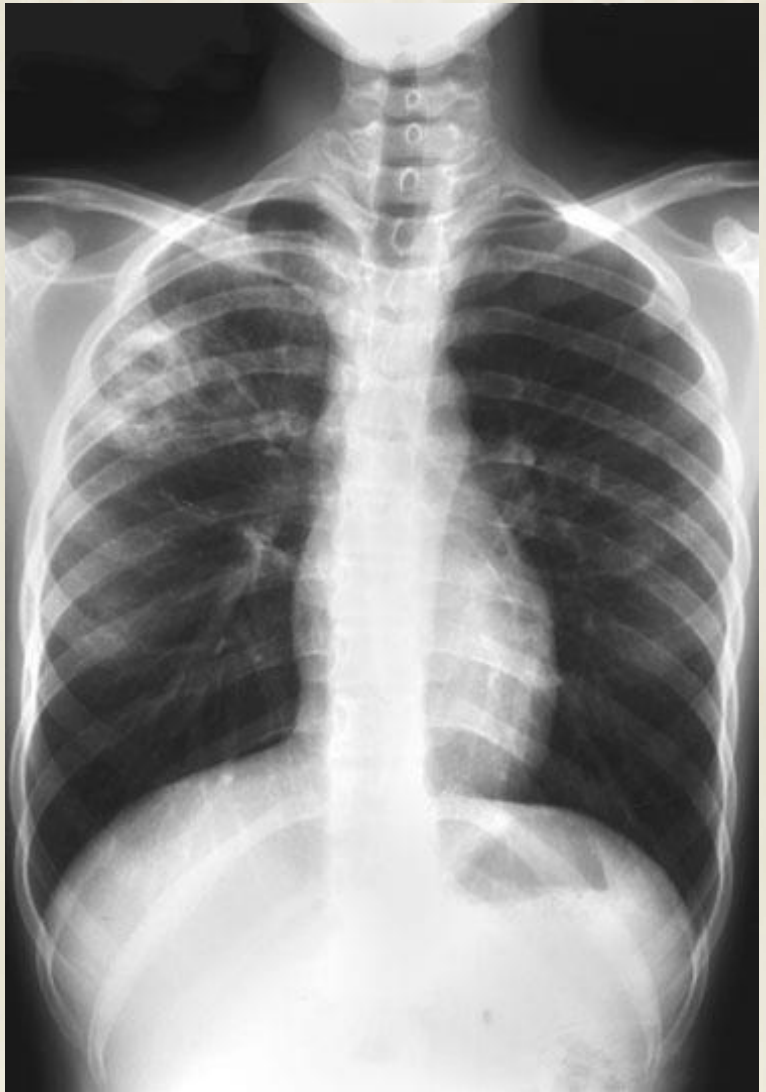

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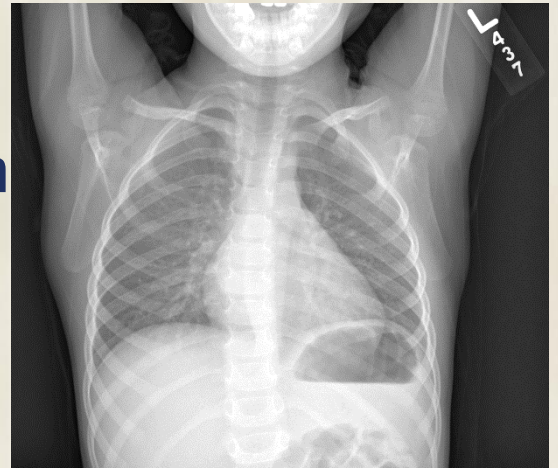
Clinical Scenario

Eligible for 4-month therapy?

- 2 year old whose father has left upper lobe cavity, AFB positive sputum smear, Xpert Positive for Mtb, negative for RIF resistance
- Child has had cough for ~ 2 weeks, fever by palpation, has lost 1.5 pounds
- QFT: 1.86/2.43
- Has a 2.5 cm fixed mass – likely

lymph node – in the right cervical chain near the supraclavicular area



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Unresolved Issues for the 4-Month Regimen

- What assessment should be done at the 4-month mark? Chest X-ray?
- How much radiographic improvement is required to feel comfortable stopping therapy?
- How do we deal with breaks in therapy due to drug intolerance or diminished adherence?
- The trial allowed for a positive Xpert but not a positive sputum smear. What about a positive culture?
- What is “significant” airway obstruction? And does it really matter [immunologic reaction vs. burden of organisms]?

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