Diagnosis of Tuberculosis 2021

New Tools, Tricks, Thinking?

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Objectives

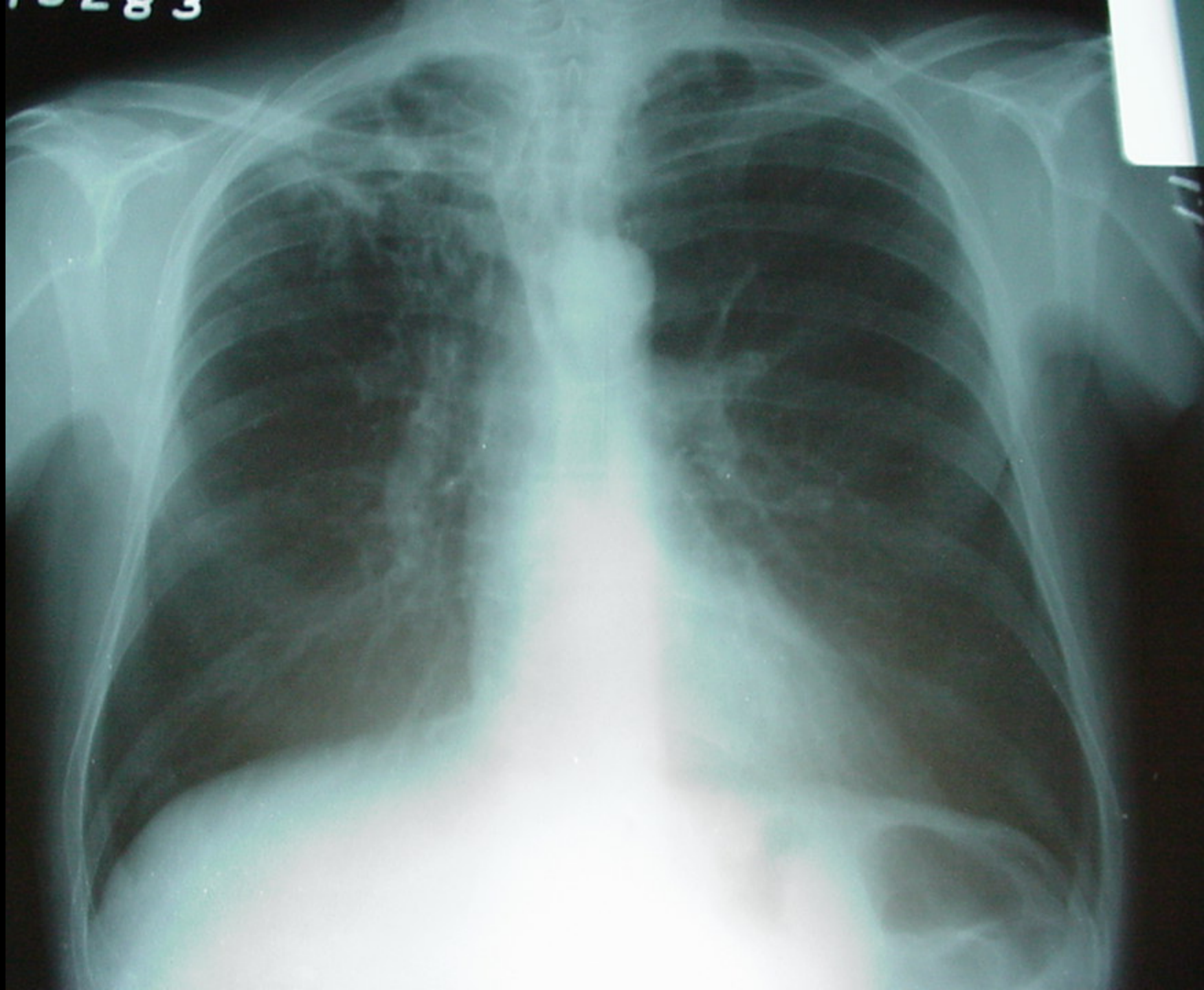
- To review the Diagnosis of Tuberculosis and the role of the Mycobacteriology Laboratory
  - How the Lab works
  - What the Lab does
  - How to interpret results
- Discuss the potential of new tools

Will not discuss: Molecular Epidemiology (“genotyping”)
Interferon-gamma Release Assays

TB Among the Homeless

- 52 y/o gentleman, homeless; recent travel by rail (convention in WI)
- History of alcohol abuse, heavy smoking
- Presents in 4/09 with 2 months increasing cough, purulent sputum, weight loss following his trip
- Questions???

  CXR?



TB – or *NOT* TB?

- Admitted to Mass General Hospital
  - Sputum smears AFB-Positive
  - TST: 16mm induration
  - Started 4 drugs: *Findings are consistent with TB*
  - Reported to *1-888-MASS MTB*
- *Contacts???*
- NAAT (MTD™) negative for MTb complex
  - Cultures subsequently grew *M. avium*
    - Negative for MTb at 8 wk (final)
- Treatment changed to Clarithromycin + Ethambutol
- Patient's symptoms resolved rapidly

Diagnosis of TB, 2021
Some things change; some don't

- Diagnosis follows *Clinical Suspicion*
  When should we "*Think TB*"?
  - Who is at risk for TB?
  - Is TB presenting differently than in the past?
- How do we make the diagnosis?
- And…are there new ways to improve diagnostic capacity?

Diagnosis: Define Groups at-Risk

Epidemiology of recent cases

- In US, know your populations
  - Majority of cases is non-US born; from high prevalence countries
  - Community-specific (*e.g.,* homeless, substance abusers, Asian, …)
  - Children from high-prevalence groups
- Medical risk factors *(if infected)*
  - HIV 7-10%/yr
  - Diabetes ? 4%/yr
  - Immunosuppressive therapies – including *organ transplant recipients*, *anti-TNF-α agents*, *chronic steroids*
  - Age
- Recent transmission *versus* reactivation

Elderly US-born still appear (born when TB still widely endemic)

Still a problem; usually represent reactivation disease

TB is Local

Barry Chin, *Boston Globe*, 10/15/2008

Diagnosis of TB
Get Started

- History (personal)
  - TB risks?
  - Symptoms
    - Specific to system involved
      - *e.g.,* cough (pulmonary), chest pain (pericardial), neck swelling, …

      and/or
    - Nonspecific (*constitutional*)
      - *e.g.,* fever, weight loss, night sweats, fatigue, …
    - May be absent - *up to 25%*
- Physical examination
  - Findings specific to system involved; constitutional
- TB Infected: TST or IGRA?
  - Appr. 80% sensitive in TB disease - may *support* diagnosis
- Chest radiograph

Chest Radiograph
*Still a Good Screening Tool**

- Time: minutes to hours
- Sensitivity: excellent (but there are exceptions)
  - Single view adequate in most settings (but children <11 - get 2 views)
- Specificity: poor
  - *Classic*: apical/poster upper lobe; superior segment lower lobe
  - Up to 1/3 of pulmonary TB – *non-classic* radiograph
- Advantage: inexpensive screening of potentially *active* pulmonary cases
- Disadvantages: cost, radiation ?
  - Requires *skilled* interpretation
  - *AI* approaches under investigation

*** in the appropriate setting**

TB is a Clinical Diagnosis
most of the time

- Most clinicians will initiate multi-drug therapy *if the disease is suspected on clinical grounds*
  - But many cases go undiagnosed until a laboratory reports a positive culture
- How is that diagnosis confirmed?
  - ***In the laboratory***

Role of Mycobacteriology Lab

- *Target: Mycobacterium tuberculosis* Complex (MtbC)
  - Use rapid methods to detect, identify (ID), and perform drug susceptibility testing (DST)
    - *TB vs. not TB*
- Non-tuberculous mycobacteria (NTM)
  - Provide accurate / clinically relevant information (accurate ID IF clinically relevant; appropriate DST IF clinically relevant)
- Issue rapid, clinically useful, and reliable reports
- Evaluate testing and reporting algorithms as necessary
- Develop and maintain 2-way communication - clinicians, care-givers, TB program, referring laboratories, etc.

B. Metchock, CDC, 9/2010

The TB Laboratory

- Types
  - Hospital-Clinical Laboratories
    - Process samples from within an institution and its affiliates
  - Private Laboratories
    - Process samples on contract basis (*e.g.* Quest, LabCorp, ARUP)
  - Network Laboratories
    - Process samples for organization (*e.g.* VA)
  - Public Health Laboratories
    - State/federally supported facilities: *Your State Lab*
  - Reference Laboratories
    - Provide specific services – culture confirmation, molecular DST, drug level monitoring, … (*e.g.* CDC, National Jewish)
- Overall, *n* >1,932 (+ state labs)

Accommodating Escalating Complexity

- Varying *levels of service o*ffered
  - Not all laboratories perform all tests
    - Most perform basic tests: smears, primary cultures
  - Ability to perform appropriate tests
    - Equipment, personnel
  - *Secondary and Reference Laboratories*
    - Receive/process samples for more complex tests
- Communication challenges
  - Laboratory-to-laboratory
  - Provider-to-laboratory(*ies*)-to-provider-to- …
- Laboratory *competence*
  - Determined locally
  - Centers for Medicare & Medicaid Services' Clinical Laboratory Improvement Amendments (CLIA) program
    - Proficiency testing

Diagnosis of TB: *Demonstration of M. tuberculosis*

- The *Gold Standard*
- Secretions or tissue
  - Subjected to laboratory techniques *to identify the organism*
- Ability to isolate organism varies with
  - Location of disease
  - Density of organisms at disease site

Standard Mycobacteriology Laboratory Tests*

- Smear/stain for *acid-fast* organisms
  - Sputum, sterile fluids, tissue
- Culture for identification of organism
  - Includes speciation
  - Drug susceptibility studies (DST)
- Nucleic Acid Amplification (NAA)

- Therapeutic Drug Monitoring

* https://www.aphl.org/programs/infectious_disease/tuberculosis/Pages/default.aspx

Step-By-Step
"Typical" TB smear and culture (1)

- Specimen received in lab
- Specimen accessioned (assigned lab number; entered into lab computer/worklog, *etc.*)
- Specimen stored appropriately (refrigerated) until processed
  - Usually 1x/workday
- Specimen processed (digested/ decontaminated) usually by NALC/NaOH method in batch with other specimens
- Smear prepared
- Culture media inoculated (usually 1 broth and 1 solid) and put into incubator/instrument

B. Metchock, CDC, 9/2010

Step-By-Step
"Typical" TB smear and culture (2)

- Smear stained and examined and results reported same day as specimen processing
- NAA test set up if appropriate/if lab offers test; some labs also do "molecular DST"
- Culture media examined/monitored as prescribed by method (for 6-8 weeks)
- If growth detected, smear made and stained to confirm presence of AFB (acid fast bacilli)
- If AFB, go onto identification (*e.g.*, HPLC, nucleic acid probe, MALDI-TOF mass spec)
- If TB, make appropriate notifications and perform DST as appropriate

- If no growth, keep 6-8 weeks and sign out as "negative for mycobacteria"

B. Metchock, CDC, 9/2010

Specimen Collection

- Sputum: Spontaneous or induced
  - Initial: 3 *good* samples, 8-24hr apart (MMWR, 2005)
    - Can be done with young children
  - Monthly while on treatment until culture-negative
- Collect aseptically, avoid contamination
  - Sterile, leak-proof, disposable, non-breakable, appropriately-labeled lab-approved containers
  - No fixatives or preservatives
- Avoid contamination with tap water
  - NTM may be in water
- Collect initial samples prior to therapy if possible
- Transport immediately or refrigerate

Sputum Smears: *Definitions*

- Direct smear: stain performed on the **submitted sample**
- Concentrated smear: decontaminated-liquified (NaOH and NALC) and centrifuged (at 3,000xg)
  - Improves yield
  - Procedure kills >30% of mycobacteria
- Indirect smear: performed on **growth from culture**
  - Isolate from primary lab sent to *second lab*
    - For further identification (confirmation) and DST
- Kinyoun or Ziehl-Neelsen (heat) stain: Light microscopy (1000x mag/oil)
  - *"Acid-fast":* Organisms retain red color following decolorization with acid-alcohol (the *Red Snapper*)
- Fluorochrome stain: Fluorescence microscopy (450x mag)
  - Auramine O
  - Recommended initial staining procedure (incr sensitivity, decr time)

AFB Smear Microscopy

- Variable sensitivity
  - 40-70% for pulmonary TB (less in miliary TB, late HIV, children)
  - LOD >10^4 AFB/ml by Ziehl-Neelsen; >10^3/ml fluorochrome
  - Correlates with disease severity and infectiousness
- Not specific for MTb Complex
  - *Red snappers*
- Inexpensive and quick
  - Turnaround time (TAT) <24hr
- Value
  - Usually provides the 1st evidence of TB
    - Direct smear light microscopy is the primary diagnostic method in many countries
  - Used to guide therapy (AFB in smear are quantified)
  - May guide additional testing (*e.g.,* NAA)

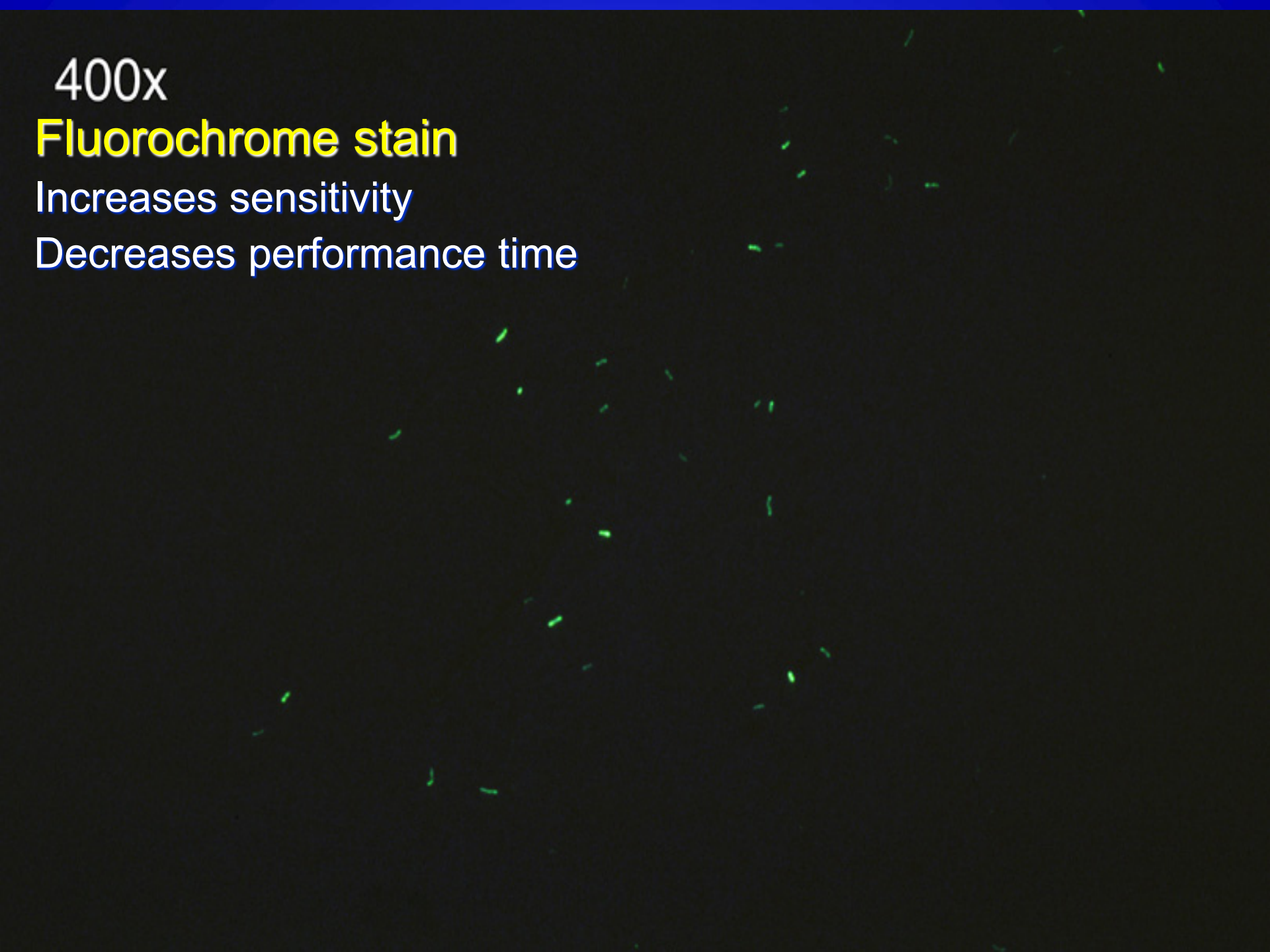
International Guidelines for Examining and Reporting Acid-Fast Smears

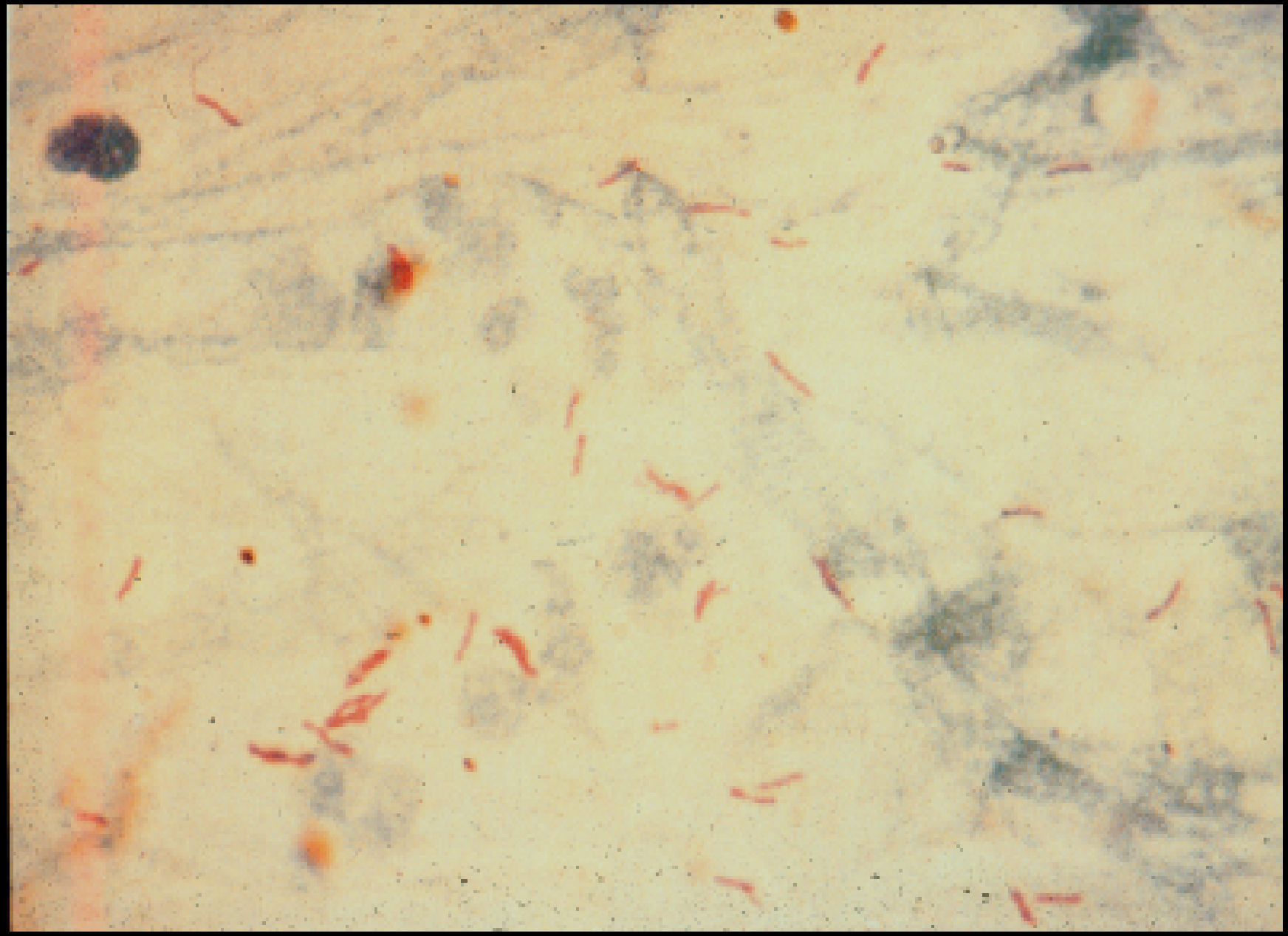
Organism Count at Specific Magnifications

Report	Number of AFB Observed	
	200x, 250x	400x, 450x
No AFB seen	0	0
Doubtful: repeat	1-2/30F*	1-2/70F
1+	1-9/10F	2-18/50F
2+	1-9/F	4-36/10F
3+	10-90/F	4-36/F
4+	>90/F	>36/F

*** number of acid-fast bacilli observed per microscopic field**

CDC


400x
Fluorochrome stain
Increases sensitivity
Decreases performance time



AFB Smears: *Rule Out TB?*

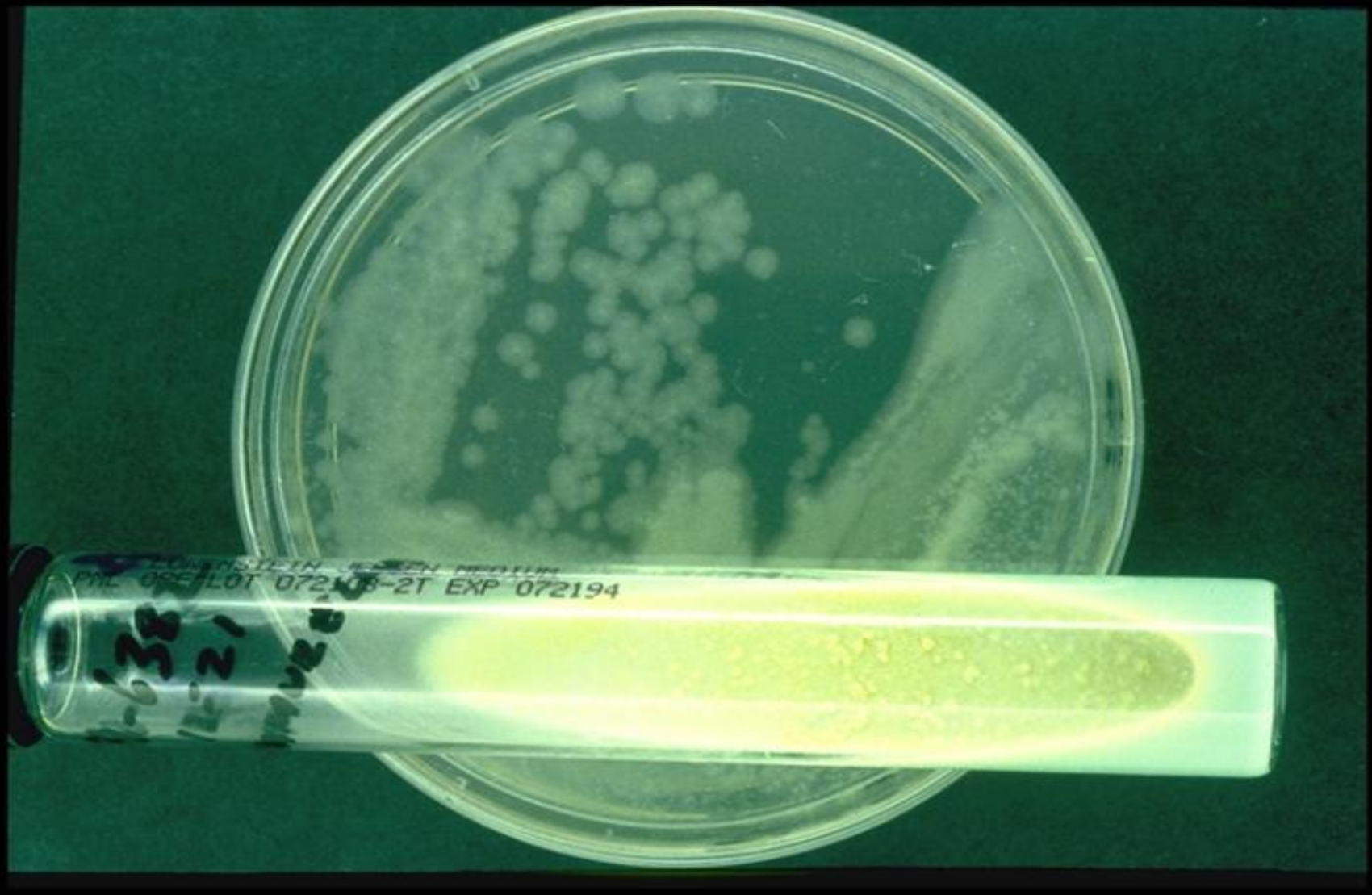
- *A positive smear does not establish diagnosis*
- *A negative smear does not exclude TB*

Culture Isolation of *M. tuberculosis*: The *Gold Standard*

- Requires appropriate laboratory equipment & trained staff: *Competence*
- Allows for identification and speciation, drug susceptibility testing
- Performed on secretions or tissue
- Sensitive
  - Limits of detection (LOD) 10 to 100 AFB/ml
    - 10,000 AFB/ml for smear (Z-N) - more specimen goes into culture

Culture Methods

- Solid media
  - Agar (Middlebrooks) and egg-based (Lowenstein-Jensen) platforms
  - Require up to 6 - 8 weeks
  - Advantage: Can identify colonies (pigmentation, morphology)
- Broth – some are highly automated
  - BACTEC MGIT 960; TREK; MB/BacT
  - More rapid recovery than solid media: 7-21 days
- Current recommendations are to use at least one type solid media *and* broth (mixed culture detection; increased sensitivity)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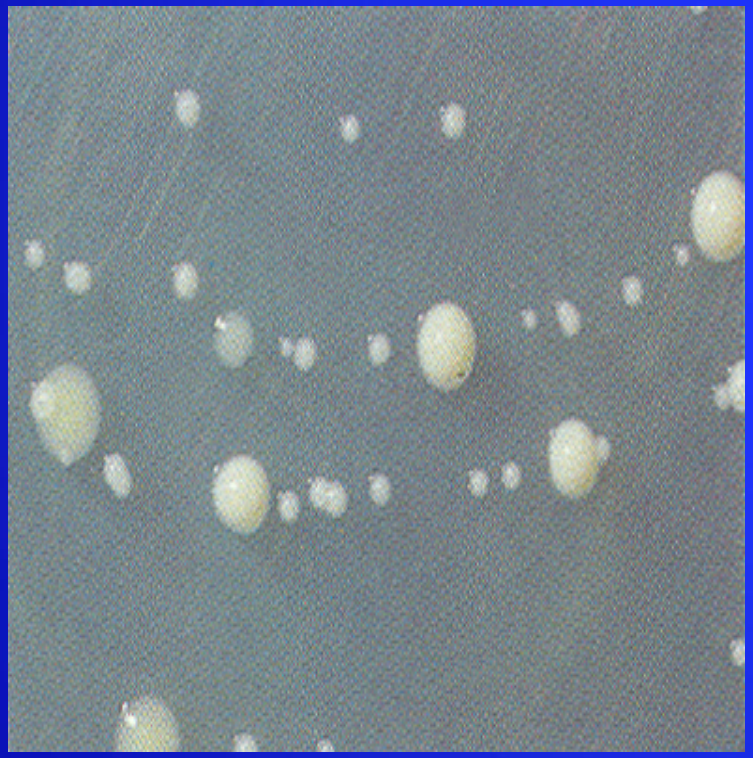
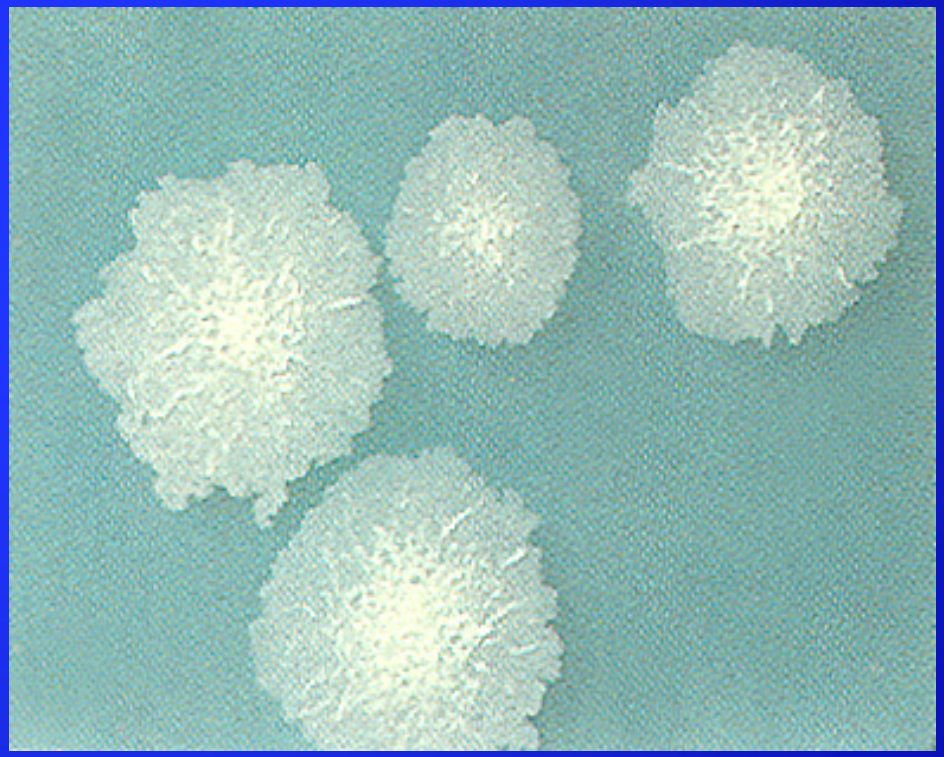
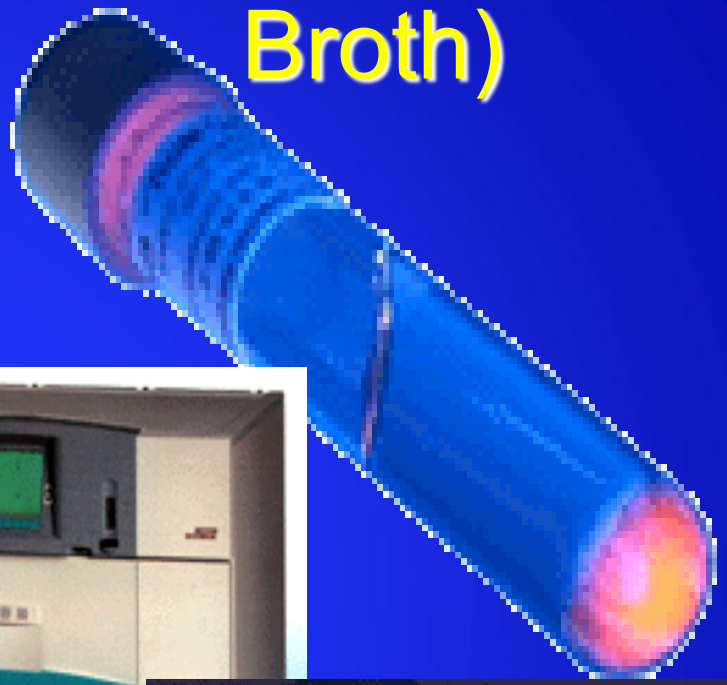
Colony Morphology





Mycobacteria Growth Indicator Tube (MGIT 960 Broth)



- Fluorescence quenched by O_2 in O_2-rich liquid media
- If mycobacteria present, O_2 used up, no quench, fluoresces under UV light
- Continuously monitored
- DST for INH, RIF, EMB, SM, PZA

B Metchock, CDC

MTB Culture Isolation

- Negative cultures do not exclude infectious TB
  - Sampling error, small inoculum, contamination, dead organisms, *etc.*
- False positive: cross-contamination?
  - Interpretation contextual
  - Depends on clinical suspicion of disease
    - *e.g.* smear negative, low probability patient
- Cultures guide management
  - Declining # colonies correlate with response to therapy
  - Monitor sputum monthly until culture conversion
  - If culture-pos at 3 mos, look for reason (malabsorption, drug resistance, *etc*)
- *Rule Out TB?*
  - *A positive culture can establish diagnosis*
  - *A negative culture does not exclude TB*

Identification of Mycobacteria

- MTb *vs.* NTM: *Treatment and public health implications*
- Preliminary ID based on growth characteristics solid media
  - Colony morphology, pigment, rate of growth (REQUIRES GROWTH)
- Conventional biochemical tests (all mycobacteria)
  - 2-21 d (may not necessarily be accurate for NTMs)
- HPLC of cell wall mycolic acids ("all" mycobacteria)
  - 2 h – usually by reference labs
- **Commercially available genetic probes**
  - ACCUPROBE, GenProbe, San Diego, CA (www.genprobe.com) probes for Mtb Complex, MAC, *M. kansasii, M. gordonae*
  - 2-4 h – many clinical labs
- **MALDI-TOF** (*Matrix Assisted Laser Desorption/Ionization–Time-of Flight*)
  - Mass Spectrometry; identifies multiple mycobacteria
  - Minutes/hours – usually by reference labs (NOT FDA cleared – 3/2018)
- "In-house" PCR/genetic sequencing/*etc*.
  - 1-2 d – reference labs/clinical labs

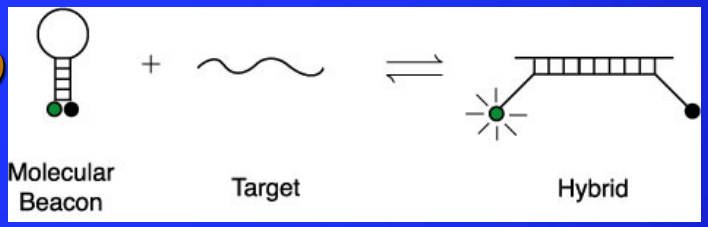
B Metchock, CDC

Direct Detection of MTb Complex: Nucleic Acid Amplification Testing (NAAT)

- *NAA assays*
  - ~~*Amplicor®-Roche*: DNA~~
  - ~~*MTD®-GenProbe*: r-RNA~~
  - *Cepheid-GeneXpert MTB/RIF®*
- Advantages
  - Excellent sensitivity (131 organisms/ml-Xpert) & specificity for MTb
  - TAT generally ≤ 48hr
  - Can affect treatment decisions, including isolation and other public health interventions, invasive procedures
- Disadvantages
  - $$ Costly $$
  - No indication of viability of organism: *CANNOT* be used to monitor therapy
- *Still requires culture for confirmation, DST*
- *Xpert:®* FDA-approved ONLY for respiratory secretions (sputum)
  - adults, sputum smear +/-; ≤3d therapy
- "Off-label" use
  - Bronchial washings, tracheal aspirates , non-sputum specimens (*e.g.*, CSF)
    - Require validation by laboratory
    - Physician education is important

GeneXpert® MTB/RIF Cepheid

- Closed, self-contained and automated platform
- rt-PCR-based amplification of MTb DNA: Molecular Beacons
  - *131 CFU/mL clinical LOD*
  - *Rapid TAT: 2-4 hours*



- Boehme NEJM 9/9/10: *1730 pulmonary TB suspects*
  - Sensitivity: 551/561 sm-pos (98.2%); 124/171 sm-neg (72.5%)
  - Specificity: 604/609 (99.2%)

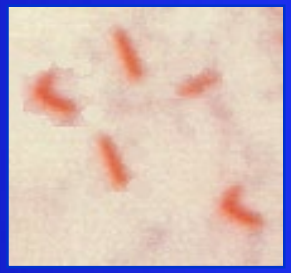
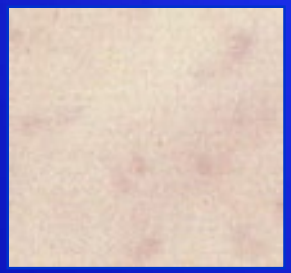
* Compares to 1,000 organisms/ml for Fluorochrome stain, 10,000/ml for Ziehl-Neelson stain; 10-100/ml for culture

Nucleic Acid Amplification Testing for Respiratory Specimens

- Becoming standard of care … *but do not test everyone*
  - Base testing on suspicion and communication with laboratory
    - Do test smear negatives when clinical suspicion of TB is high
- CDC* – "Test at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered (*i.e. Real suspects*) but has not yet been established, *and* for whom the test result would alter case management and TB control activities"

* MMWR (58:7-10), 2009

Xpert®: Application and Interpretation

Sputum	NAA Positive	NAA Negative*
	Dx of TB established; *cult. still required*	Consider clinical picture and repeat testing (likely NTM)
	Consider clinical picture and repeat testing	Start treatment and await culture result or clinical response **

** controlled for inhibitor*
** does not replace clinical judgment*

Respiratory Isolation?*

- Consider "Infectiousness": *The Source*
  - Correlates:
    - Coughing, hoarse? (Pulmonary or airways disease)
    - Sputum smear-positive; NAAT-positive (?)
    - … however, smear-negative may be infectious
- Consider risk to others if infectious: *The Setting*
  - If vulnerable (*e.g.,* inpatient unit or shelter, or …)
    - Risk of acquiring infection and
    - Possible consequences
- Most suspected cases are managed OPD
  - *Judgment!*

***Not a trivial thing**

Remove from Isolation?

- Airborne precautions can be discontinued when infectious TB disease is considered unlikely and either
  - another diagnosis is made that explains the clinical syndrome,
  - the patient has three negative AFB sputum smear results, or
  - the patient has a sputum specimen that has a negative NAA test result and two additional sputum specimens that are AFB-smear negative.*

or

  - GeneXpert ® neg x 1 (or 2) - *Good* Sputum samples!**

* CDC Expert Panel on NAAT, MMWR 11/2008
Campos, M, *et al* AJRCCM 178:300-305, 2008
** FDA, 2015

Nucleic Acid Amplification Testing and A.I.I. Decisions

- In February, 2015, the FDA approved a change in the package insert for the GeneXpert to reflect expanded claims related to A.I.I.*

  Specifically:

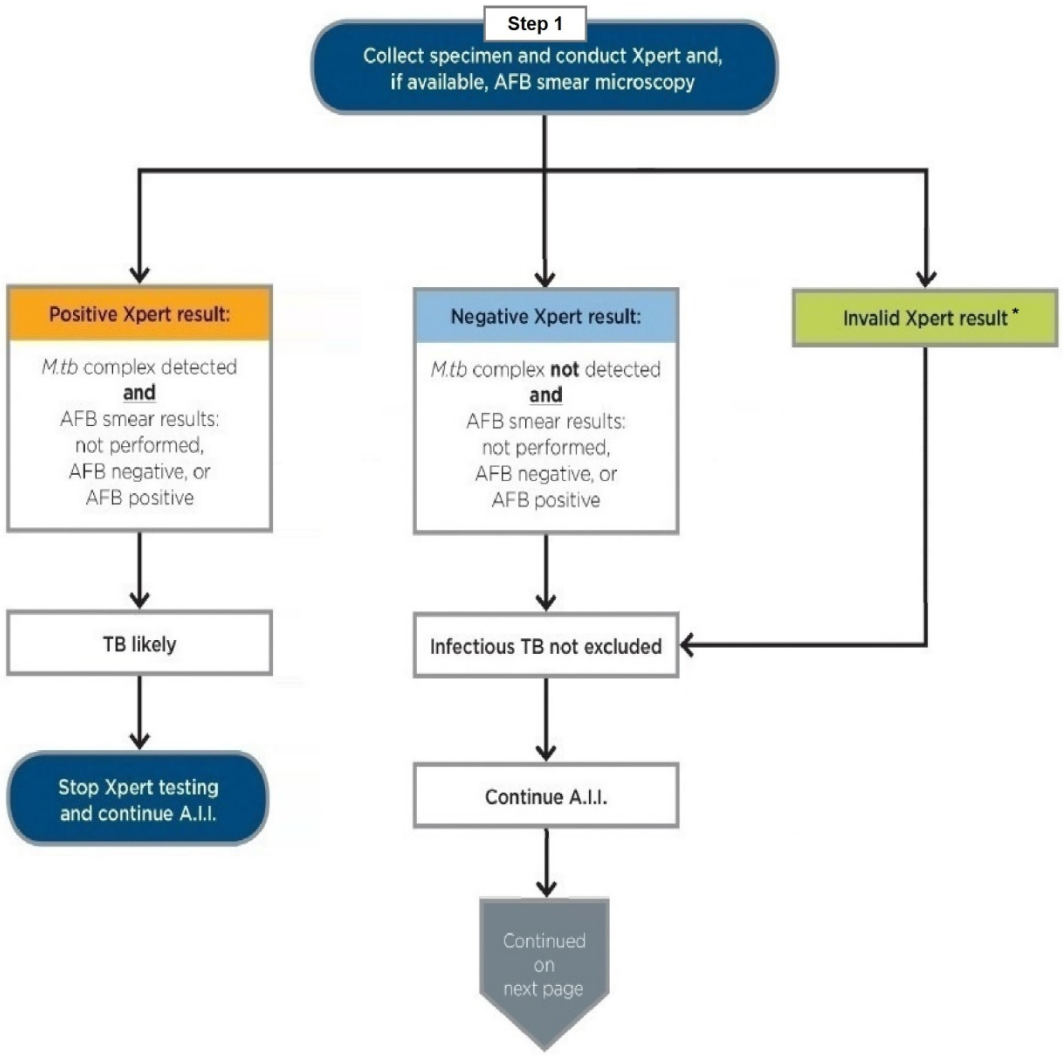
  … results using this assay on "either one or two sputum specimens" can be used as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision to discontinue AII for patients with suspected pulmonary TB.

*** CDC. MMWR, 2/26/2015**

Consensus statement on the use of **Cepheid Xpert MTB/RIF®** assay in making decisions to discontinue **airborne infection isolation** in healthcare settings

http://www.tbcontrollers.org/resources/airborne-infection-isolation/#.WQnZY4czXcs

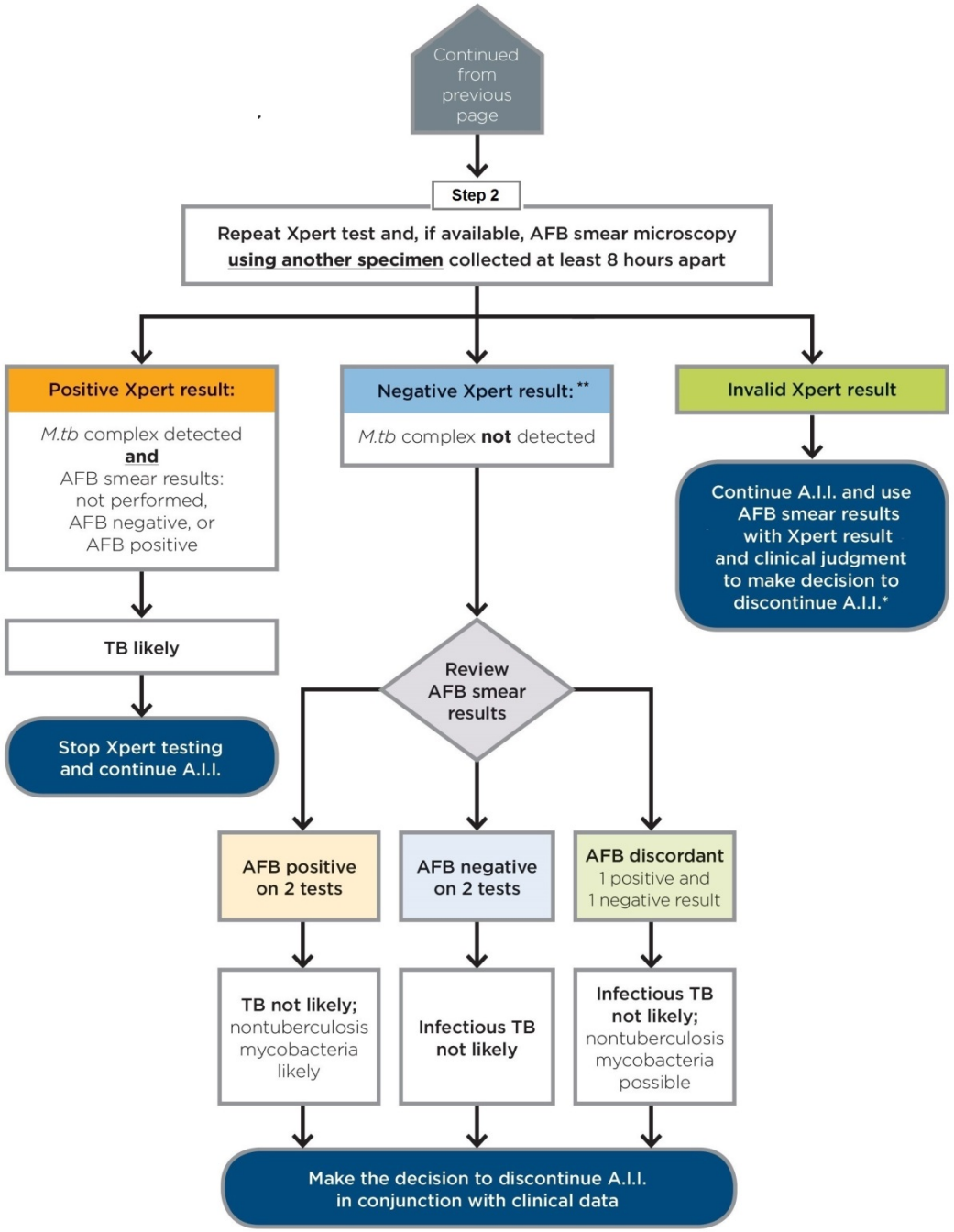
Sputum collection and processing



***M. tb*:** *Mycobacterium tuberculosis* **A.I.I.:** Airborne infection isolation

Note: * Most laboratories/protocols will automatically retest leftover sample if an initial Invalid (failed) result is obtained; in such cases, a reported Invalid result reflects repeat testing of a single specimen (see text).

Adapted from the ***GeneXpert in A.I.I. Discharge Decisions*** statement issued by the National TB Controllers Association (www.tbcontrollers.org) and the Association of Public Health Laboratories (www.aphl.org), 2016.



Note: ** If this result is Negative following an initial Invalid result in Step 1 and infectious TB still is clinically suspected, a repeat test (repeat Step 2) using a new specimen, if available, is recommended in order to improve sensitivity. Alternatively the clinician may use the single Negative Xpert result from Step 2 with smear results and clinical information to make the decision to discontinue or maintain A.I.I.

Drug Susceptibility Testing (DST)

- Mandatory on all new patients
  - 1st isolate from each site of disease; at 3mos if still cult pos.
  - Guides treatment decisions
    - Initially: for case and contacts
    - During treatment: determine reason for failure (emergence of resistance, absorption)
- Accurate and *timely* reporting of results is essential
  - Direct test; TAT 1 – 3 weeks
    - Smear positive cases; primary sample is tested
  - Indirect test; TAT 7+ weeks
    - Requires growth
    - Liquid media: 3 – 4 wk (can also do MIC for 1st line drugs)
- Direct agar proportion method: *Gold Standard*
    - Can test for multiple drugs, cheaply
    - Resolve agar/liquid media discrepancies

Susceptibility Testing of *M. tuberculosis Complex*

- Use rapid method (Broth-based)
  - Perform on all initial patient isolates
  - Test isolates from relapse or re-treatment cases; also if drug resistance suspected
- Test first-line drugs:
  - INH, RIF, EMB, PZA, SM*
- Test second-line drugs and higher conc. INH, EMB, SM:
  - If R to rifampin or any 2 primary drugs
- Second-Line DST
  - Technically difficult (*e.g.,* CS not recommended); not widely available
  - Cross-resistance
  - Methodologies not standardized – especially broth methods
  - Poor correlation with clinical response

NCCLS Standard M24-A, 2003

* M24A2 will drop SM, add AK and LQN

Discordance in DST

- Occurs between different labs, different methods, and within the same method
  - What do they mean?
  - Which is right?
- Many possible reasons…
  - Human
    - labeling, cross-contamination, …
  - Bacteria-specific
    - direct *vs* subculture, clumps, …
  - Methodology related
    - inoculation method, drug conc, media components, …

Laboratory Consortium (4 public health labs and CDC)

- Discordance INH (low level)
  - Within lab (BT vs. AP) – 2.4%
  - Interlab (BT) – 6.0%
  - Interlab (AP) – 12%
- Discordance EMB
  - Within lab (BT vs. AP) – 6.1%
  - Interlab (BT) – 20.2%
  - Interlab (AP) – 8.7%
- Discordance PZA
  - Interlab (BT) – 4%

B Metchock, CDC

Molecular DST

- Molecular assays for INH, RIF most common
  - Detect polymorphisms associated with drug resistance
  - Performed on clinical specimens or culture isolates
- In-house assays
  - Molecular beacons - RT-PCR
  - Whole genome sequencing
- Commercial assays
  - HAIN and INNO-LIPA line probe assays; Cepheid GeneXpert® Rif *
- Some Issues
  - Multiple mutations may confer resistance – not identified
  - Silent mutations – flagged but not really resistant

* Approved by FDA July, 2013

Molecular Detection of Drug Resistance (MDDR) Service at CDC: Rationale

- Clinical/Program: *available to providers*
  - Make rapid confirmation of MDR TB available
  - Make laboratory testing data available to clinicians about second-line drug resistance in cases of Rif-resistant or MDR TB
- Development
  - Continuous correlation of molecular (genotyping) results and DST (phenotypic) results
  - Addition of new drugs and alleles
- Research
  - Determination of mechanisms of resistance

B. Metchock, CDC

MDDR Service: Drugs and Genes for Panel

Drug	Gene(s)
RIF	*rpo*B
INH	*inh*A, *kat*G
KAN	*rrs*, *eis*
AMK	*rrs*
CPM	*rrs*, *tly*A
FQ	*gyrA*
PZA	*pnc*A
EMB	*emb*B

B. Metchock, CDC

CDC-TB-LAB

JAN 2014

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (NCHHSTP)
Division of Tuberculosis Elimination (DTBE) Laboratory Branch
Reference Laboratory

Report Status: Interim

CLIA ID # 11D2030855

Original Submitter:

Lemuel Shattuck Hospital
Clinical Laboratrory
170 Morton St
Jamaica Plain, MA 02130

Submitter to CDC:

William Hinton State Laboratory Institute
305 South Street
Jamaica Plain, MA 02130

Jasmine Guillet/ Lab

CDC Specimen ID: 3000
Specimen: *M. tuberculosis* complex isolate
Medium: MGIT Broth

Date Collected: 12/30/2014
Date Received: 01/16/2015
Date Reported: 01/21/2015

Patient: J *Submitter Specimen Identifiers:*

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel); Conventional Drug Susceptibility Test in progress.

Locus (region) examined*	Result	Interpretation (based on in-house evaluation of 550 clinical isolates)
rpoB (RRDR)	Mutation: TCG>TTG; Ser531Leu	Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)
inhA (promoter)	No mutation	Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are INH-R.)
katG (ser315 codon)	Mutation: AGC>ACC; Ser315Thr	
embB (Met306,Gly406)	Mutation: ATG>GTG; Met306Val	Ethambutol resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R).
pncA (promoter, coding region)	No mutation	Cannot rule out PZA resistance. (86% of PZA-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
gyrA (QRDR)	Mutation: GAC>TAC; Asp94Tyr	Ofloxacin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are OFL-R.)
rrs (1400 region)	No mutation	Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates: • 91% of AMK-R isolates have a mutation in the rrs locus; • 87% of KAN-R isolates have a mutation in either the rrs locus or the eis locus; • 55% of CAP-R isolates have a mutation in either the rrs locus or the tlyA locus.)
eis (promoter)	No mutation	
tlyA (entire ORF)	No mutation	

*A negative results (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.

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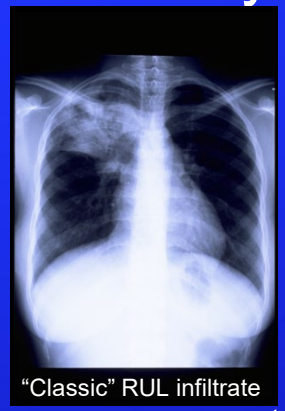
False-negative and False-positive results

- False-negative cultures
  - Improper collection/transport; overheating during transport/centrifugation; over-decontamination; media not inoculated correctly; clerical (labeling, transcribing, etc.)
- False-positive results
  - Another patient's specimen or isolate; splashes; transfer on tools or aerosols during processing; contaminated reagents; AFB in water; clerical
- Clues
  - Increased number of sm +/ cult – detected by lab
  - Single positive culture among many submitted on patient
  - Delayed, scanty growth; multiple positive cultures on rack
  - Clinician: … *No Way this is TB*…
- Resolution
  - Lab must have process in-place
  - Molecular testing often helpful

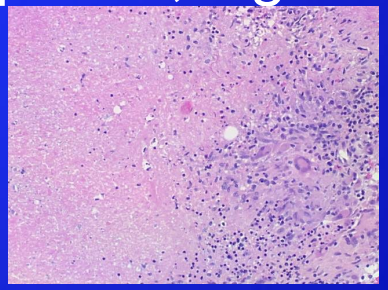
In the Absence of a Culture Isolate

- Clinical Diagnosis of TB
  - 7,087 (79.5%) of 8,916 US cases in 2019 were culture-confirmed
  - Accepted by most states, using specified criteria, including:
    - Evidence of TB infection (pos TST, IGRA)
    - Supporting clinical information: symptoms, signs
    - Supporting radiography



"Classic" RUL infiltrate

    - Supporting pathology



Caseating (cheese-like) granuloma

    - Clinical/radiographic improvement with therapy

The TB Laboratory: Challenges

- Declining case rates
  - Reduced competencies in low-incidence areas
  - *Level of service*: small labs "farming out" tests
- Shifting public health priorities
  - Reduced categorical funding for TB labs
  - Increased support for "crisis" responses (Anthrax, BT)
- Increasingly complex technologies: Rapid diagnosis
  - Capital investments
  - Training/educational needs of staff, users of services
- Demand for high-quality services
  - Budget issues
  - Public *vs* private
- Erosion of Public Health Laboratory's key roles

Effective TB Control depends on an integrated system that includes clinicians, laboratories and TB Controllers

APHL Task Force: *The Future of TB Laboratory Services*, 2003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