Clinical Presentation & Diagnosis of Tuberculosis Disease

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CITC Clinical Intensive

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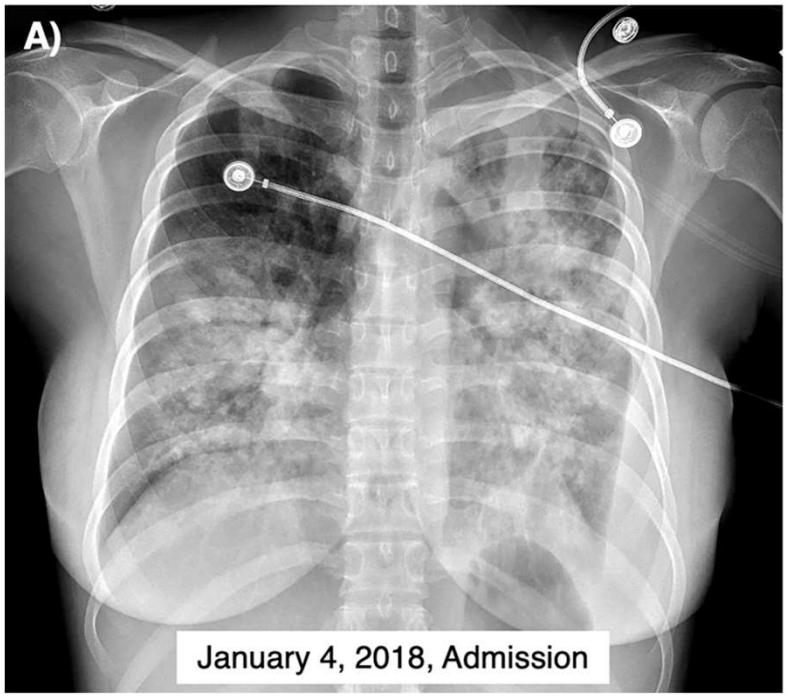
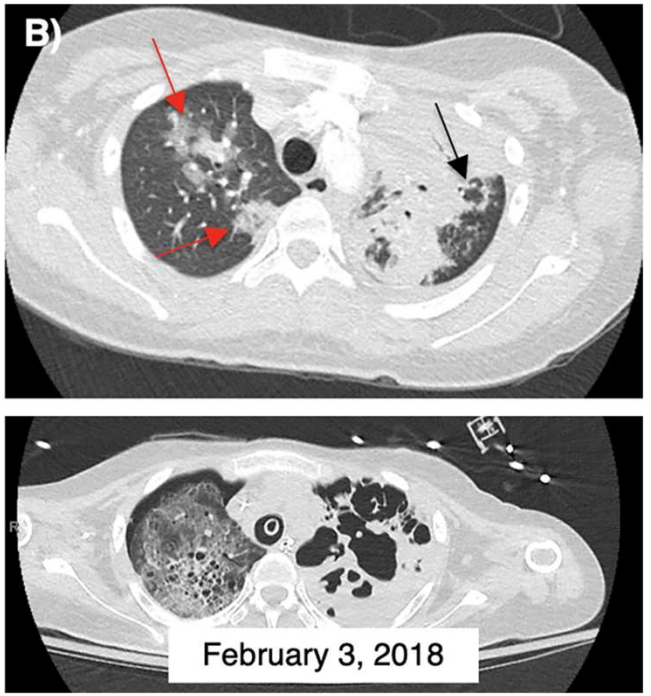
Disclosures

- No relevant relationships or interests in commercial entities to disclose
- Financial ties: WA DOH only
- Off-label uses: NAAT on non-respiratory specimens

Cautionary Tale

"A 19-year-old [3-wk post-partum] woman originally from the Republic of the Marshall Islands presented with diffuse pneumonia and acute hypoxemic respiratory failure. She dies one month into her hospitalization, but the diagnosis of pulmonary tuberculosis (TB) was not made until one day before her demise. A contact investigation screened a total of 155 persons with 36 (23%) found to have latent TB infection and seven (4.5%) with active pulmonary TB."





Source: Rockstrom M, et al. J Clin Tuberc 2023 (https://doi.org/10.1016/j.jctube.2023.100351).

Missed TB Diagnoses California, 2005-2011

Table 2. Counts and Prevalence of Potential Misdiagnoses for Various Potential Misdiagnosis Window[a]

Potential Misdiagnosis Window	TB Cases With Previous Visit and Respiratory Diagnosis	TB Cases With Previous Visit and No Respiratory Diagnosis	Potential Misdiagnosis Prevalence
5–30	513	261	15.9%
5–60	714	426	22.2%
5–90	826	528	25.7%
5–120	880	609	27.3%
5–180	953	741	29.6%
5–270	1027	871	31.9%
5–360	1078	963	33.5%

Abbreviations: TB,tuberculosis.

[a] Proportion of TB patients (of 3220 patients in the final sample) having a previous visit with a respiratory diagnosis occurring in a given potential-misdiagnosis window.

About ¼ of cases might have been diagnosed earlier when seen in the preceding 3 months

Miller A, et al. Open Forum ID 2015. DOI: 10.1093/ofid/ofv171

Types of Delay

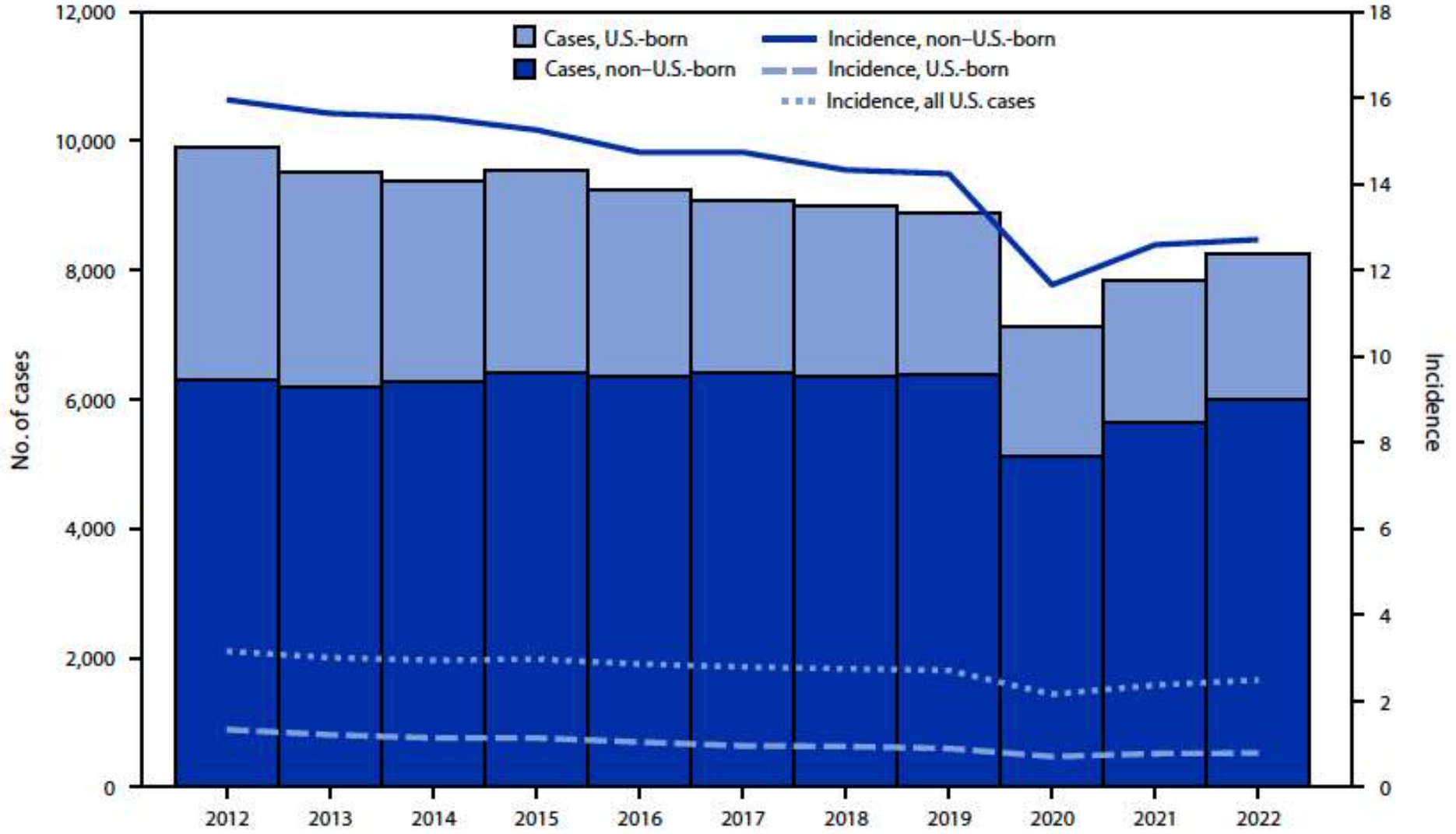
- Individual
- Healthcare provider
- Healthcare system

Consequences of Delay

- Sicker patients
- More lung damage
- Longer infectious period
- More health care exposures
- More community exposures

System Impacts: COVID-19

FIGURE. Tuberculosis disease cases* and incidence,† by patient U.S. birth origin status§,¶ — National Tuberculosis Surveillance System, United States, 2012–2022

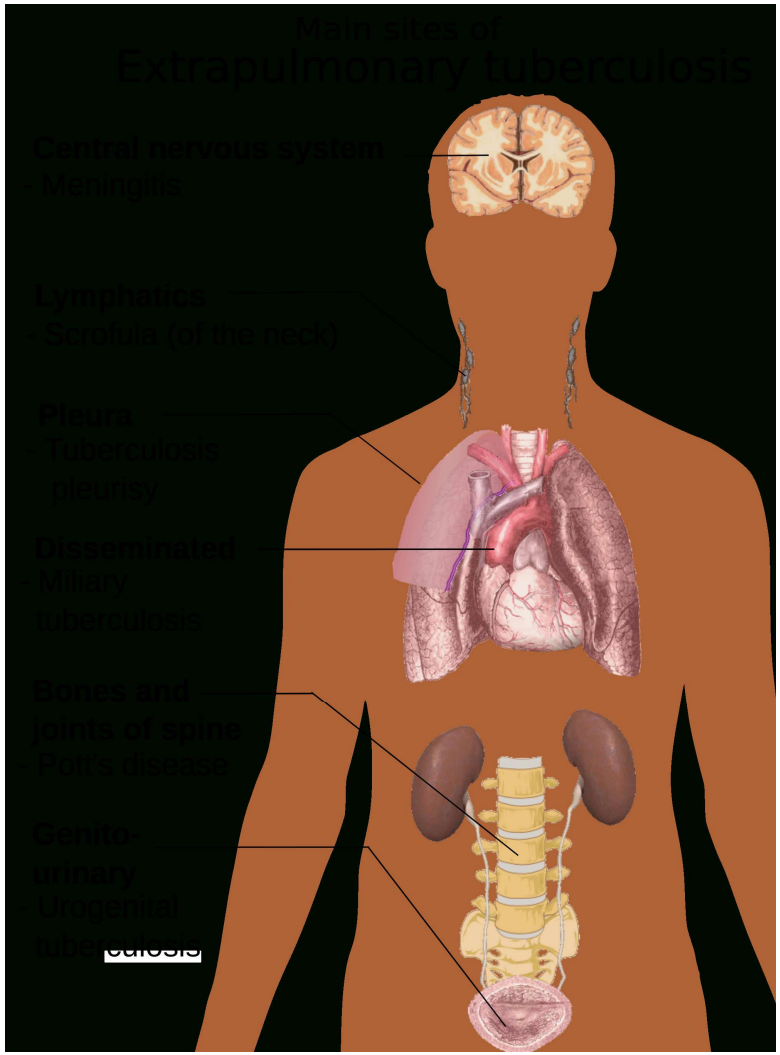


Source: CDC. MMWR 2023.

Learning Objectives

- Recognize symptoms and findings suggestive of active TB.
- Conduct a comprehensive medical evaluation for tuberculosis to assess for disease when appropriate.
- Apply CDC's national guidelines on diagnosis of tuberculosis to aid medical and public health decision making.

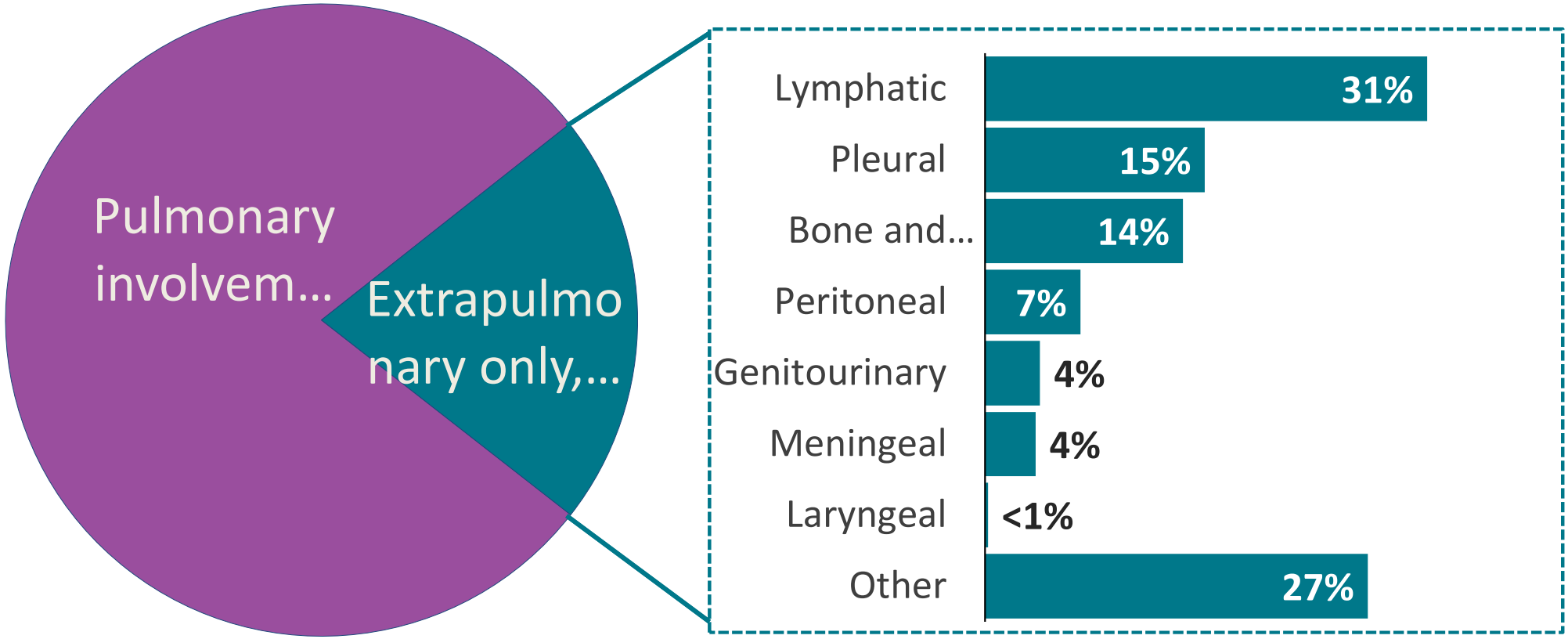
Sites of Involvement



- Lungs
- Lymph Nodes
- Pleura
- Peritoneum
- Bones
- Brain
- Liver/Spleen
- Urinary tract
- Genitals
- Eyes
- Skin

Source: http://anatomyid.com/diagrams-for-tuberculosis/diagrams-for-tuberculosis-fileextrapulmonary-tuberculosis-symptoms-svg-wikimedia-commons/ (accessed 06 May 2018).

Percentage of TB Cases by Site of Disease,* United States, 2021

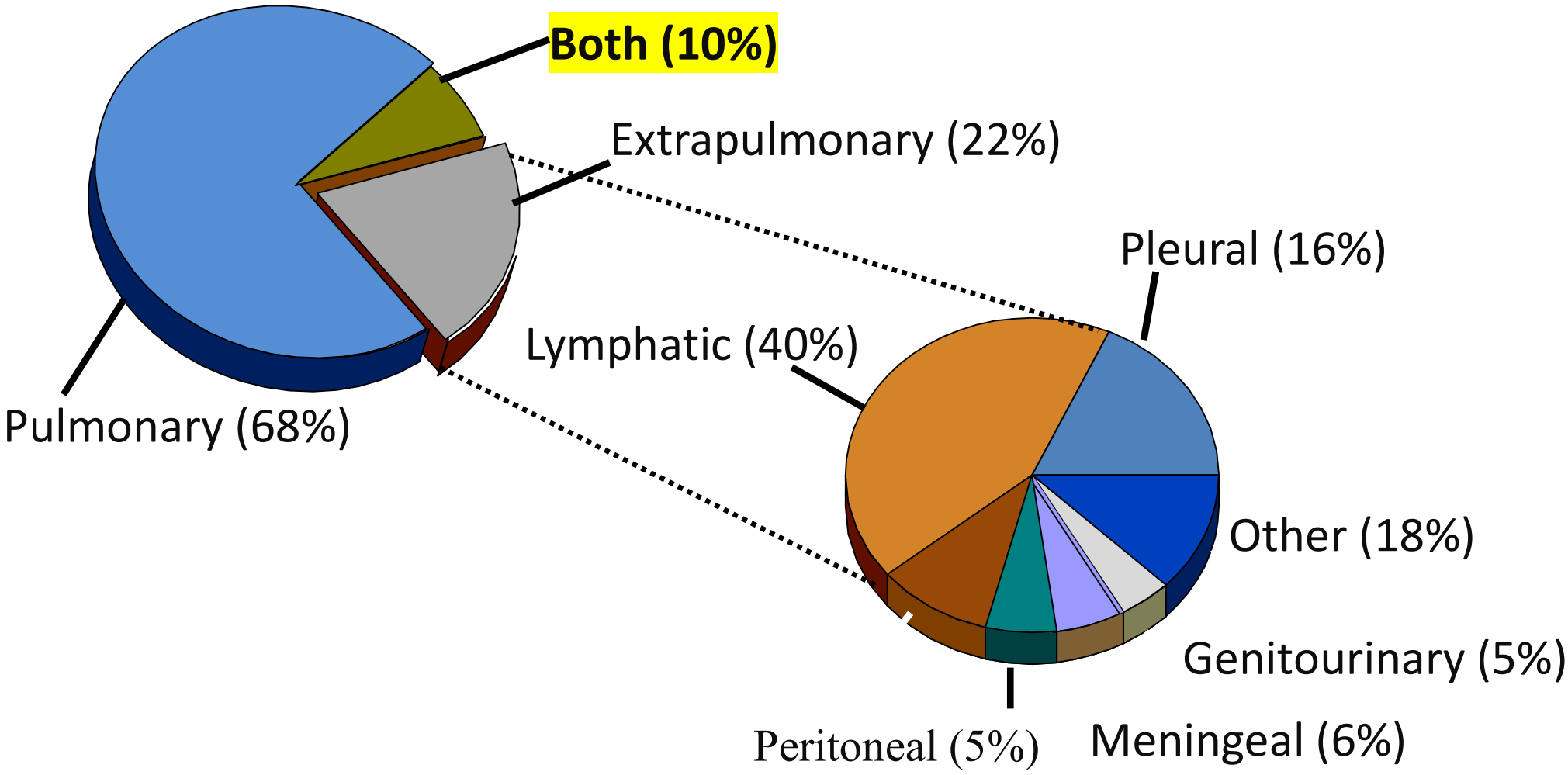


*Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.
†Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

Source: CDC, 2021.

Clinical Presentation: Site of Disease

CDC Reported TB Cases by Form of Disease United States, 2015



Diagnostic Elements

- Clinical syndrome
- Epidemiologic risk
- Physical exam findings
- Imaging
- Specimen collection
- Accessory testing (HIV, TST/IGRA, CMP, CBC/DIFF, viral hepatitis serologies)
- Results-->medical decision making

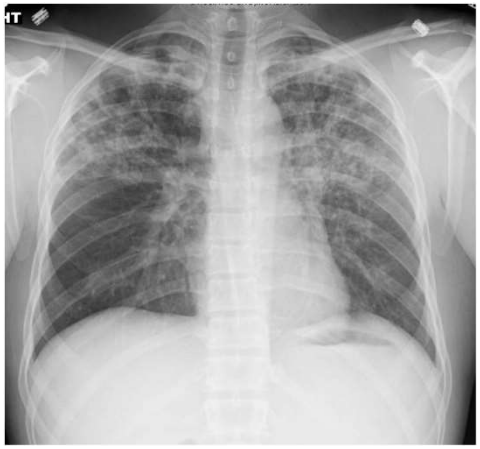
Clinical Evaluation

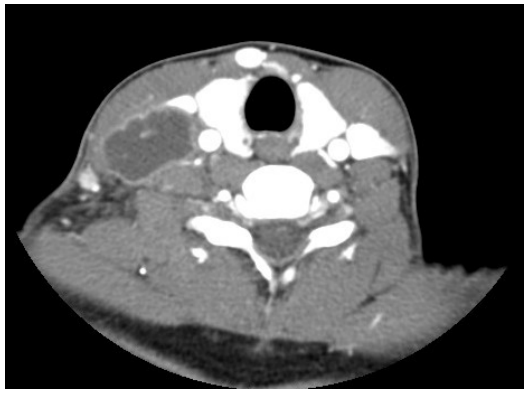
- History
  - Prior TB diagnosis/treatment
  - Epidemiologic risk
  - Predisposing medical conditions/therapies
- Exam
  - General, temperature, weight/BMI
  - Lymphadenopathy
  - Chest auscultation abnormalities
  - Abdominal distension or tenderness
  - Spine tenderness or deformity
  - Neurologic abnormalities

Differential Diagnosis

- Community acquired pneumonia
- Malignancy
- Septic emboli
- Lung abscess
- Non-TB mycobacteria
- Fungal infection (cocci, crypto, histo, blasto)
- Parasite (e.g., paragonimiasis)
- Sarcoidosis
- Rheumatologic disease (e.g., Wegener's, RA)
- Other systemic infections (e.g., brucellosis, Q-fever, melioidosis, relapsing fever, etc.)

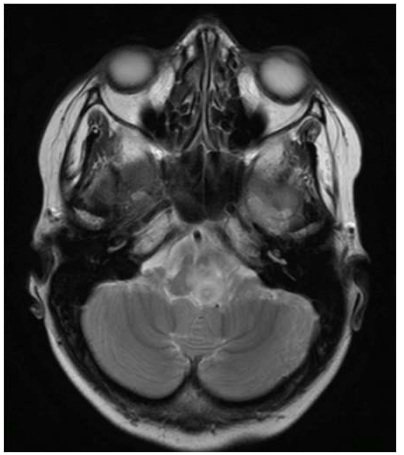
CXR



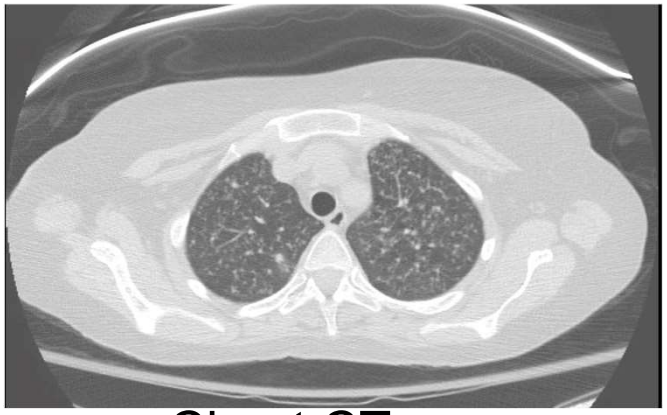


Neck CT

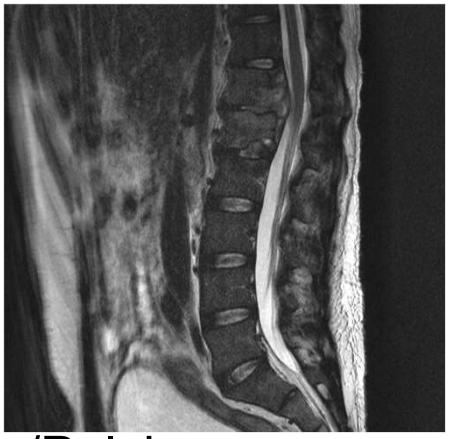
MRI brain



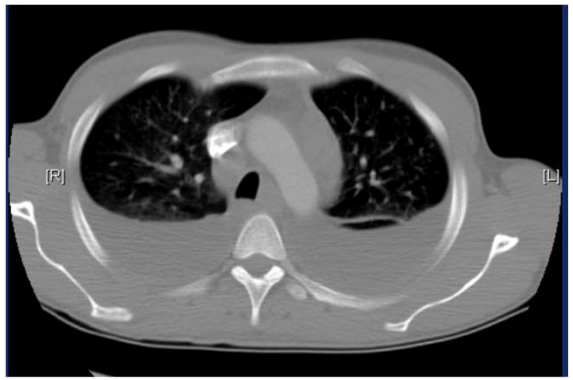
Imaging

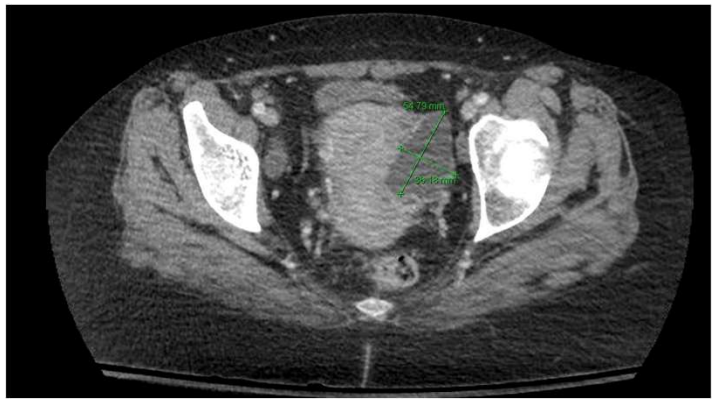


Chest CT

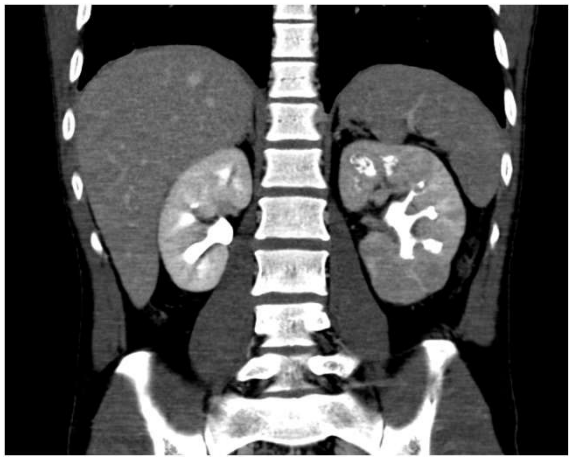


MRI spine





CT Abdomen/Pelvis



Plus ultrasound for aspiration of LNs and effusions

General Patterns in Presentation of TB

Primary/immunosuppressed

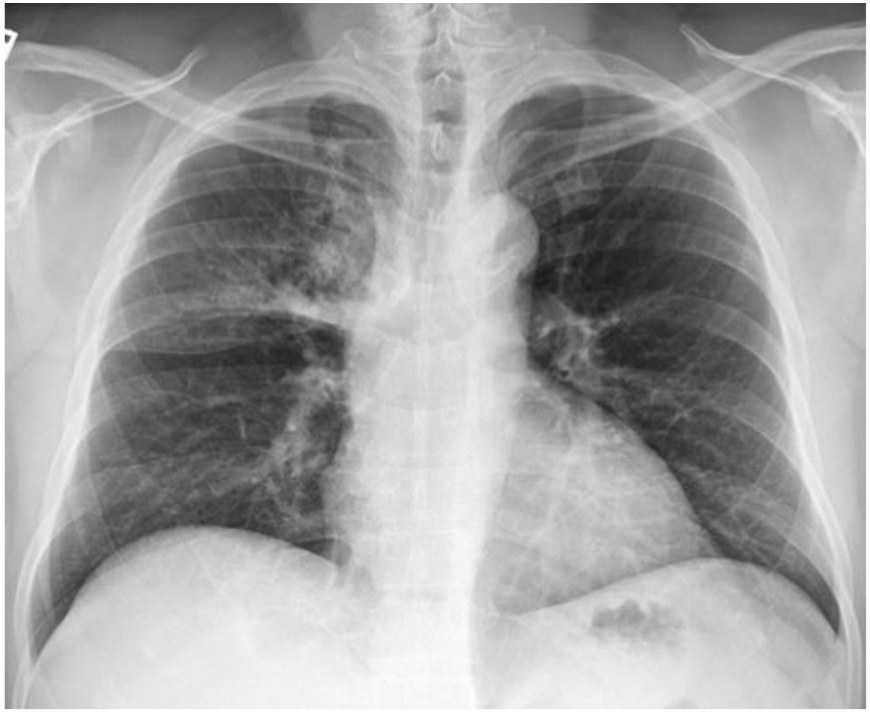
- Adenopathy
- Effusions
- Dissemination
- Extrapulmonary sites
- Smear-negative more common
- More IRIS

Reactivation/adult

- Pulmonary
- Reactivation type
- Cavitation
- Less extrapulmonary
- Smear positive more common
- Less IRIS

Case A

- 34 y/o Filipino male
- Cough, fever, sweats x 2 weeks

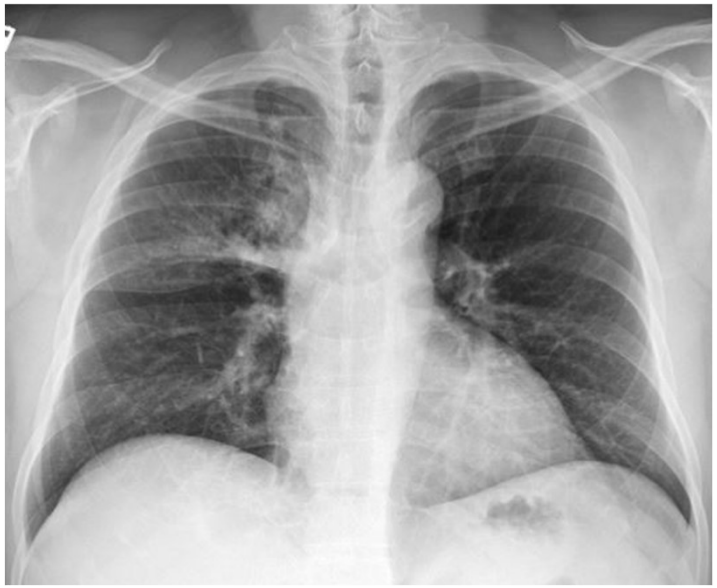


Interactive Question 1

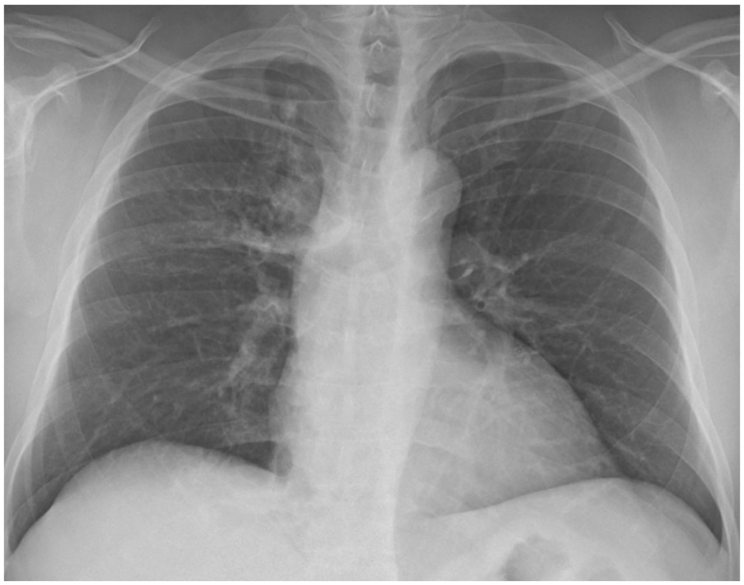
What would you do next?

a) Start HRZE
b) Isolate
c) Collect sputum x3 for AFB smear/culture
d) Submit for TB PCR x2
e) Treat with broad spectrum antibiotics and follow clinically and radiographically
f) B, C, and D

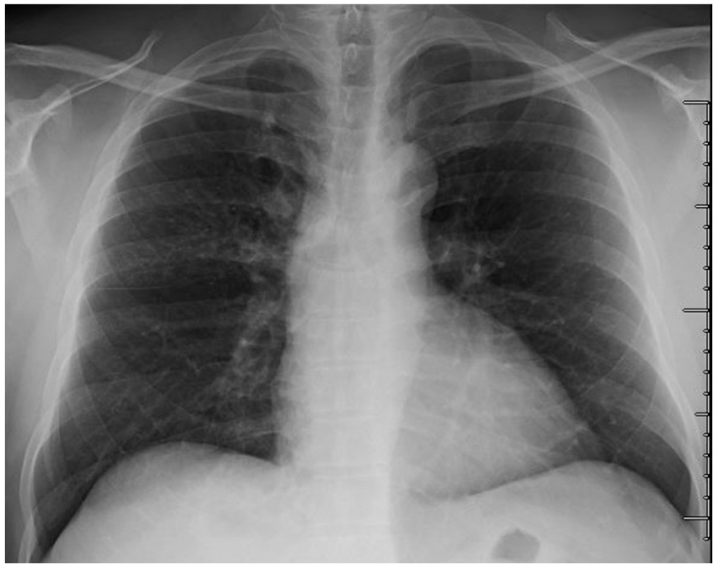
FQN Delays TB Diagnosis



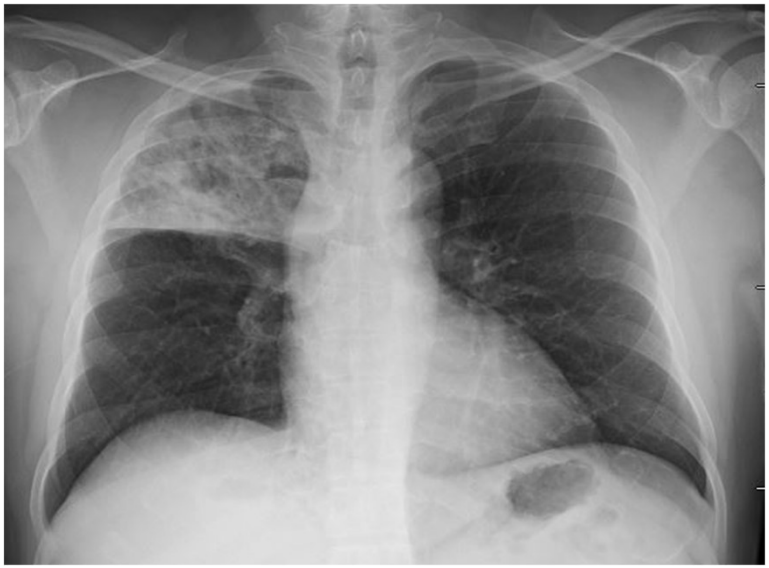
t=0; azithromycin



t=3wks, moxifloxacin



t= 6wks; all better!



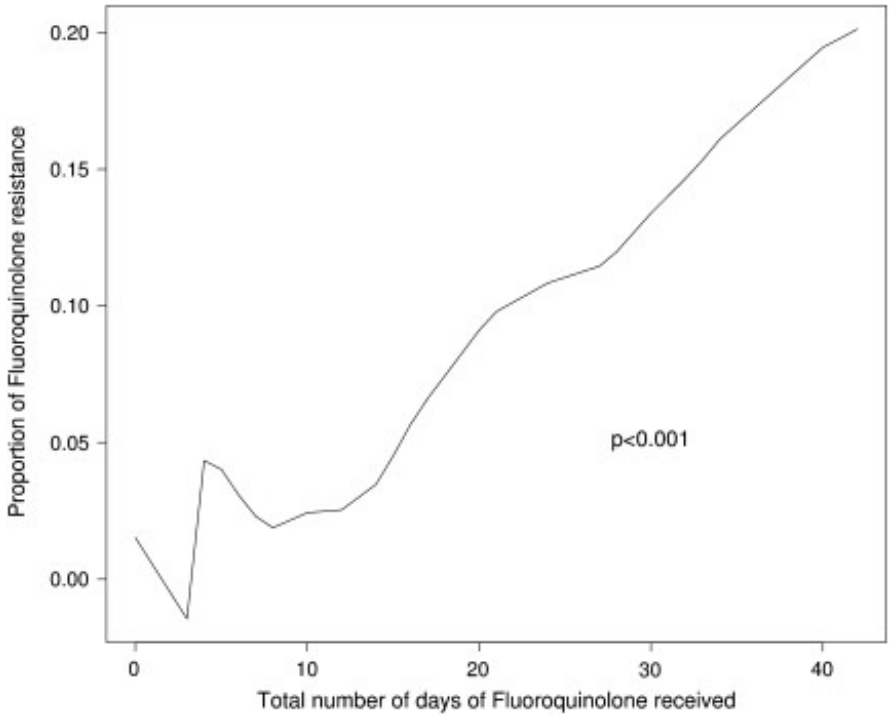
T=24wks

Caution in Empiric Fluoroquinolone Use

- Diagnostic Delays
  - Fluoroquinolones add 12.9 days to time-to-diagnosis.
  - Impact greater for AFB smear-negative cases

Hogan CA. Impact of fluoroquinolone treatment on delay of tuberculosis diagnosis: A systematic review and meta-analysis. J Clin TB & Other Myco; 2016. http://dx.doi.org/10.1016/j.jctube.2016.12.001

- Resistance



- Recent prior FQN use in 10% of sensitive but 30% of resistant cases
- OR ~10 for >10 days use
- Devasia, et al. Fluoroquinolone Resistance in
- Mycobacterium tuberculosis

Devasia RA, et al. FQN Resistance: The Effect of Duration and Timing of Fluoroquinolone Exposure. AJRCCM 2009;180:365-370.

Specimen Collection

Airway

- Spontaneous sputum x 3
- Induced sputum (at least 2)
- Endotracheal aspirate
- BAL

Other

- Gastric aspirate
- Trans-bronchial bx
- Pleural fluid
- Pleural biopsy
- LN/abscess FNA
- LN excisional biopsy
- CT-guided needle biopsy
- Fluids
  - Pleura/peritoneum/pericardium
  - CSF
  - Joint
- Other tissues (peritoneum, gut, endometrium, etc.)

Collection of Respiratory Specimens

- Sputum Expectoration:
  - 3 specimens (at least 8 hours apart)
  - 1 spot specimen (induce prn)
  - 2 consecutive first-morning specimens
- Induction (if unable to raise specimen)
- Bronchoscopy
- Post-bronchoscopy sputum
- Gastric Aspiration

ATS/IDSA/CDC 2017 Dx Guidelines: sputum→induction→bronchoscopy

Bronchoscopy Indications

- Unable to obtain specimen via induction or gastric aspirate
- Sputum smear/PCR negative but clinical suspicion of TB still high
- Sputum smear negative and MDR is a high concern
- Specimen needed for testing to address suspected non-TB conditions

Post-Bronchoscopy Sputum

- 57 sputum smear-negative or non-productive[1]
  - 33% AFB smear-positive PBS
  - 7% PBS sole culture-positive specimen
- 56 culture-confirmed cases with negative sputum AFB smears or non-productive[2]
  - AFB smear sensitivity:
    - BAL 57%
    - PBS 77%
    - BAL + PBS 84%

ATS/IDSA/CDC 2017 Dx Guidelines
Routinely collect post-bronch sputum

[1]*George PM, et al. Respir Med 2011;105:1726.*
[2]*Malekmohammad M, et. al. J Scand Infect Dis 2012;44:369.*

Specimen Testing

Mycobacteriology

- Acid-fast bacillus stain & culture
- TB nucleic acid amplification x 1-2
- *Unfixed* tissue specimens for PCR and culture!!

Other (but TB-focused)

- Cytology/histopathology
- Cell count and differential
- Protein, glucose, LDH
- Adenosine deaminase
- Interferon-gamma release assay (e.g., QuantiFERON, T-Spot)

ATS/IDSA/CDC 2017 Dx Guidelines

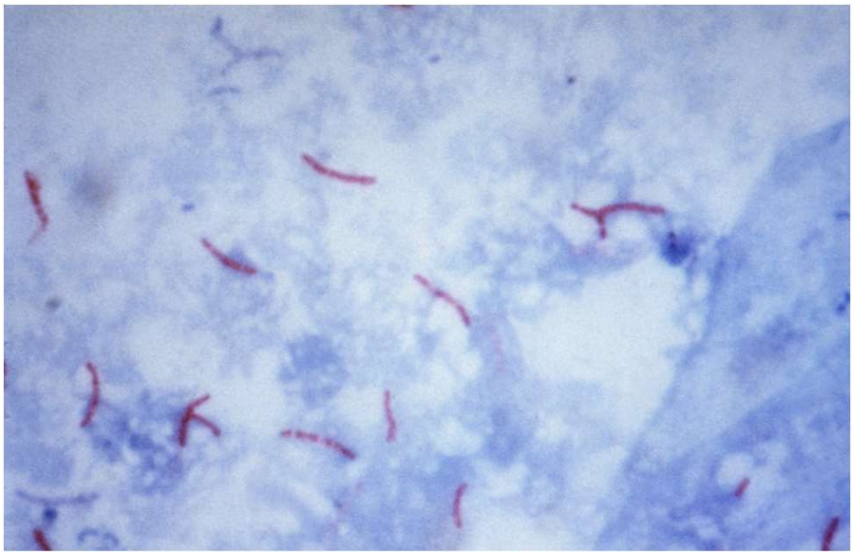
Mycobacteriologic Examinations for TB

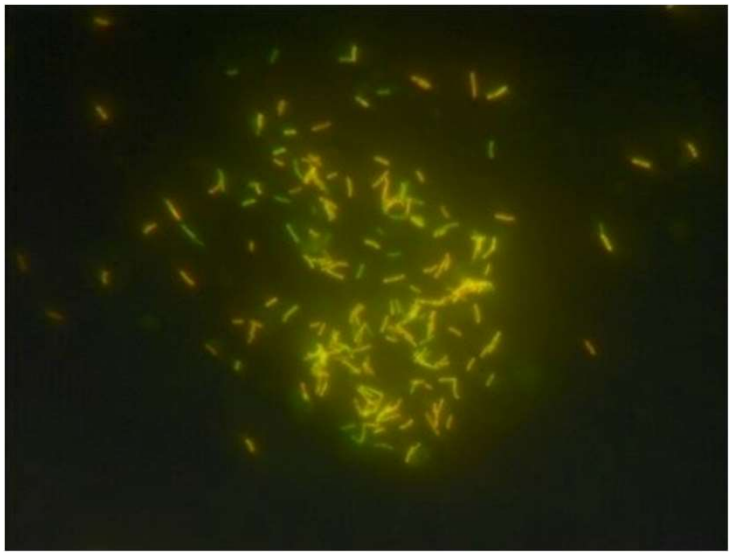
Test	Time Required
I. Nucleic acid amplification test, detection (NAAT-TB)	1 d
II. Nucleic acid amplification test, resistance markers (NAAT-R)	1–2 d
III. Acid-fast bacilli microscopy	1 d
IV. Growth detection Liquid Solid	Up to 6–8 wk (average 10–14 d) (average 3–4 wk)
V. Identification of Mycobacterium tuberculosis complex by DNA probe or HPLC	1 d[a]
VI. First-line drug susceptibility testing (liquid medium)	1 to 2 wk[a]
VII. Second-line and novel compound drug susceptibility testing	
i. Liquid (broth-based) medium	1 to 2 wk[a]
ii. Solid (agar- or egg-based) medium	3 to 4 wk[a]

Abbreviation: HPLC, high-performance liquid chromatography.[a]After detection of growth.

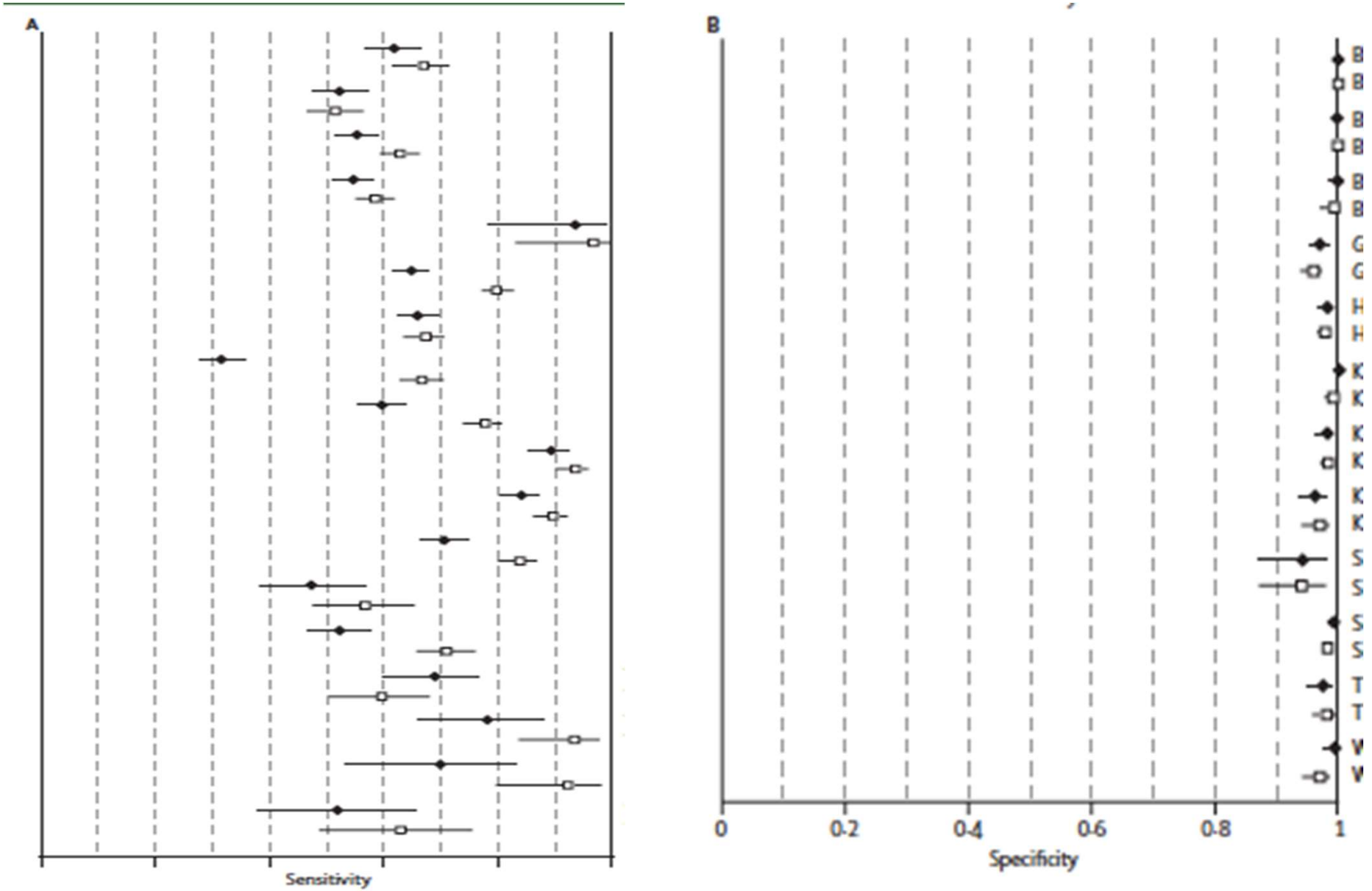
Source: IDSA-ATS-CDC TB Diagnosis Guidelines, Clin Infect Dis 2017.

Acid Fast Staining





AFB Smear Performance



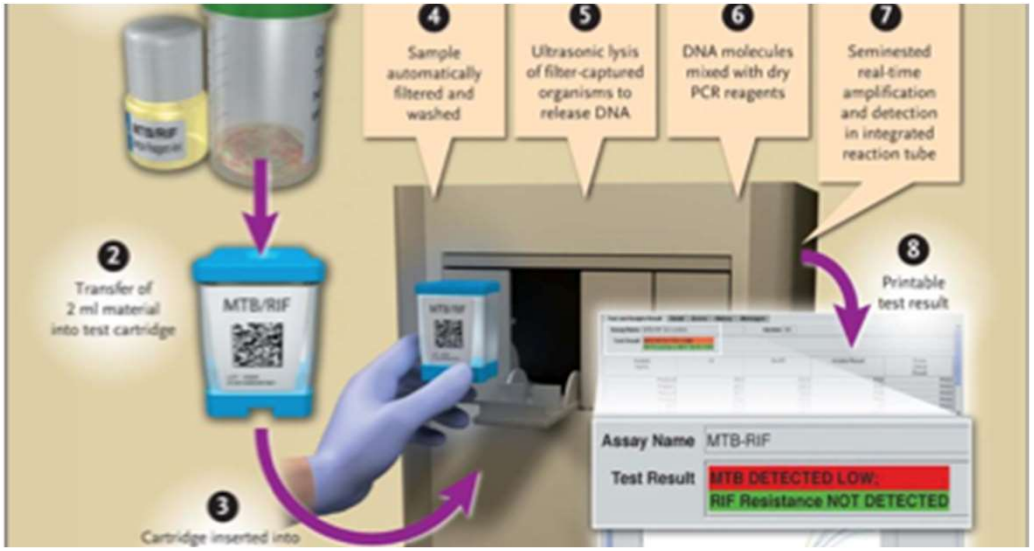
Steingart K, et al. Lancet ID 2006:6(10):664

Nucleic acid amplification tests (NAAT)

- FDA-approved direct amplification tests
  - Xpert MTB-RIF
  - Hain MTBDRPlus
- Use directly on specimens, result < 1 day
- Caution: in patients with
  - Current TB treatment > 7 days → false-negative
  - Recent TB treatment within past 12 months → false-positive ATS/IDSA/CDC 2017 Dx Guidelines: Yes

Slide c/o M Narita

Expert MTB-RIF



Sensitivity of Xpert in Pulm TB Dx Low & High Burden Settings

TEST	SENS	SPEC	PPV	NPV
Xpert x 1	81.4%	98.7%	94.6%	99.7%
Smear pos	98.5%			
Smear neg	54.8%			
Xpert x 2	95.0%			
Smear pos	100%			
Smear neg	71.4%			

- **N = 992 (US, Brazil, S Africa)**
- **Sensitivity of AFB smear: 60%**
- **No difference between high and low prevalence settings**

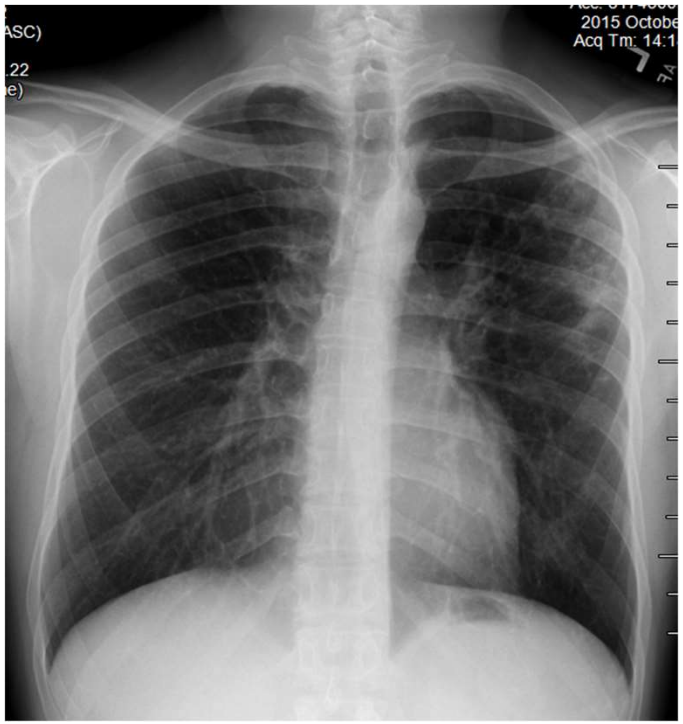
Leutkemeyer AF, et al. CID 2016

AFB Smear- & PCR-Negative TB

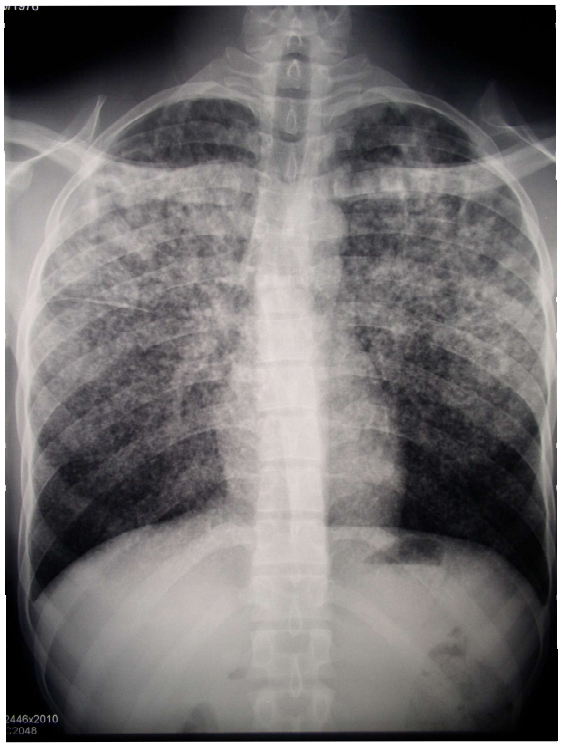
- Up to 50% of TB cases are AFB smear-negative
- low bacillary load—usually but not always
- low infectiousness--usually
- negative smears-and-PCR do not exclude disease
  - ...nor heavy bacillary load
  - ...nor capacity to transmit

AFB Smear- & PCR-Negative TB

- 54 y/o male
- High risk nation of origin
- Cough, sputum x 2 weeks



- 35 y/o RA patient
- High risk nation of origin
- TNF alpha blockade



Caution with NAAT in Previously Treated Patients

Theron, et al. CID 2016

- –45/321 (14%) positive were culture negative
- –Recency of prior treatment
- –Low DNA
- –CXR not suggestive of TB

Boyles, et al. IJTLD 2014

- –4 false positive case reports
- –1, 2, 5 and 66 months after prior treatment

Dorman, et. al. Lancet ID 2018

- – Xpert Ultra increases sensitivity but decreases specificity, especially in previously treated cases (Xpert Ultra 93% vs Xpert 98%)

Indications for Rapid Molecular Testing Resistance-Conferring Mutations

Indication

- Prior treatment for TB
- Contact to known MDR case
- HIV infection
- MDR Hotspot

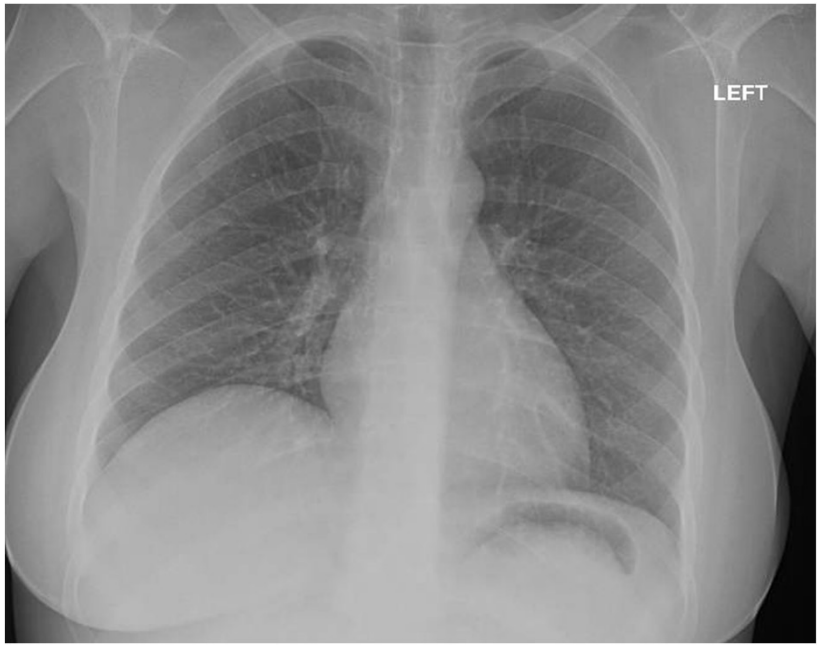
Targeted sequences (MDDR c/o CDC)

- RIF: rpoB
- INH
  - kat G
  - inhA
- PZA: pncA
- EMB: embB
- FQN: gyrA
- Bedaquiline
- Linezolid

ATA, IDSA, CDC. Diagnosis of TB in Adults and Children. Clin Infect Dis 2017;64(2):e31-e33

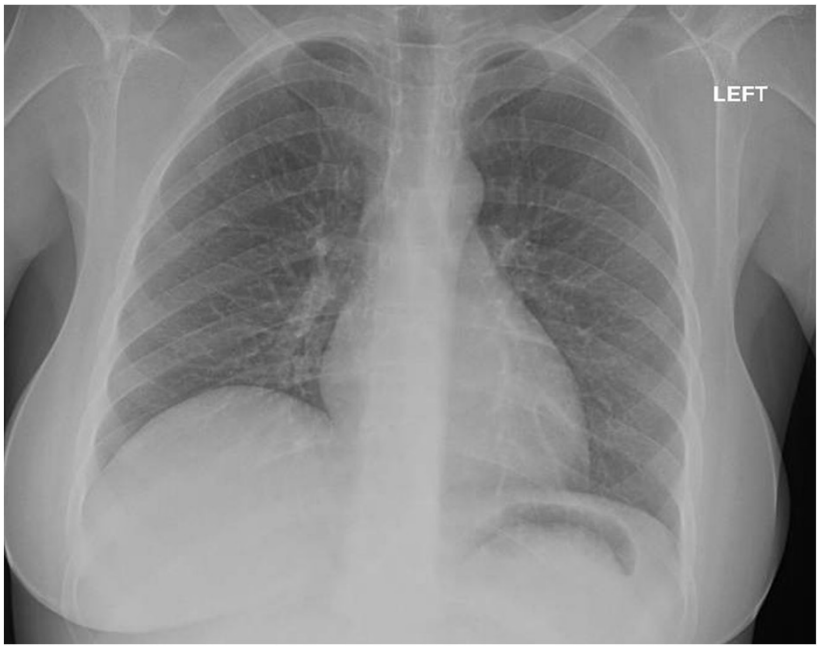
Case B

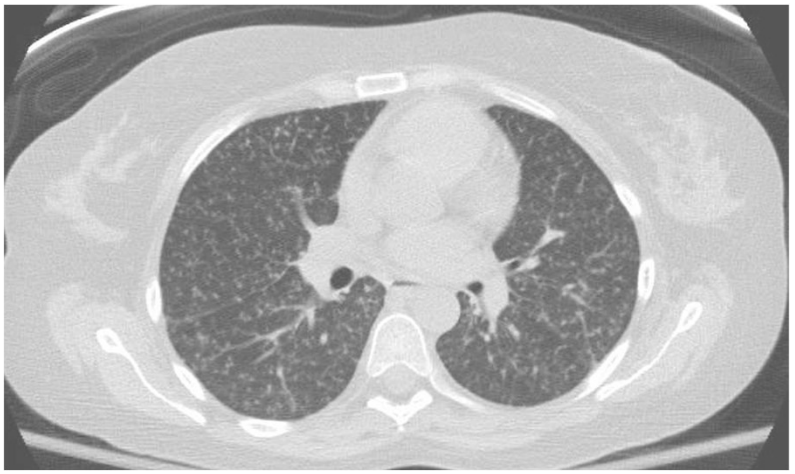
- 28 y/o Ethiopian woman
- Cough, dyspnea, fever, abdominal pain, blood in stools, headache, fatigue
- Sputum AFB smear- and NAAT-negative
- CXR “normal”

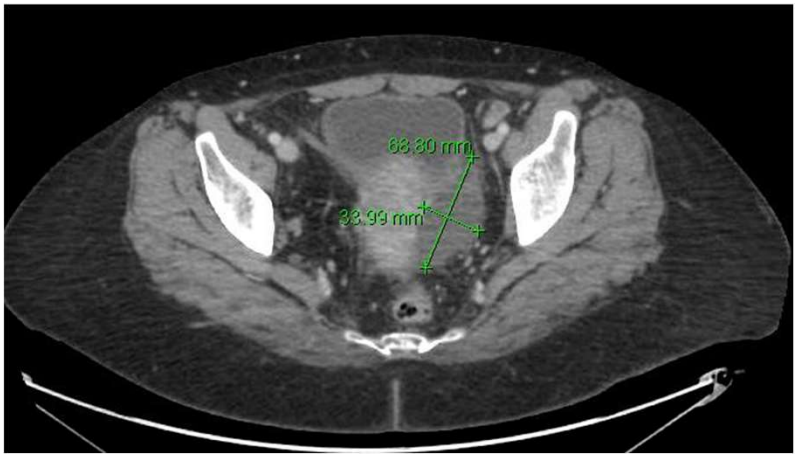


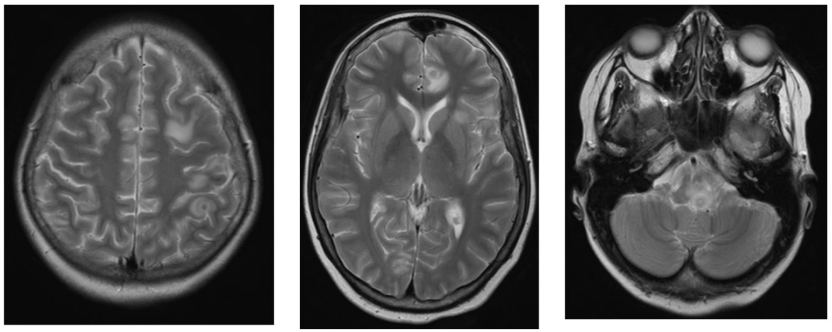
Case B

- 28 y/o Ethiopian woman
- Cough, dyspnea, fever, abdominal pain, blood in stools, headache, fatigue
- Sputum AFB smear- and NAAT-negative









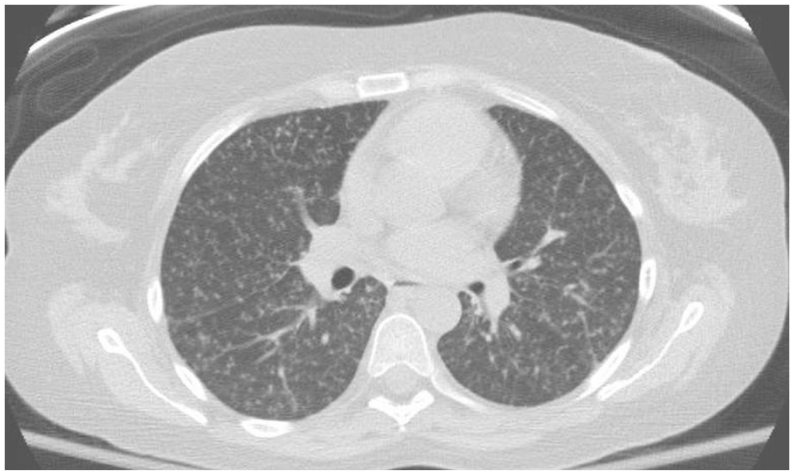
Interactive Question 2

What single procedure would you prioritize?

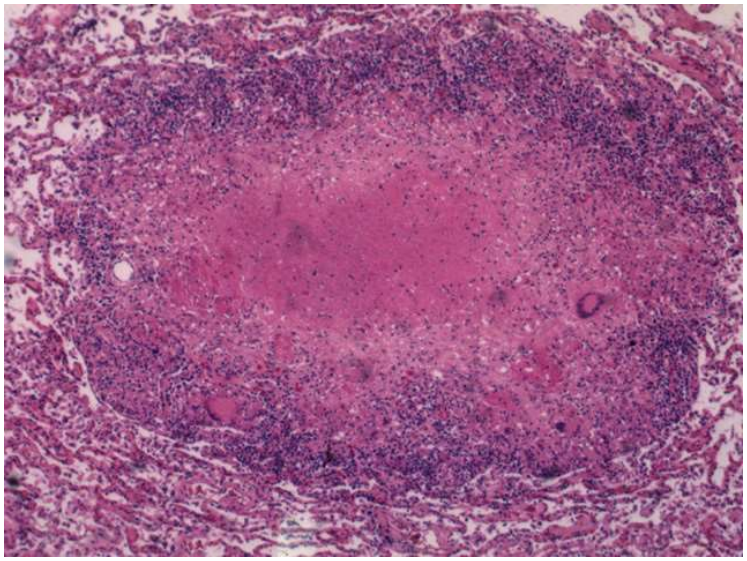
a) BAL and transbronchial biopsy
b) Brain biopsy
c) Laparoscopy
d) Lumbar puncture

Case B—Miliary TB

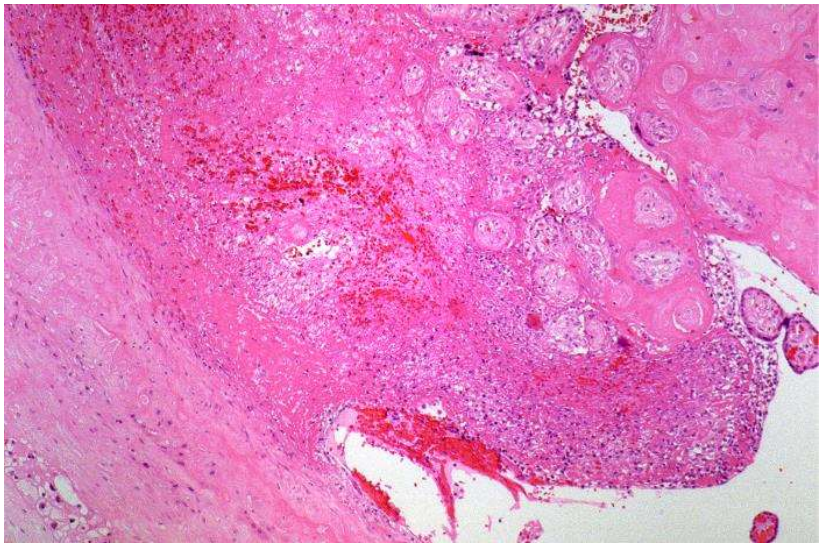
- 28 y/o Ethiopian woman
- Cough, dyspnea, fever, abdominal pain, blood in stools, headache, fatigue
- Sputum AFB smear- and NAAT-negative
- **BAL AFB smear neg/PCR neg**
- **TBBx**
  - **necrotizing granulomata**
  - **AFB smear-neg**
  - **TB PCR positive**
- **BAL and TBBx culture = MTB**



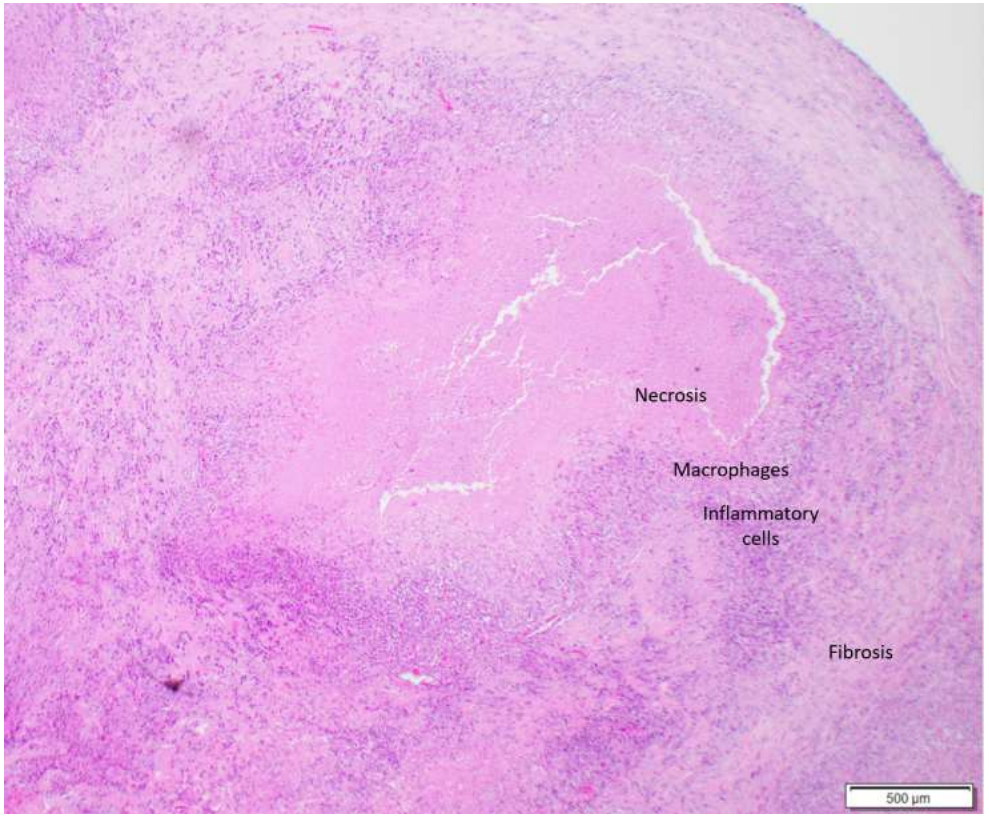
Histopathology
Caseating Granulomata



Source: MedPics. UCSD.



Source: Image Library. CDC.



Source: Tuberculosis with Caseating Granuloma. Adventures in Neuropathology.

AFB Culture

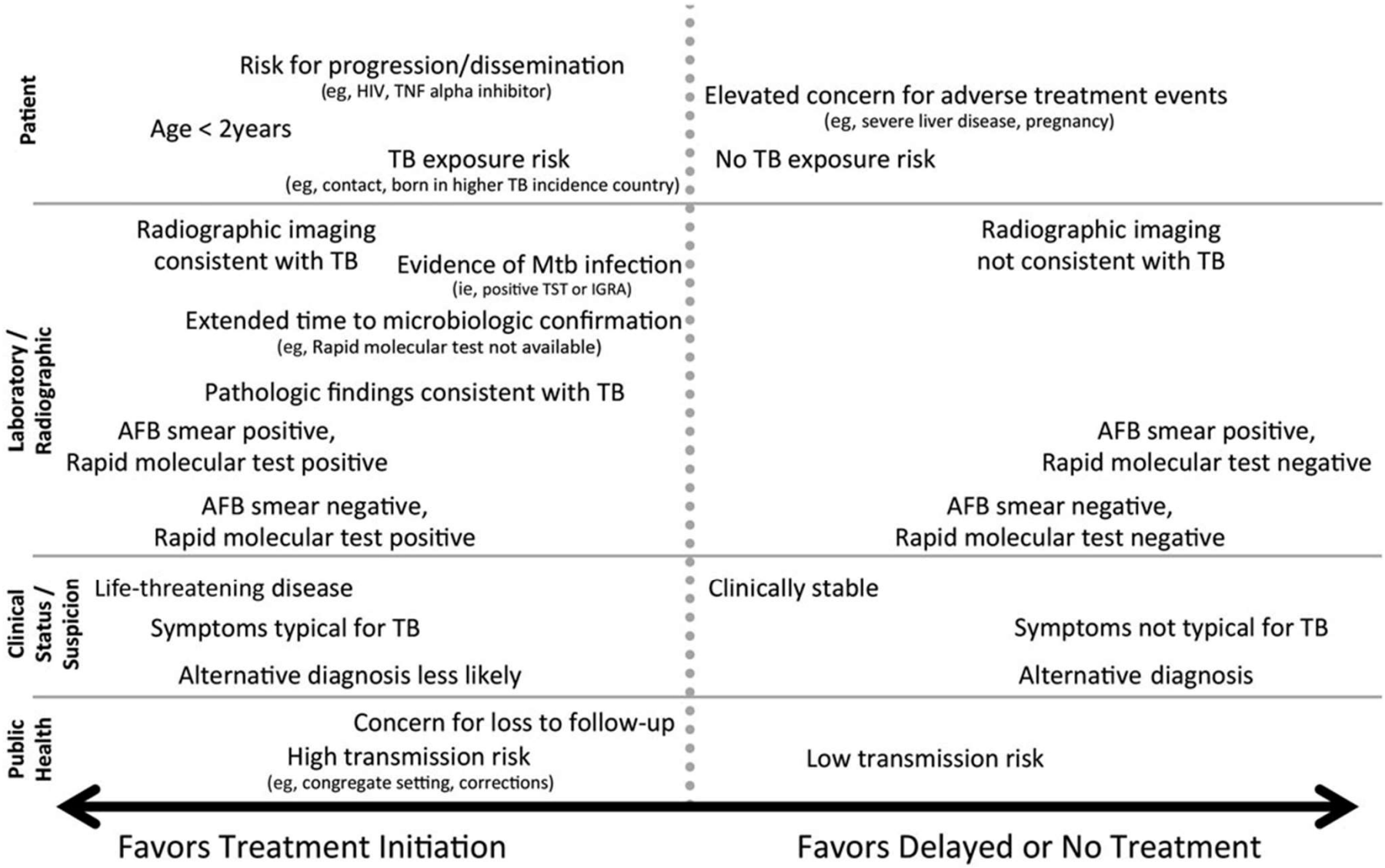
- Broth (faster, more expensive, complex)
  - Liberation of $^{14}CO2$ (defunct)
  - Emission of fluorescence (MGIT)
- Plates (slower, less expensive, “simpler”)
  - Lowenstein-Jensen slant
  - 7H11 plates
- Identification of AFB growth
  - Phenotypic characteristics
  - Nucleic acid hybridization
  - DNA sequencing
  - HPLC

ATS/IDSA/CDC 2017 Dx Guidelines:
Both broth and plates suggested

AFB Culture Limitations

- False Positive (up to 3% of total)
  - Laboratory cross contamination
  - Specimen mis-handling
- False Negative
  - Small inoculum
  - Delay in inoculation
  - Difficult-to-grow strain

Medical Decision Making



ATA, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis 2016:63(7):e147-e195.

Summary

- Cough, sputum, fever, night sweats or weight loss highly sensitive but very non-specific
- Diagnosis: epi/med background+clinical findings→imaging→mycobacteriology+accessory tests→medical decision making
- 3 respiratory specimens for AFB smear/culture.
- NAAT (e.g., Xpert, PCR) on 1-2 specimens
- Collect specimens from additional suspected sites
- Avoid FQN use for pneumonia in patients with a reasonable likelihood of TB

Culture-negative TB Diagnostic Criteria

- Compatible clinical and radiographic syndrome
- AFB cultures negative
  - 10-15% pulmonary
  - 30-40% extrapulmonary
- Clinical/radiographic improvement on therapy
- Other causes reasonably excluded
- Positive TST-or-IGRA helpful but not required

ATS/CDC/IDSA 2016 Rx Guidelines

"Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have thorough clinical and radiographic follow-up after 2 months of therapy. If there is clinical or radiographic improvement and no other etiology is identified, treatment should be continued."

Approach to the smear-negative patient when the lab reports AFB growth

Level of clinical suspicion (especially based on epi risk factors and imaging)

Low | **Uncertain/Unclear** | **High**

No Rx
Isolate
Wait for
Final ID

Consider Rx if benefits>risks
1. Risk of progression
2. Risk of transmission
3. Risk of adverse effects

Initiate Rx
If no response (or worsening)

Re-assess for TB and other diagnoses when ID is still pending
1. Repeat or additional imaging (e.g., CT)
2. Collect additional sputum

Adapted from M Narita

Questions/Comments

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