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CHICAGO DEPARTMENT OF PUBLIC HEALTH

Screening for Tuberculosis Infection: Making the Most of Imperfect Tests

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Disclosure

- No disclosures or conflicts of interest

Objectives

- Review features of the main tests for the diagnosis of latent TB infection and TB disease
- List pro's and con's of each test
- Describe when to report suspected TB cases to public health

TB Diagnosis – Ideal State

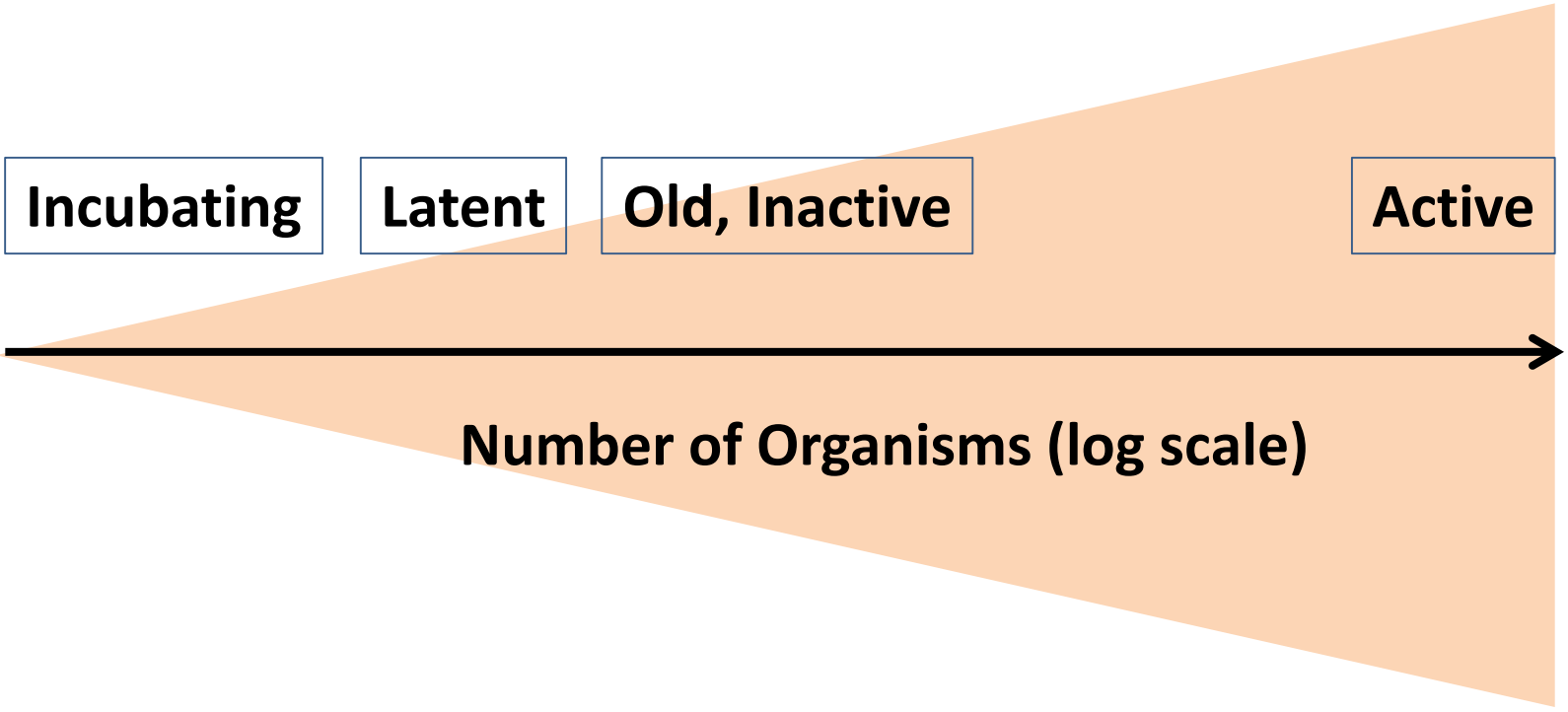
Tests would be

- **Sensitive**
- **Specific**
- **Rapid**

TB Diagnosis – Reality

- **Screening tests lack sensitivity**
- **TB is less common--clinicians need to think TB**
- **Culture takes weeks**

Mycobacterial Burden

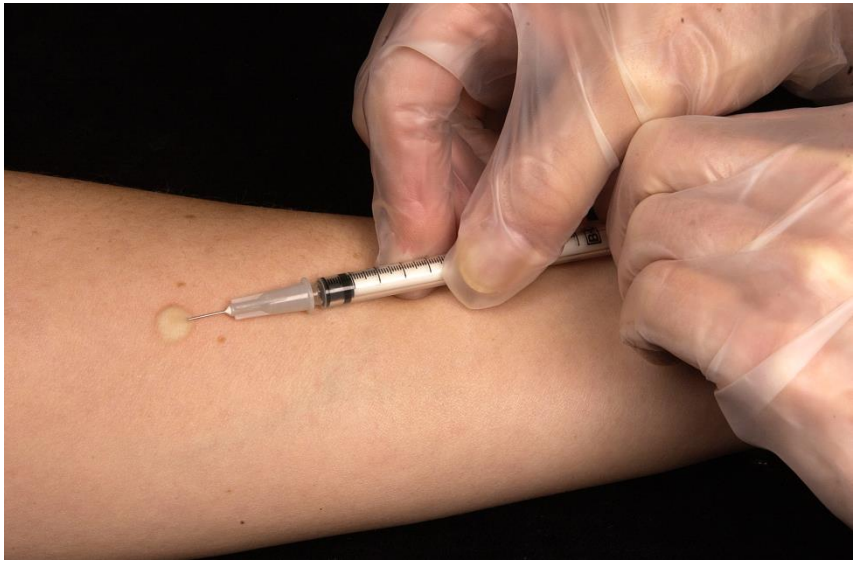


Latent Infection vs. TB Disease

Latent TB Infection (LTBI)	TB Disease (in the lungs)
Inactive, tubercle bacilli contained	**Active**, tubercle bacilli multiplying
TST or blood test results usually positive	TST or blood test results usually positive
Chest x-ray usually **normal**	Chest x-ray usually **abnormal**
Sputum smears and cultures **negative**	Sputum smears and cultures may be **positive**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

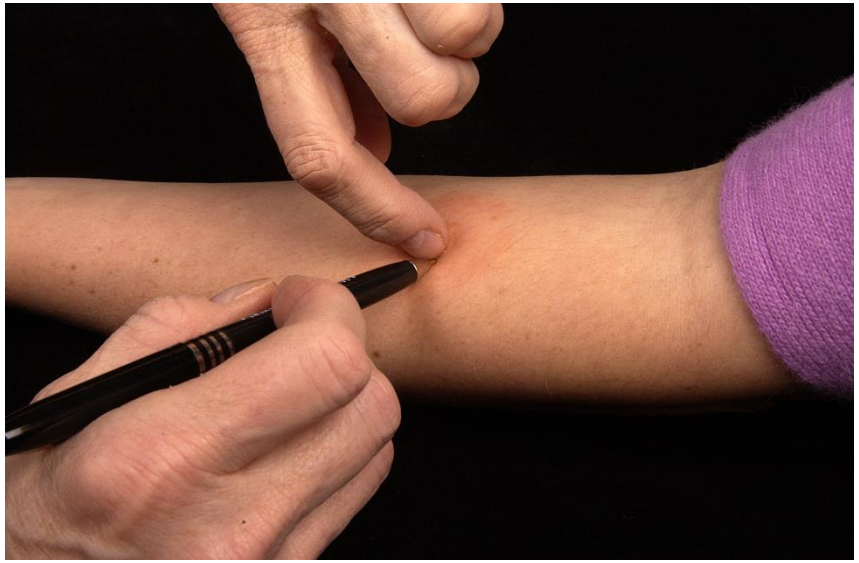
Tuberculin Skin Test (TST)

Requires proper placement



- Inject 0.1ml of PPD intradermally in forearm

Requires proper reading



- Read 48-72hrs post-placement
- Read induration, not erythema
- Read diameter across forearm
- Record results in millimeters

Interferon Gamma Release Assays (IGRAs)

- Blood tests that indirectly detect *M. tb* complex infection
- Expose T cells to 2 or 3 TB antigens. If the T cells were previously sensitized to these antigens they will release interferon-gamma
- These antigens are absent from most non-TB mycobacteria
  - ❑ Exceptions: *M. kansasii, M. marinum, M. szulgai*
- Two FDA approved IGRAs commercially available in U.S.
  - ❑ QuantiFERON-TB Gold In-Tube
  - ❑ T-SPOT.TB

- PRO's: not affected by BCG vaccination, requires one visit
- CON's: increased cost compared to TST, reproducibility?

QuantiFERON-Gold In-Tube (QFT)

Collection and processing considerations

- Draw blood into 3 proprietary 1 ml tubes
- Do not overfill; shake 10 times
- Get tubes at 37^{o}C as soon as possible and w/in 16hrs
- Incubate upright for 16-24hrs
- Centrifuge and carefully remove ≥150 µl plasma to assay

QuantiFERON-Gold In-Tube (QFT)

- Nil tube: no additives, used to determine if the patient has a background immune response that could result in a false +. In order for a test to be valid, the nil tube must have a value ≤8.0 IU/ml.
- Mitogen tube: contains a non-specific stimulator of T cells, serves as the positive control. In order for test to be valid, the mitogen tube must have a value ≥0.5 IU/ml higher than the value of the nil.
- TB antigen tube: assay tube. For a test to be considered positive, the antigen tube value minus the value of the nil tube must be ≥0.35 IU/ml

QuantiFERON-Gold In-Tube (QFT)

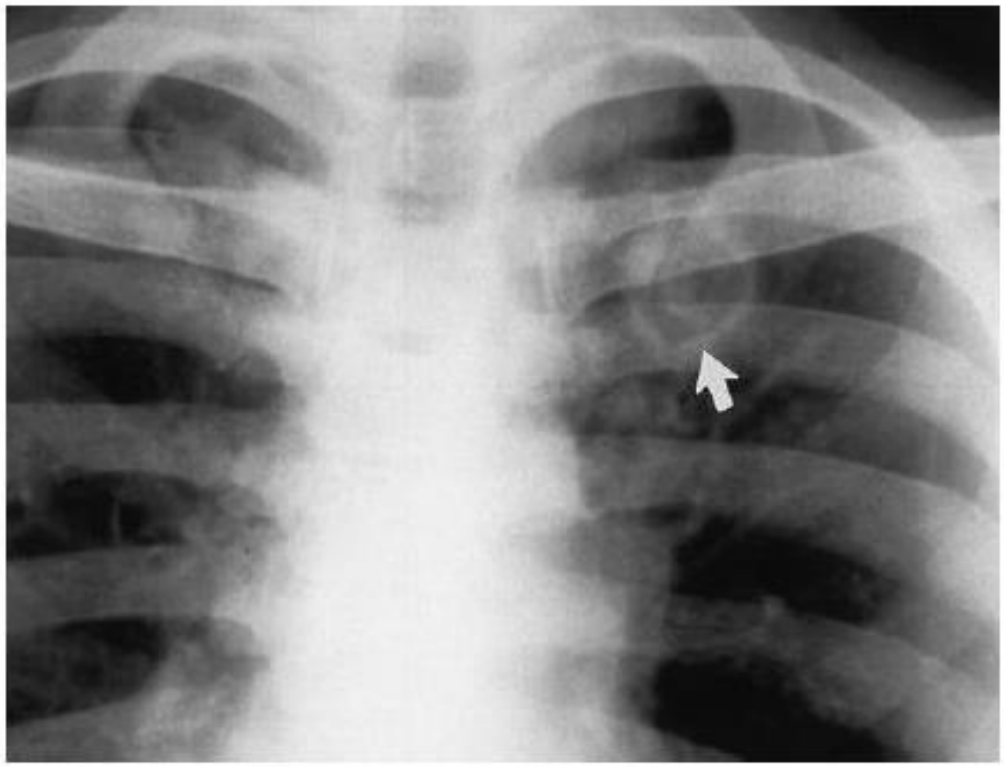
- Test cut-off designed to maximize sensitivity in comparison to culture-positive patients and specificity to people unlikely to have disease
- But no gold-standard for LTBI

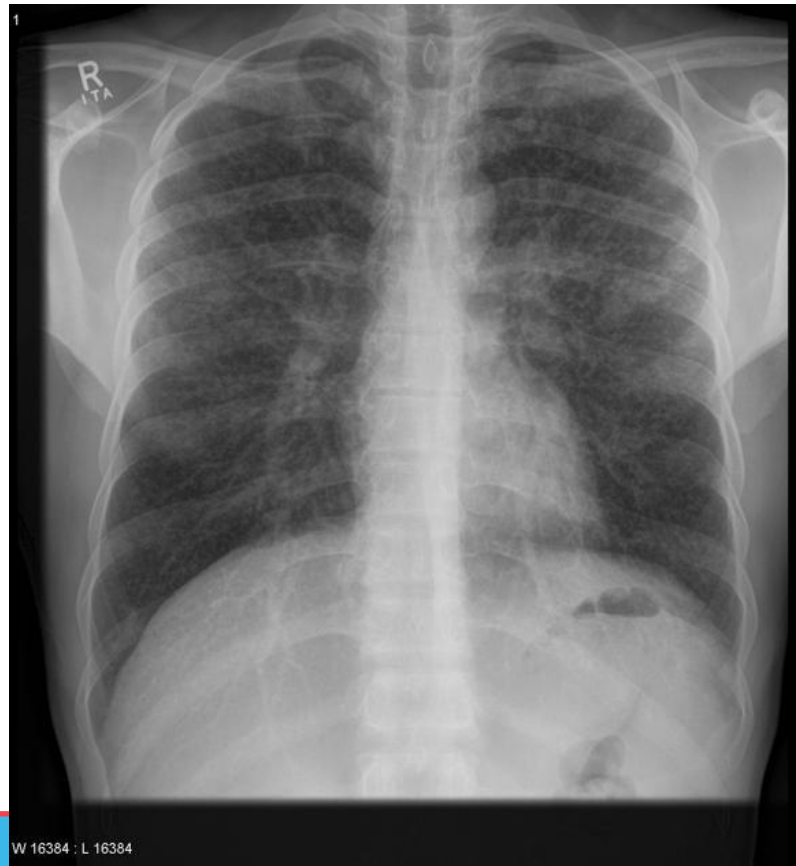
- Among individuals with values just above or just below the cut-off threshold, conversions and reversions were common
- Confirming a positive QFT in a low-risk individual may be prudent before starting LTBI therapy

- “Indeterminate” result not equal to “intermediate”

Chest Imaging

- Primary TB infection: infiltrates, hard to distinguish from CAP
- Reactivation TB: apical cavity (left) is classic finding
- Miliary pattern (right) indicates hematogenous spread

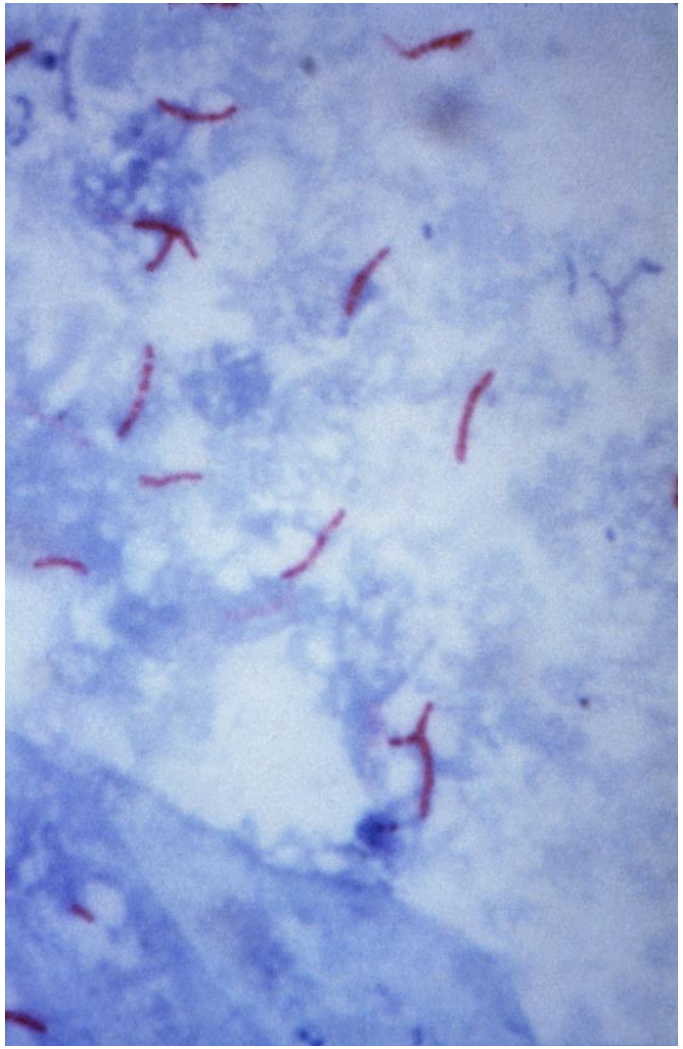




Mycobacteriologic Examination

- **Proper specimen collection**
  - Collect at least 3 sputum specimens at 8-24 hr intervals, at least one should be collected early morning
  - Coughing, induction, bronchoscopy, gastric aspirates
  - Follow infection control precautions during collection
- **Acid-fast bacilli (AFB) smear**
- **Direct identification by nucleic amplification test**
- **Specimen culturing and identification**
- Drug susceptibility
- Genotyping

Acid-Fast Bacilli (AFB) Smear



- Microscopic exam
- Need at least 10,000 AFB/ml to be positive
- Results in 24 hrs
- Positive result supports diagnosis of TB disease; however does not distinguish between viable and dead organisms
- Does not distinguish between MTB and non-tuberculosis mycobacteria

Nucleic Acid Amplification Test (NAAT)

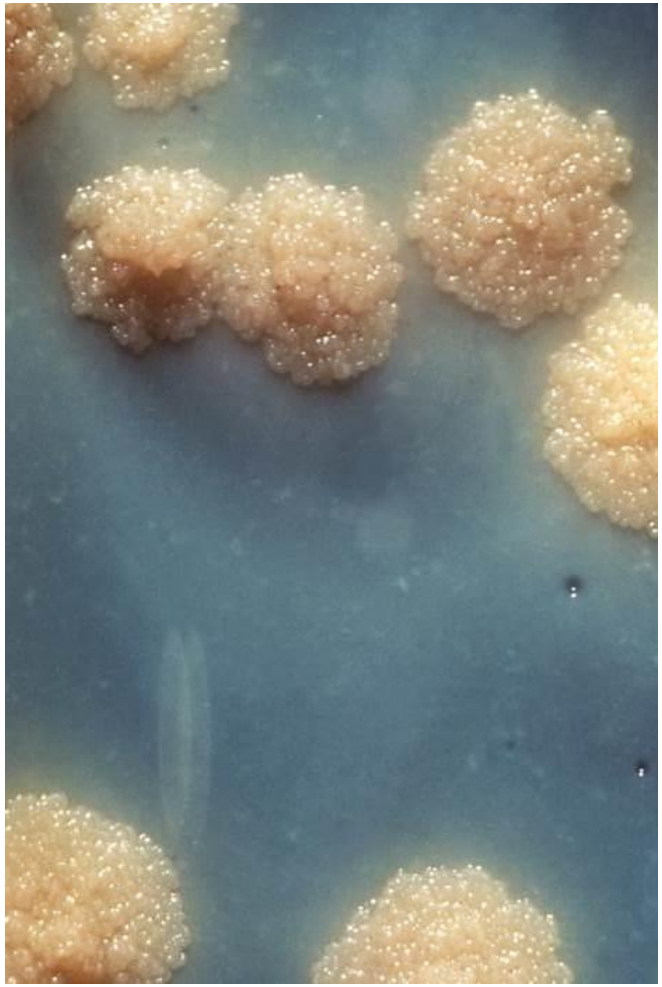
- Performed directly on pulmonary specimen: sputum, bronch, tracheal

- Should be done on a respiratory specimen from each patient with signs and symptoms of active pulmonary TB for whom a diagnosis of TB is being considered

- PRO's: earlier diagnosis leads to earlier treatment and reduced period of infectiousness, earlier infection control decisions, earlier public health interventions

- CON's: does not replace AFB culture, adds lab cost, is labor intensive, susceptible to contamination

AFB Culture and Identification



- More sensitive than smear: need only 10 AFB/ml for a positive result
- Results as soon as 4-14 days if liquid media used
- Incubate at least 6 wks to confirm no growth
- Once there is growth many labs can do DNA probe identification (*not* amplified)
- Also, biochemical identification

Xpert MTB/RIF Assay

- Is a nucleic acid amplification (NAA) test that uses a disposable cartridge with the GeneXpert Instrument System
- Detects *M. tuberculosis* complex and rifampin resistance
- Sputum from a suspect TB patient is mixed with a reagent and a cartridge containing this mixture is inserted in the machine

- PRO's: Results available in a few *hours*, minimal technical training needed
- CON: cost

Case #1

- 61 yr old woman, born in Philippines, in U.S. since 1995
- Cough x 1-2 weeks, dyspnea, 5 lb wt loss, fatigue
- CXR/chest CT: cavitary lesions
- Sputum AFB smear 4+, AFB culture pending

- What test will help you most at this juncture?
  - TST
  - IGRA
  - NAA test on sputum
  - Bronchoscopy with AFB smear and culture

Case #1 – cont.

- The NAA test is performed directly on the sputum sample and detects *M. tuberculosis* complex RNA
  - Positive result → highly suspicious for TB disease (although still not confirmatory)
  - Negative result → doesn't rule out TB disease

- TST and IGRA won't help advance the diagnostic process
- Bronchoscopy only if for some other pulmonary indication

- This patient was NAA+ and was started on 4-drug TB therapy*

* Report case to public health

Case #2

- 69 yr old woman, HIV-, born in Mexico, in U.S. since 1979
- Mild cough and dyspnea x 1 week
- CXR: patchy infiltrates, perihilar lymphadenopathy
- Rx with levofloxacin for CAP
- One month later develops neck mass
- TST = 32mm, QFT = positive (test placed/collected same day)
- 4-drug TB treatment started* upon TST+ and QFT+

- What tests are indicated next?

* Report case to public health

Case #2—cont.

- What tests are indicated next?
  - Chest CT
  - Biopsy of neck mass for AFB smear and culture
  - Ultrasound of neck mass
  - Sputum for AFB smear and culture
  - Urine for AFB smear and culture

Case #2—cont.

- ➢ Chest CT
- ✓ Biopsy of neck mass for AFB smear and culture
- ➢ Ultrasound of neck mass
- ✓ Sputum for AFB smear and culture
- ➢ Urine for AFB smear and culture

- Chest CT and neck U/S won't help advance the diagnostic process
- Urine for AFB smear/culture only if GU symptoms

- This patient was AFB smear negative on lymph node and sputum specimens but grew *M. tuberculosis* from both sites

Case #3

- 49 yr old man, HIV+, born in Mexico, in U.S. since 2004
- Cough, diarrhea w/ melena, weakness, 35lb wt loss over 3 mos.
- Not on HIV meds, CD4 = 2; has diabetes and cirrhosis
- Treated for culture-negative pericardial TB in 2009

Case #3 – cont.

- Duodenal biopsy: AFB seen on the stain but not sent for culture
- CXR – normal
- Chest CT – mild abnl but no cavity, no miliary
- Sputum smear negative
- Therapy for TB and Mycobacterium avium started*

- *Should you order a NAAT on the sputum specimen?*
- *Should you order a TST or IGRA?*

* Report case to public health

Case #3 – cont.

- NAAT would be helpful if positive
- TST or IGRA: positive result would tell you the patient is infected, but negative result doesn't help b/c of immunocompromised state

- This patient's sputum grew an AFB which was eventually identified as Mycobacterium avium complex (MAI or MAC)
- TB meds stopped
- No TST, IGRA, or NAAT performed

Case #4

- 25 yr old man, HIV-, born in Guatemala, in U.S. since 2012
- Neck swelling x 1 month; otherwise healthy
- Immigration physical : pt reports TST+, CXR had a “shadow”, no diagnosis of LTBI or TB given

- CXR – nl; chest CT – multiple nodules upper lobes, no cavity
- TST = 40mm
- Lymph node biopsy: necrotic granulomas, AFB smear positive
- 4-drug TB therapy started*

- *Should this patient be in airborne isolation?*

* Report case to public health

Case #4 – cont.

- Should this patient be in airborne isolation? YES

- How to know when to release from AII room?
  - ❑ Sputum smear negative x 3
  - ❑ Xpert MTB/RIF negative result x 1
  - ❑ Consider at least 5 days of effective TB therapy

- This patient had 3 sputa specimens collected—all were AFB smear negative. One specimen grew an AFB, later identified as *M. kansasii*.

Conclusions

- Diagnosing TB typically requires multiple tests, interpreted in the clinical context
  - Good communication with your labs
  - Try to build in reflex testing algorithms
  - Consult public health for help

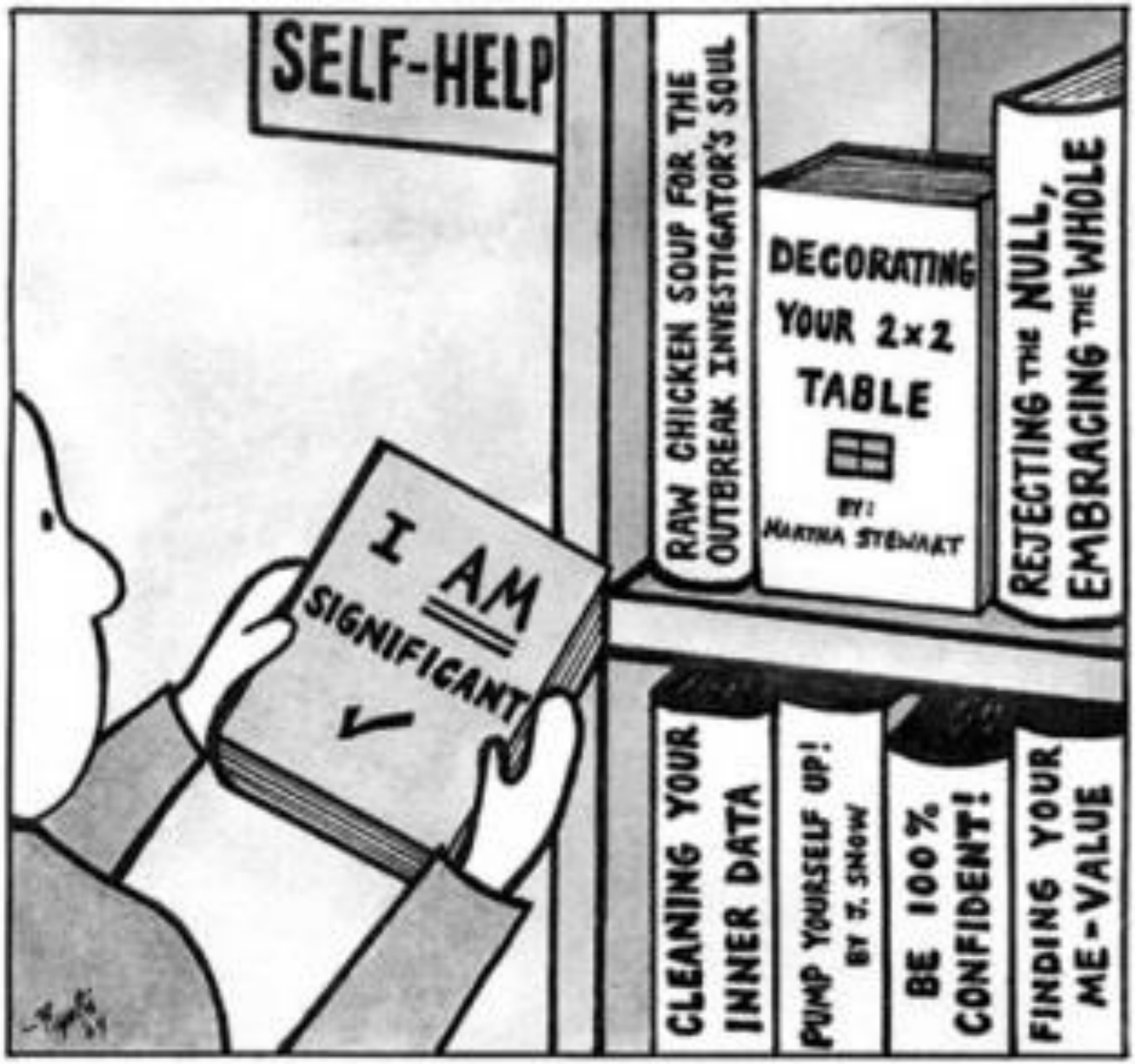
- Collect specimens from as many sites as indicated to increase yield

- Even suspect TB cases are reportable to public health
  - If patient starts TB medications, report

CDPH TB Control Program—Key Points of Contact

- To report cases
  - Juan Elias (Senior Comm Dis Investigator): 312-746-6013
  - Nereida Bruno-Otero (Senior Nurse Case Manager): 312-746-6036
- Clinical consultation
  - Dr. Kathy Ritger: 312-746-5992
- General program information
  - Nancy Rivera (Program Director): 312-746-5987

Self-Help for the Epidemiologist



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