

# TB Diagnosis and Treatment



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CRITICAL CARE MEDICINE

# Disclosures

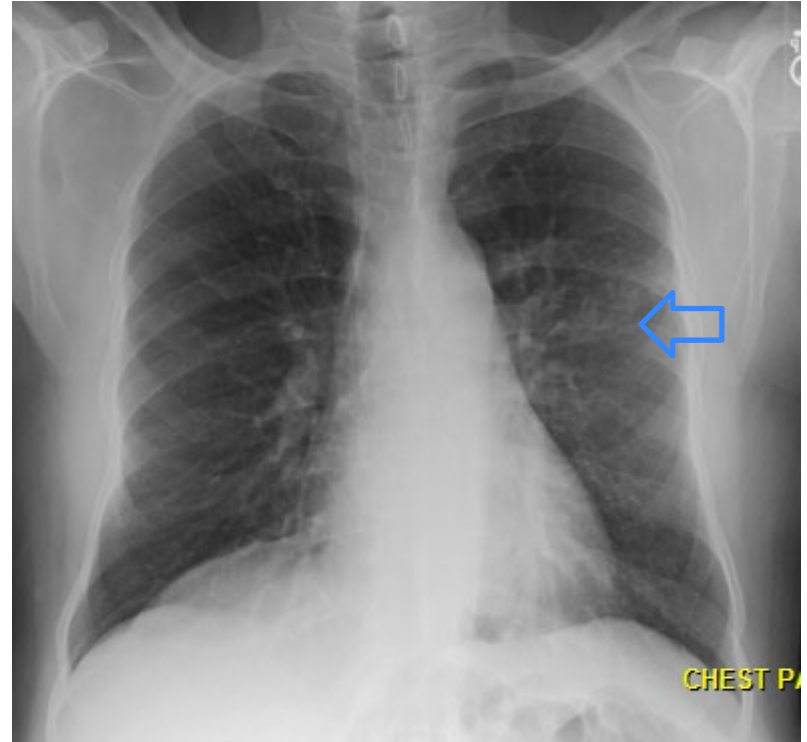
- Patent applications for technology related to LTBI and TB immunodiagnostics
- No relevant financial relationships
- No off-label/investigative use of a commercial product/device

# Learning Objectives

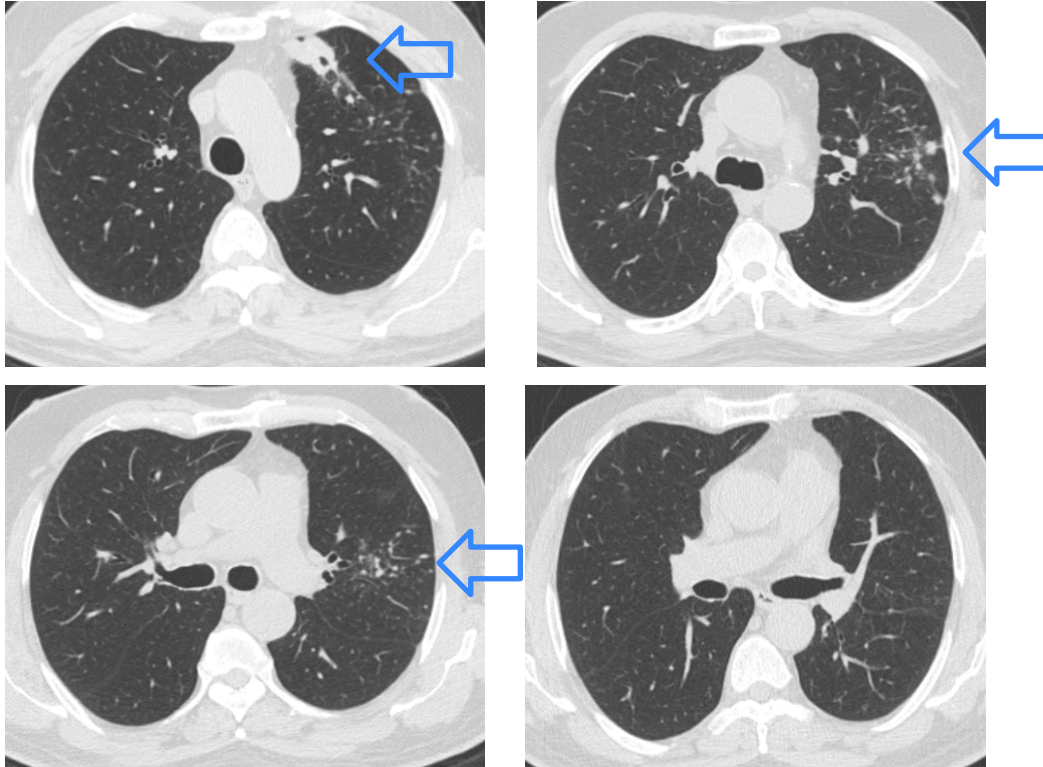
- To update about the status of the TB epidemics
- To describe the newest evolving concepts in Mtb infection
- To develop effective diagnostic strategies for TB in low-incidence TB settings
- To discuss treatment and management options for TB

# Case 1

- 65 yo man from Somalia
- Lived in Djibouti/UAE, immigrated to the US 5 years ago
- No prior TB, no TB exposures
- Asymptomatic
- Job screening: QFT=5.02 IU/mL
- 30 ppd Hx. Quit smoking 12 y ago
- PMH:
  - HTN, osteoarthritis
  - Type II DM (HgA1c=9.7)



# Asymptomatic 65 yo M QFT(+) & LUL opacities

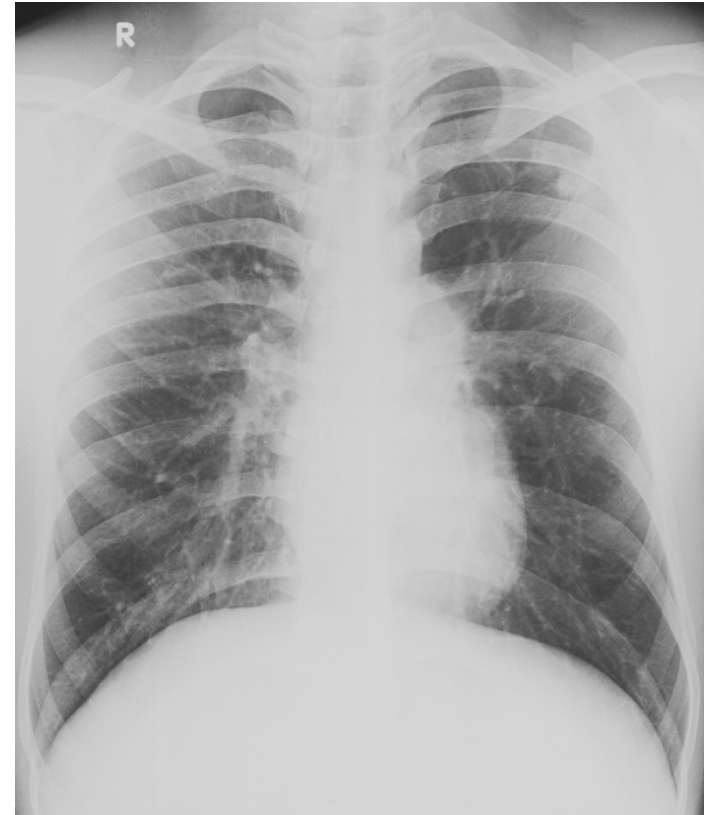


Diagnosis?

Approach?

## Case 2

- 45 yo non-smoker man from India
- Asymptomatic, abnormal CXR
- 2 out 3 sputum (+) cultures in 2014
- Treated with RIPE in India, but DST showed resistance to INH, ethambutol, and PZA, but sensitive to rifampin and streptomycin
- RIPE changed to Rifampin + INH + streptomycin x 4-5 mo
- He was offered IV antibiotics, but he declined



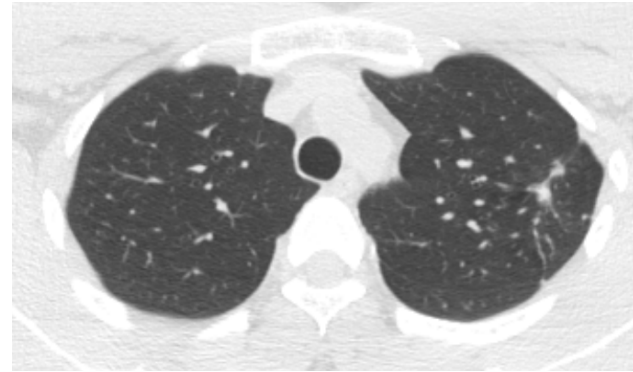
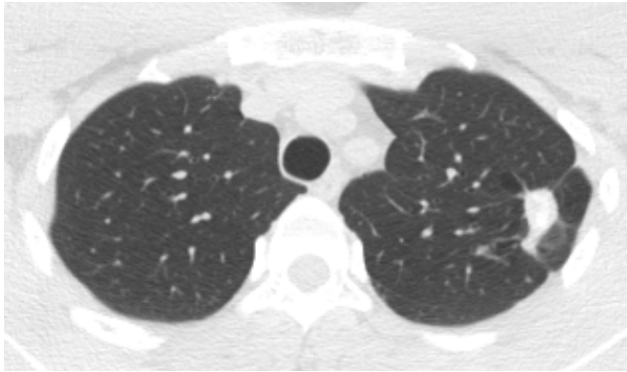
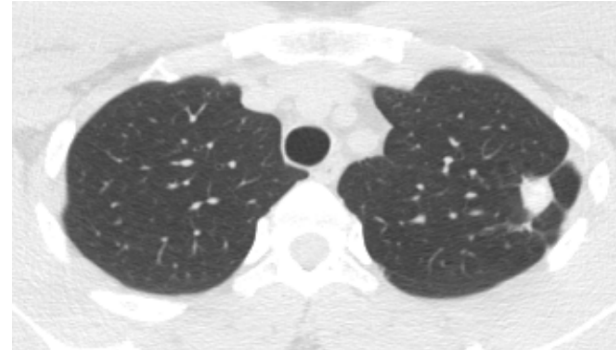
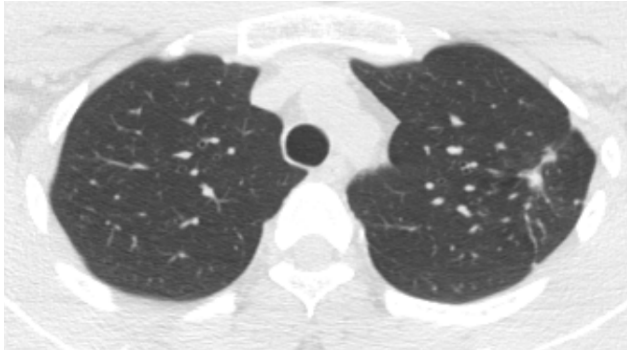
## ...2 years later

- Moved to USA to enter engineering school in 2016
  - QuantiFERON (+) 6/15/16
  - Abnormal CXR
- PMH:
  - No prior TB or TB contacts
  - No immunosuppression, no DM
  - Otherwise (-)
- Exam
  - Unrevealing
- Labs
  - Sputum x3 (-) AFB smear/cultures & MTB-PCR in January 2017
  - HIV(-)





# Chest CT



# Chest CT



1/2017

# 24 yo M asymptomatic, nodular lung lesion and prior treatment for DR-TB in India

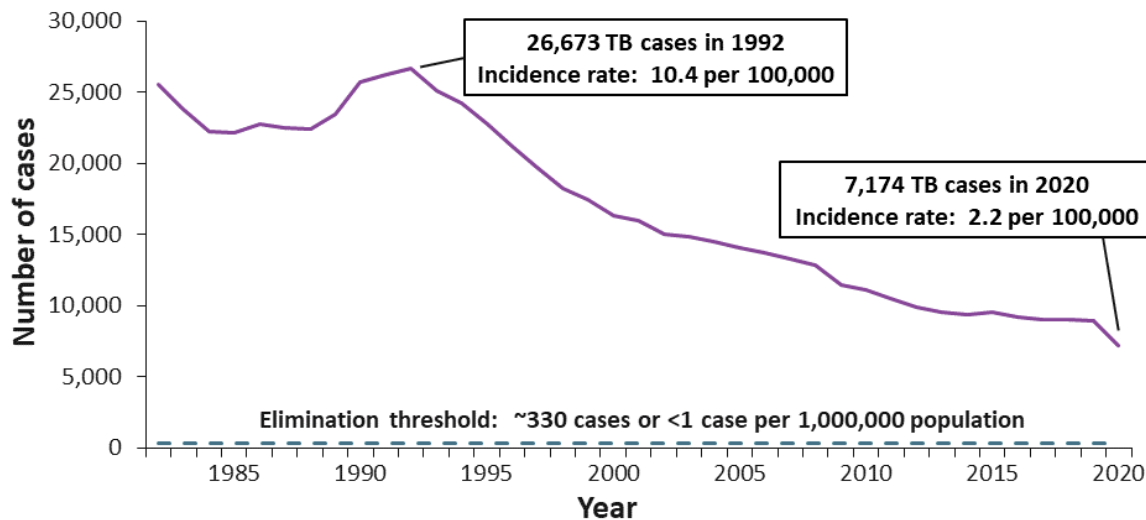
- Pt remains asymptomatic
- f/u Chest CT on 9/12/17: Unchanged
- BAL (LUL): Negative MTB-PCR and cultures
- Diagnosis?
- Approach?

# Global TB Epidemics

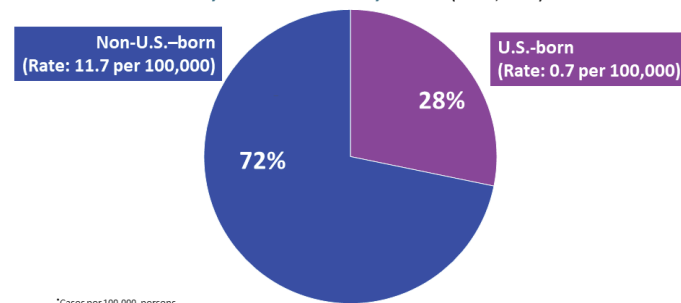
- 1.7 billion people infected
- 10 million new cases (↑ 41% undiagnosed after COVID)
- 60% in India, China, Indonesia, Nigeria, Pakistan, and South-Africa
- 480,000 new cases of multidrug-resistant (MDR-TB) in India, China, and Russia
- 1.3 million of TB deaths, including 214,000 with HIV
- BCG vaccination is ineffective for pulmonary TB



## Progress Towards TB Elimination, United States, 1982–2020

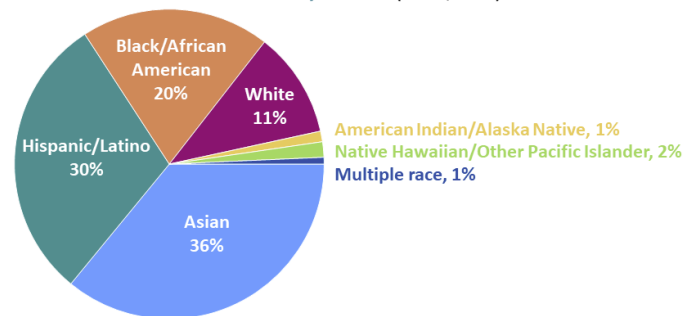


TB Incidence Rates\* and Percentages by Origin of Birth, United States, 2020 (N=7,145)

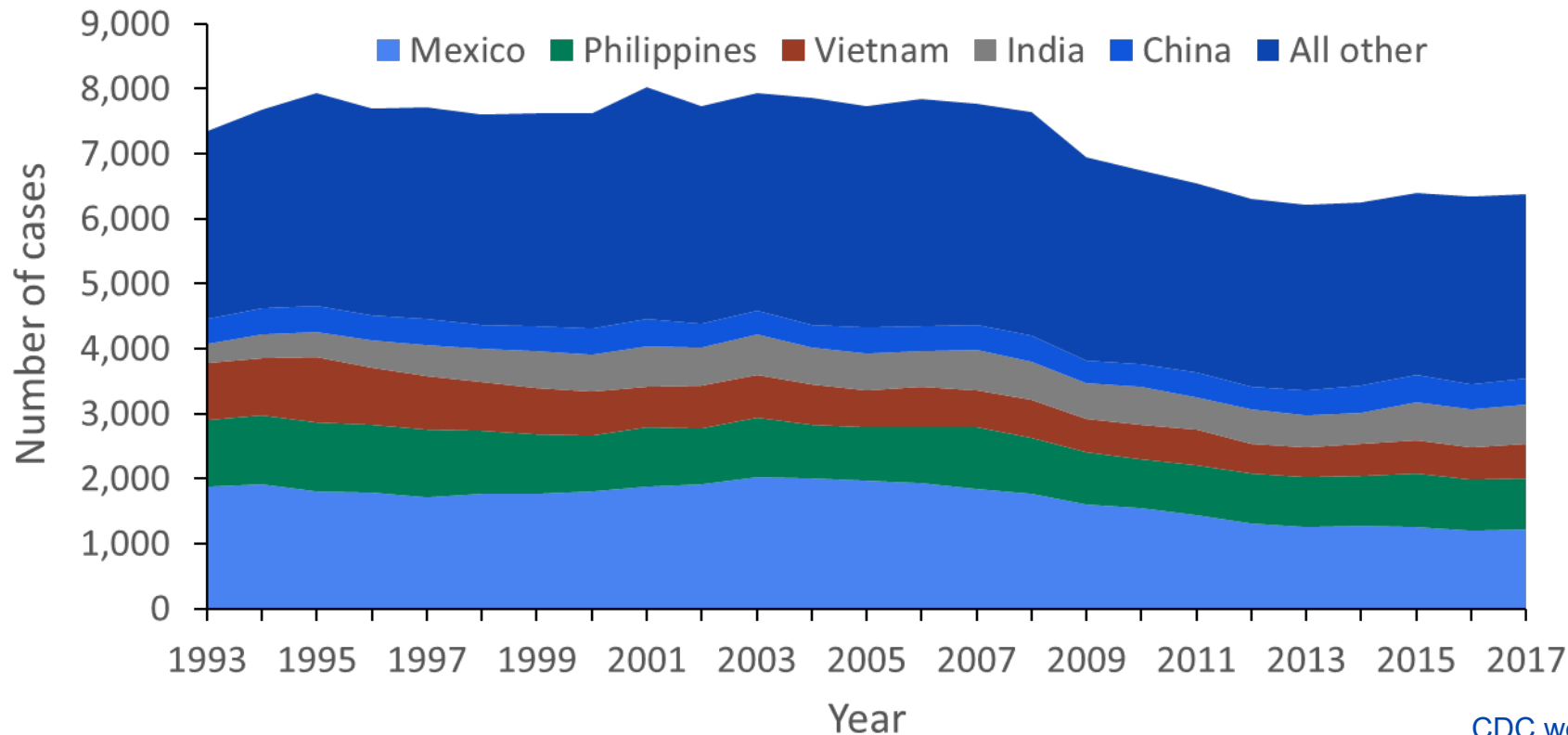


\*Cases per 100,000 persons

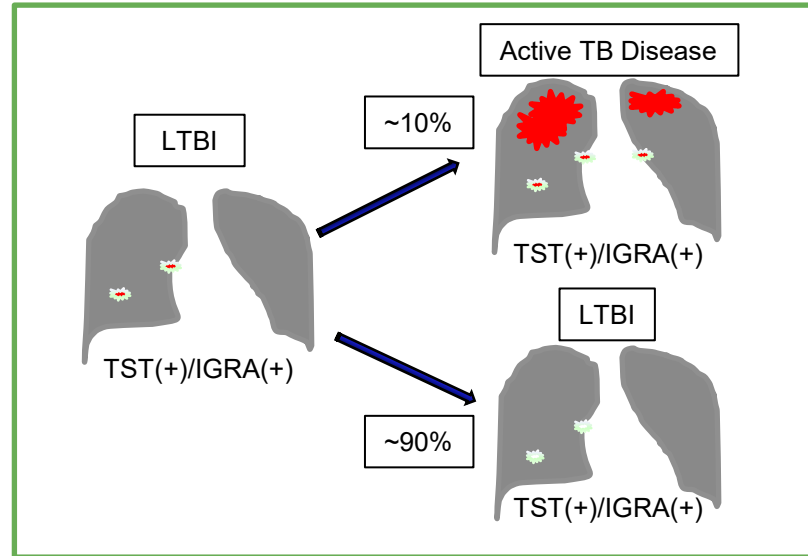
Percentage of TB Cases by Race/Ethnicity,\*  
United States, 2020 (N=7,174)<sup>†</sup>



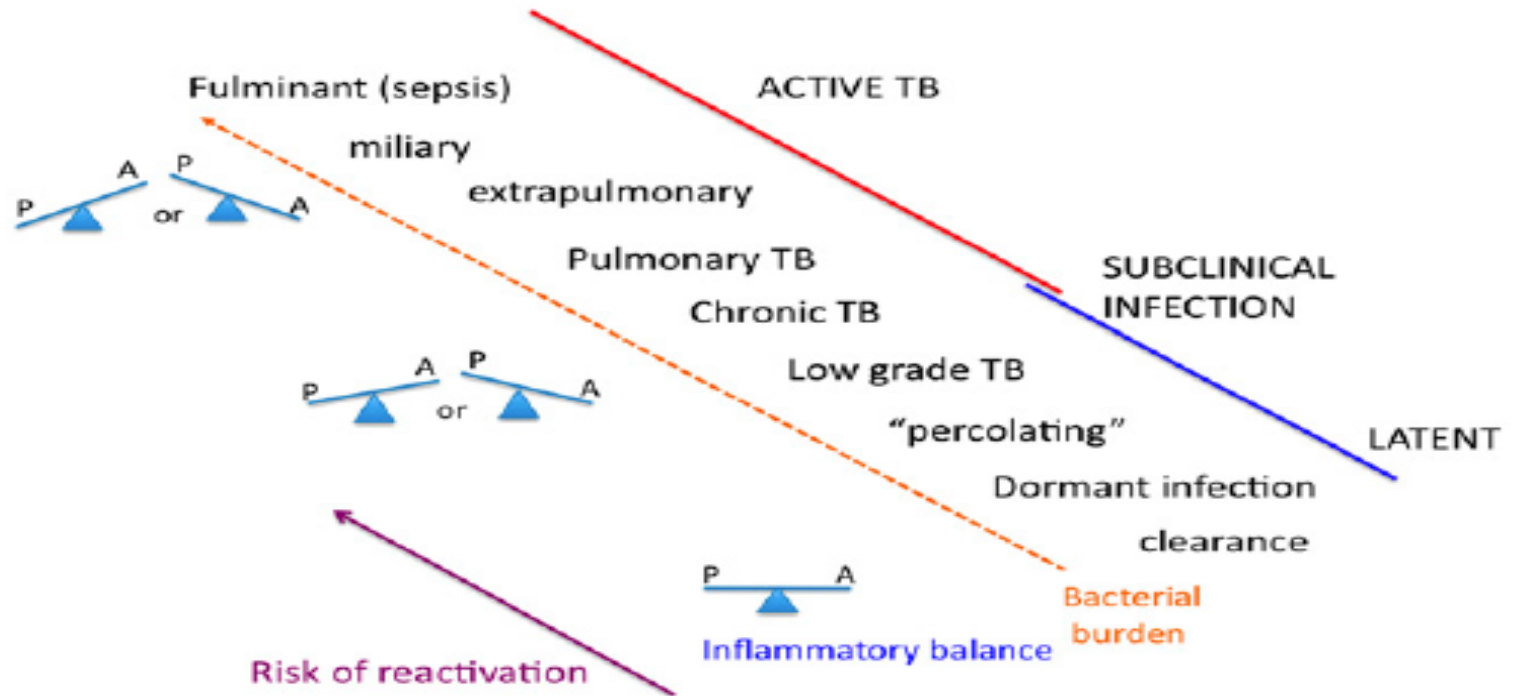
# Countries of Birth Among Non-U.S.–Born Persons Reported with TB, United States, 2017



# Natural course of LTBI and TB reactivation

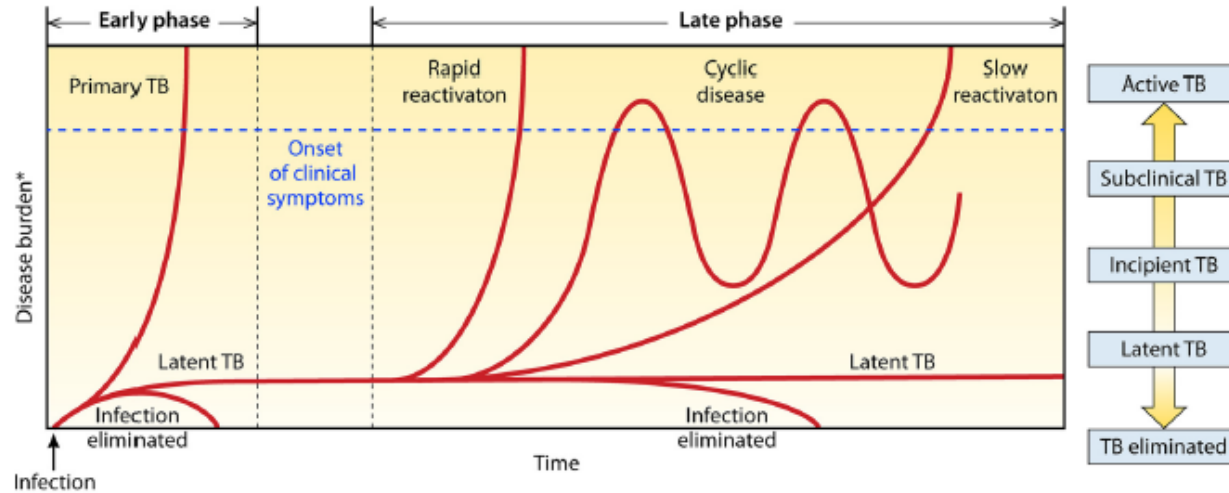


# Spectrum of TB infections





# Trajectory and fate of TB infection



Precipitating factors:

- HIV
- Uncontrolled diabetes
- TNFA and immunosuppressive drugs
- Malnutrition
- Vitamin D deficiency
- Viral infections

# Diagnostic Accuracy of LTBI Testing

Test	Sensitivity				Specificity			
	No. of Studies	Participants, No.	Pooled Estimate (95% CI)	$I^2$ , %	No. of Studies	Participants, No.	Pooled Estimate (95% CI) <sup>a</sup>	$I^2$ , %
TST induration threshold, mm								
5	8	803	0.79 (0.69-0.89)	94.6	4	47 <sup>40</sup>	0.30 (0.19-0.44)	NA
						2848 <sup>65</sup>	0.95 (0.94-0.96)	
						1750 <sup>76</sup>	0.94 (0.92-0.95)	
						551 <sup>77</sup>	0.97 (0.95-0.98)	
10	11	988	0.79 (0.71-0.87)	91.4	9 <sup>b</sup>	9651	0.97 (0.96-0.99)	94.3
15	7	740	0.52 (0.35-0.68)	95.5	12	9640	0.99 (0.98-0.99)	91.7
IGRA								
T-SPOT.TB	16 <sup>c</sup>	984	0.90 (0.87-0.93)	63.6	5	1810	0.95 (0.92-0.98)	79.1
QuantiFERON TB Gold	17	1073	0.77 (0.74-0.81)	55.3	4	699	0.98 (0.90-1.0) <sup>d</sup>	NA <sup>d</sup>
QuantiFERON TB Gold In-Tube	24	2321	0.80 (0.77-0.84)	74.3	4	2053	0.97 (0.94-0.99)	93.4

Both the TST and IGRA are moderately sensitive and highly specific within countries of low TB burden

# IGRAs

- IGRAs cannot differentiate LTBI vs. active TB
- Low sensitivity in immunosuppressed subjects
- TST+/IGRA- results in LTBI are probably not always related to false+ TST results<sup>1</sup>
- IGRA results variability over time, especially in HCWs<sup>2</sup>
- Low positive predictive value (<5%)<sup>3</sup>
- QFT-Plus vs. QFT-IT: Very similar diagnostic accuracy<sup>4</sup>

(1) Pollock NR, et al *Infect Control Hosp Epidemiol* 2008

(2) van Zyl-Smith RN, *Am J Respir Crit Care Med* 2009

(3) Pai M et al. *CMR* 2014

(4) Theel ES, et al. *J Clin Microbiol* 2018

# IGRA and TST for LTBI Diagnosis

- IGRA preferred, but TST is acceptable:
  - Children >5 y and adults at risk of TB infection
  - Low likelihood to return for TST reading (e.g. homeless, drug abusers)
  - Prior BCG vaccination (improve acceptance of LTBI Tx)
- TST preferred, but IGRA is acceptable:
  - Children < 2 y
- Either TST or IGRA may be used without preference
  - Recent TB contacts with active case (Repeat testing 8-10 wks after end of exposure if negative test)
  - Screening of HCW
- Both TST and IGRA can be considered:
  - High risk of TB infection and progression, and risk of poor outcome
    - HIV (and severe immunosuppression)
    - Children > 2 y and < 5 y

# Recent LTBI treatment trials and Guidelines

- Rifampin is not inferior to INH to prevent TB
- 4-mo Rifampin had a higher rate of treatment completion than 9-mo INH
- 4-mo Rifampin had a better safety profile than 9-mo INH
- In children-adolescences (<1y – 17y), similar rates of efficacy and safety, but 4-mo Rifampin had better adherence
- Evidence-based treatments for LTBI:
  - INH x 6-9 mo
  - Rifampin x 4 mo
  - Rifapentin + INH x 3 mo (self-administrated vs. DOT: similar completion rate)
  - Rifampin + INH x 3 mo

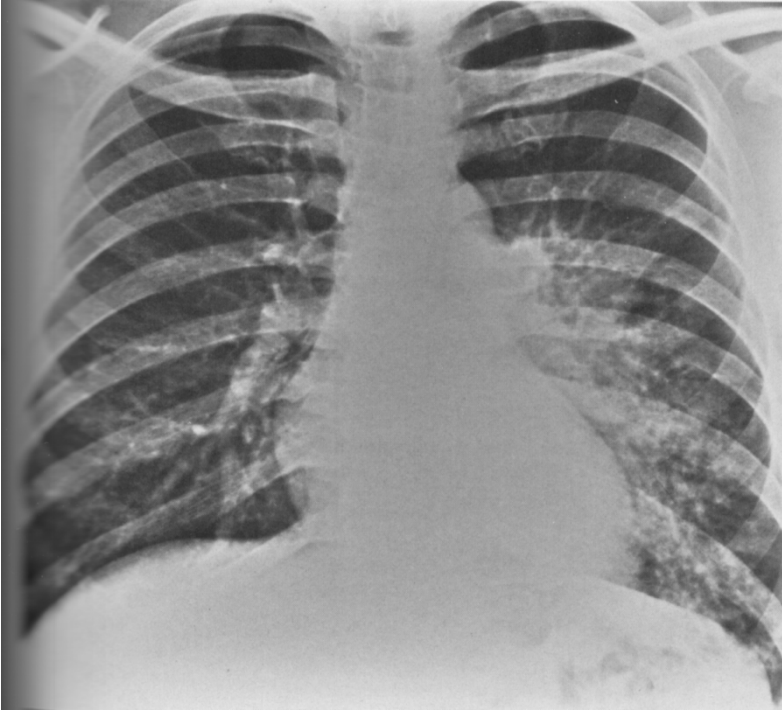
Menzies D et al. *N Engl J Med* 2018

Diallo T et al. *N Engl J Med* 2018

Hamada Y, et al. *Int J Tuberc Lung Dis* 2018

Sterling TR, et al. NTCA/CDC. *MMWR* 2020

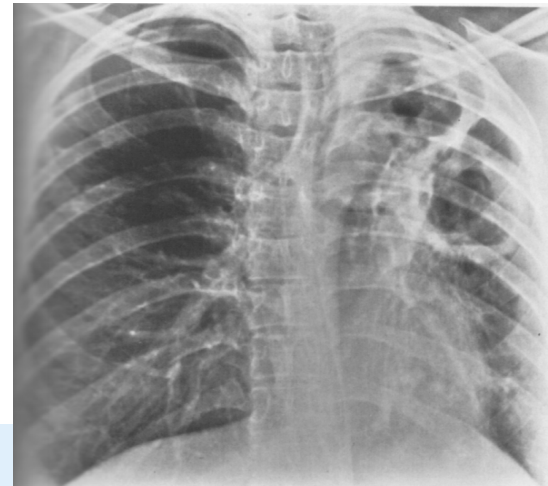
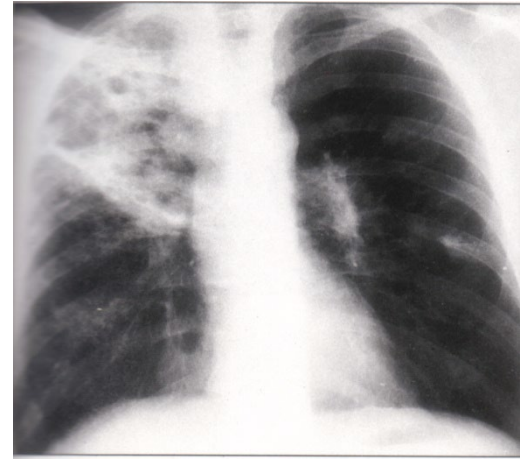
# Radiological Manifestations: Primary TB



Ghon's focus and Rhanke complex

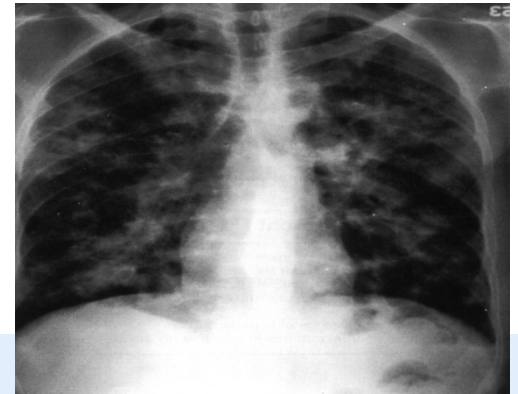
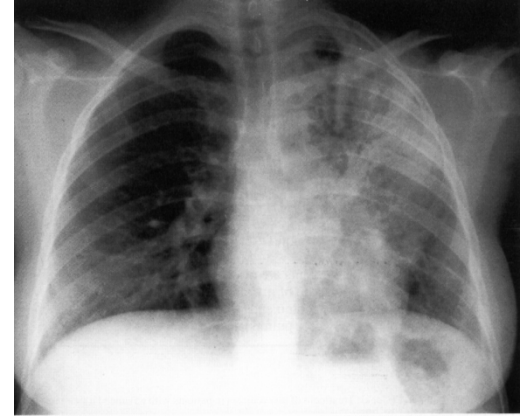
# Pulmonary TB (TB Reactivation)

- Variable time of progression
- Early **granulomatous** lesion → broncho-pneumonic infiltration
- Necrotic center ("**caseation**") may be discharged into the bronchi, → cavity
- Infected sputum can be spread to other lung segments → **bronchogenic spread**
- Chronic parenchymal lesions: **upper lobe** destruction, fibrosis, and over-distended emphysema
- **Hemoptysis**: erosion of blood vessels within the TB lesion



# TB in immunosuppressed patients

- HIV and TB:
  - Can present with **normal chest x-ray**, or with infiltrates in any lobes and any location
- No radiological appearance is pathognomonic of TB



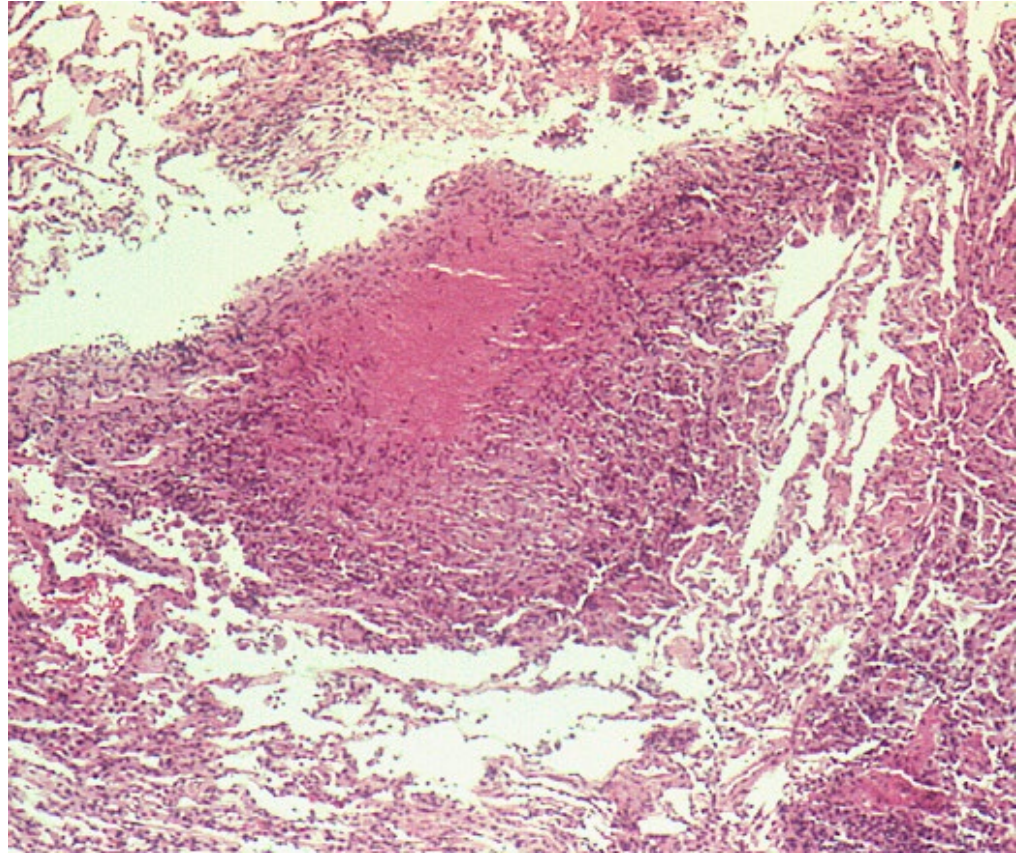


# TB Cases with Pulmonary Involvement by Chest X-Ray Result, Minnesota

<u>Chest X-Ray Result</u>	<u>Cases No. ( %)</u>
Normal	15 ( 2)
Abnormal, cavitory	135 (21)
Abnormal, non-cavitory (TB)	487 (75)
Abnormal, non-TB	8 ( 1)
Not done/unknown	2 (<1)
<hr/> Total	<hr/> 647 (100)

# Pathology

- Necrotizing granulomatous reaction is the main host's tissue immune response against TB
- Other granulomatous reactions: fungal, other mycobacterial infections, Sarcoidosis, foreign body reactions, etc.



# Current Diagnostic Approach

- Clinical-Radiological Assessment
- Three separate, including one morning sputum specimens:
  - Positive for AFB stain in 40-70% of active pulmonary TB cases
- If patient is unable to cough up a sample:
  - Sputum induction can be attempted with nebulized saline
- Other methods of obtaining specimens:
  - Bronchoscopy BAL
  - Gastric aspirate (e.g. infant cases)
- Mycobacterial cultures and rapid molecular testing

# Diagnostic approach: Laboratory

- Organ systems-directed:
  - Sputum, CSF, urine, pleural fluid, lymph nodes, etc
- Mycobacterial culture in MGIT or special media:
  - Important but not crucial to initiate TB treatment
  - Culture and DST to rule out drug resistance
  - The slow growing MTB
    - Liquid media 2-4 weeks
    - Solid media 4-6 weeks
- Molecular-based tests such as DNA-RNA hybridization and RT-PCR:
  - Can allow early detection and mycobacterial differentiation (MTB vs non-MTB)

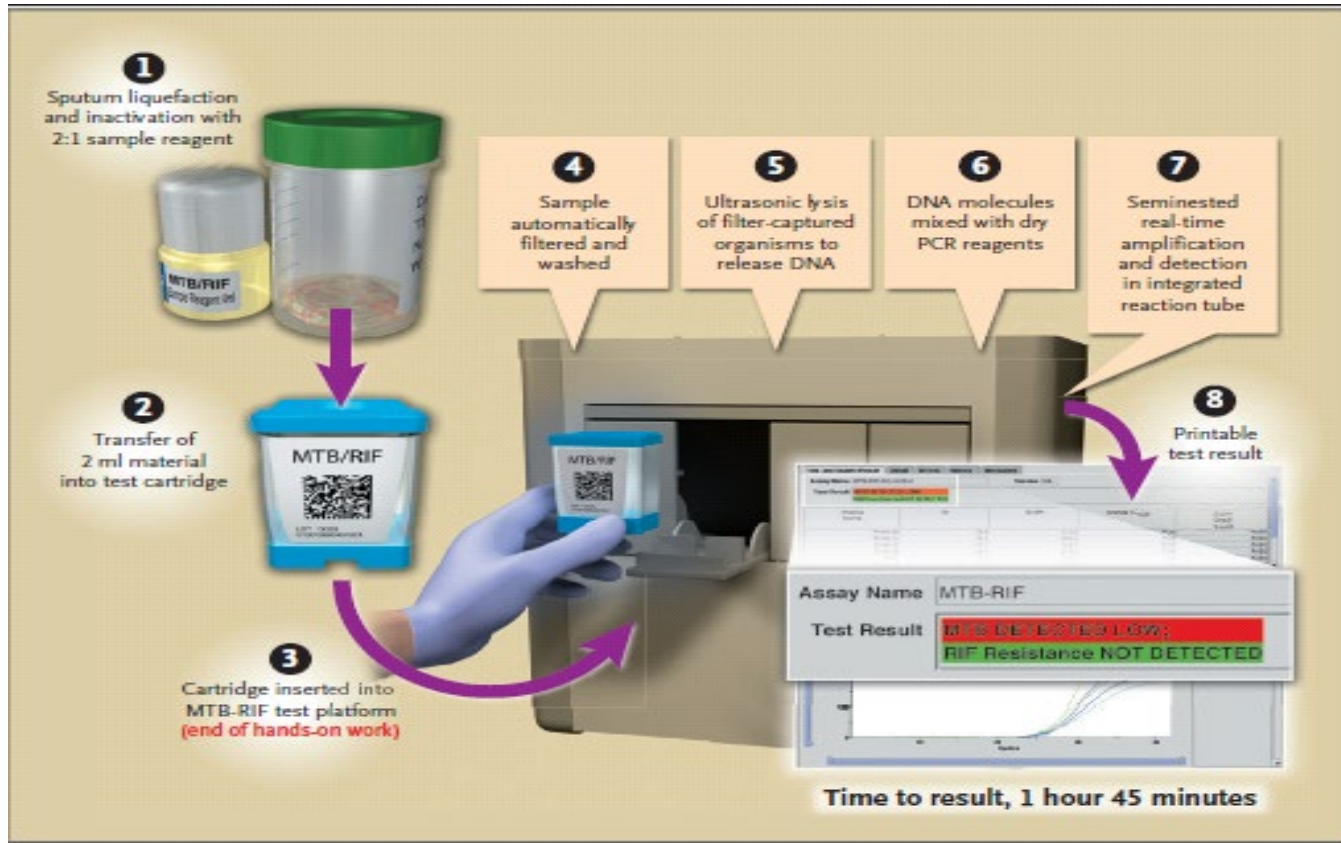
# TB Cases by Mycobacterial Culture Result, Minnesota

<u><b>Mycobacterial Culture</b></u>	<b>Cases</b>	
	<u><b>No.</b></u>	<u><b>( %)</b></u>
Positive	793	(75)
Negative	237	(22)
<u>Not done/unknown</u>	<u>34</u>	<u>( 3)</u>
Total	1,064	(100)

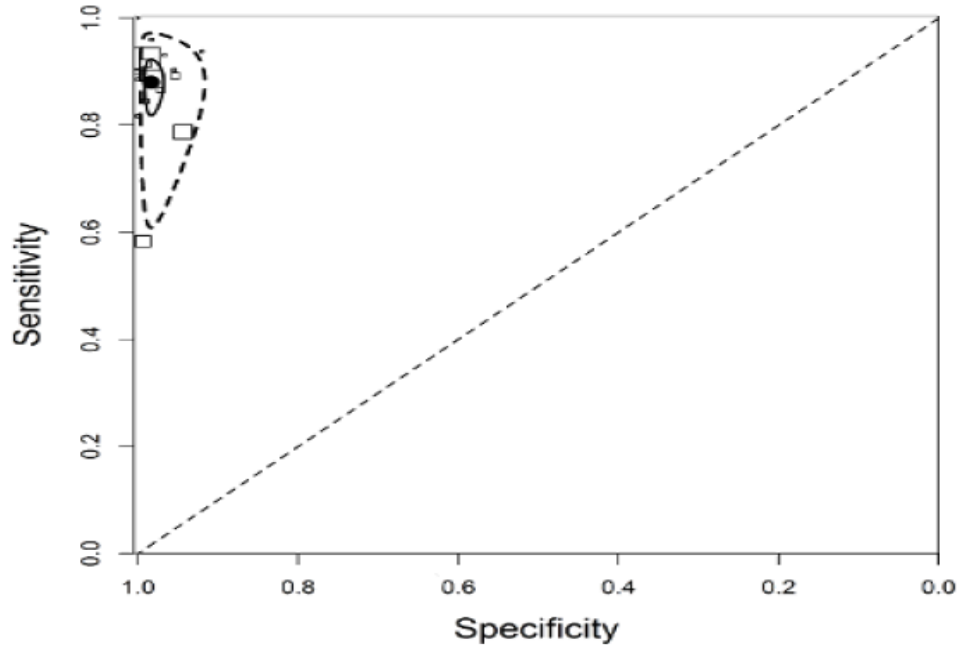
# Rapid Molecular Diagnostics for DR-TB

- Rifampin resistant as a marker of MDR-TB
- Accurate for rifampin and isoniazid resistance, less so for others
- ↓ Time results turnaround
- Combined with automatic liquid cultured system (molecular probes)
- Direct specimen testing, including point-of-care (POC) testing
  - Xpert MTB/RIF test and Xpert MTB/RIF Ultra
  - Molecular Beacons (MDDR-CDC)
  - New whole genome sequencing (TBNGS)
  - Others

# (Gene)Xpert MTB/RIF Test



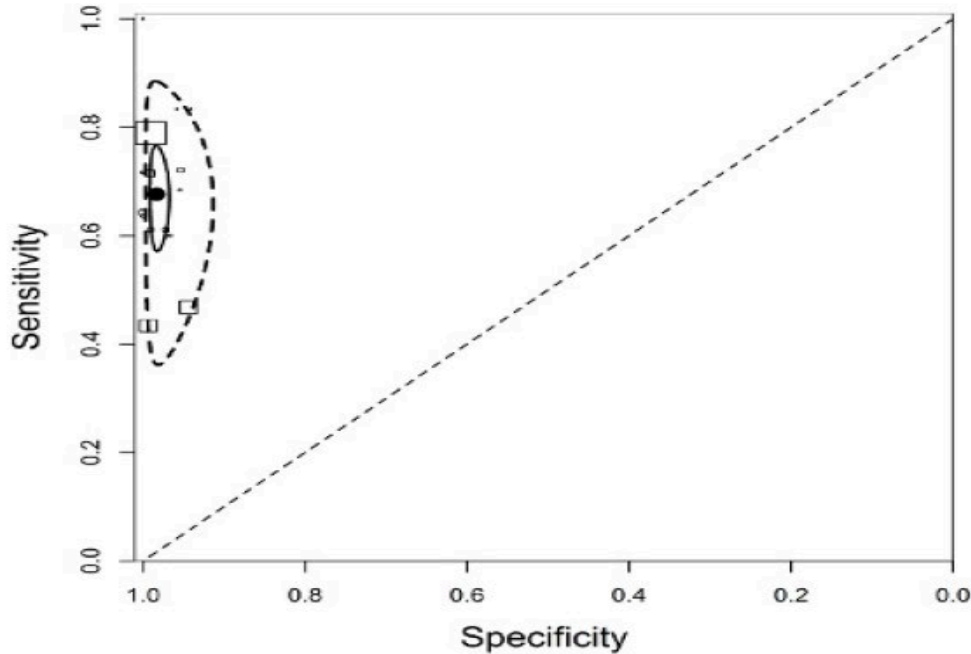
# Xpert Test: AFB(+) Smear



Sensitivity = 98% (95%CrI 97-99)  
Specificity = 100%



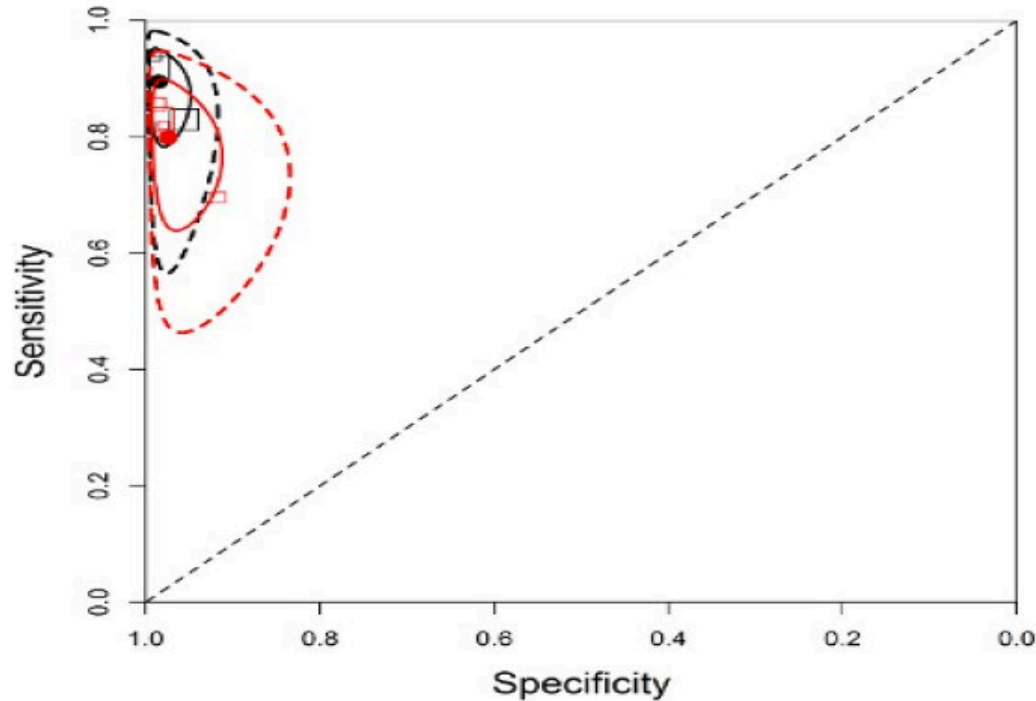
# Xpert Test: AFB(-) Smear



Sensitivity = 67% (95%CrI 60-74)  
Specificity = 99% (95%CrI 98-99)

In comparison to smear microscopy, ↑ TB detection by 23%

# Xpert Test: HIV(-) vs. HIV(+)



HIV(+)

Sensitivity = 79% (95%CrI 70-86)

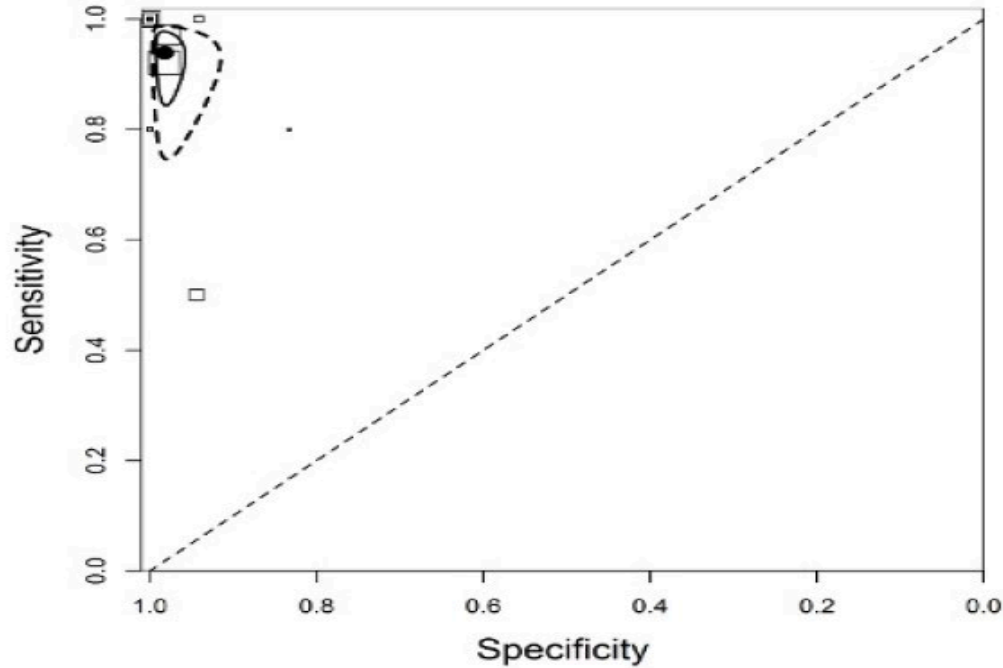
Specificity = 98% (95%CrI 96-99)

HIV(-)

Sensitivity = 86% (95%CrI 76-92)

Specificity = 99% (95%CrI 98-100)

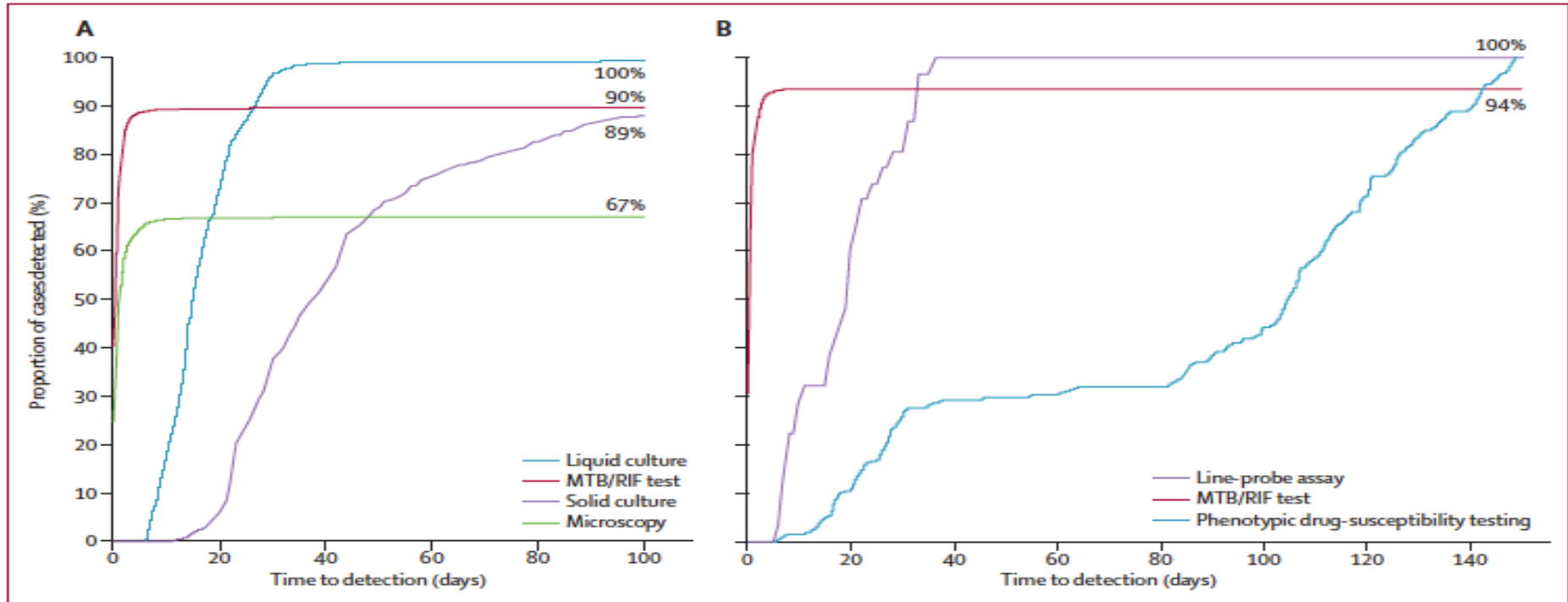
# Xpert: Rifampin Susceptibility



Sensitivity = 95% (95%CrI 90-97)  
Specificity = 98% (95%CrI 97-99)

# Xpert Test vs. Other Methods

## Time to Detection and Accuracy



# Xpert MTB/RIF for Extrapulmonary TB

- Meta-analysis (16,213 non-respiratory samples)<sup>3</sup>
- Pleural fluid
  - Sensitivity \* = 0.51 (0.40-0.63) Specificity \* = 0.99 (0.98-1.00)<sup>3</sup>
- Central nervous system fluid (CSF)
  - Sensitivity \*\* = 0.71 (0.61-0.80) Specificity \*\* = 0.98 (0.97-0.99) [Xpert]<sup>1</sup>
  - Sensitivity \* = 0.90 (0.55-1.0) Specificity \*\* = 0.90 (0.83-0.95) [Xpert Ultra – 1 study (N=129)]<sup>2</sup>
- Fine needle biopsy/aspiration of lymphadenopathy
  - Sensitivity \* = 0.96 (0.72-0.99) Specificity \* = 0.93 (0.70-0.99)<sup>1</sup>
- Gastric aspirate
  - Sensitivity \* = 0.78 (0.69-0.86) Specificity \* = 0.99 (0.98-0.99)<sup>1</sup>
- Urine
  - Sensitivity \* = 0.83 (0.70-0.91) Specificity \* = 0.99 (0.95-1.00)<sup>3</sup>
- Rifampin resistance
  - Sensitivity \* = 0.95 (0.90-0.98) Specificity \* = 0.987 (0.978-0.994)<sup>3</sup>

(\*) Pooled estimate (95% CI)

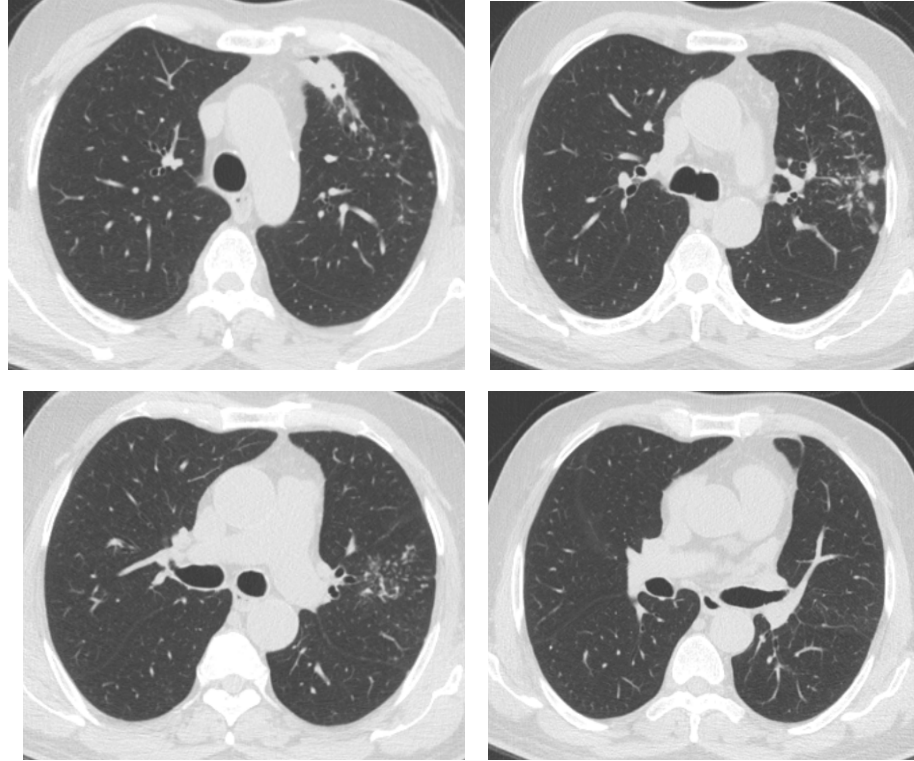
(\*\*) Media (IQR)

(1) Maynard-Smith L et al. *BMC Infect Dis* 2014

(2) Bahr NC, et al. *Int J TB Lung Dis* 2017

(3) Kohli M, et al. *Cochrane Rev* 2018

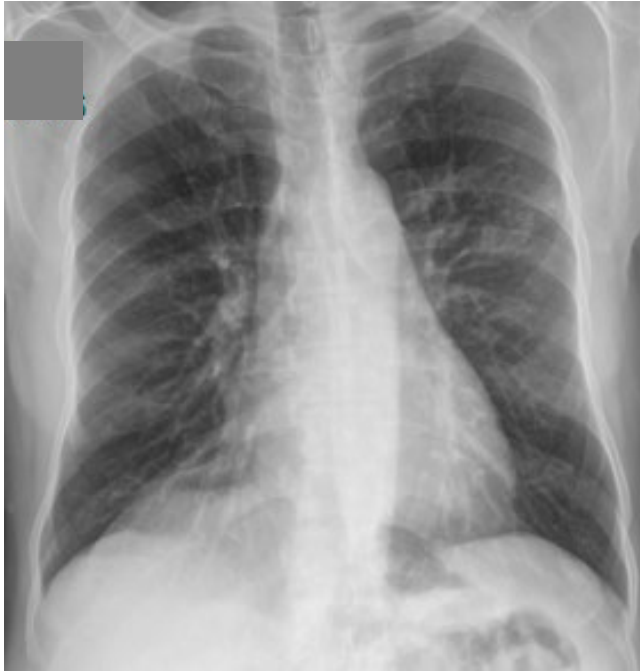
# Asymptomatic 65 yo Somali M IGRA(+) 2 mo after RIPE



2/2018

BAL = AFB(-)/MTB-PCR(-)/cultures(-)

# Asymptomatic 65 yo Somali M IGRA(+) 6 mo after RIPE

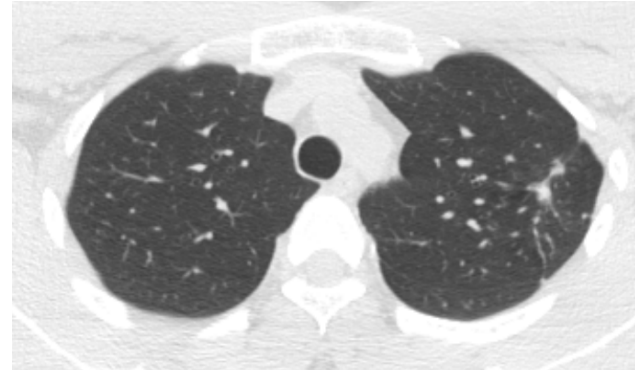
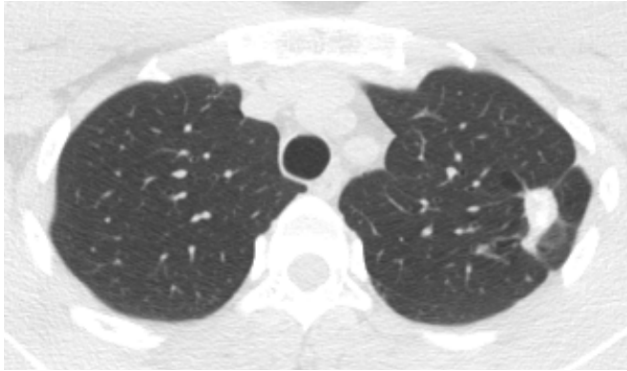
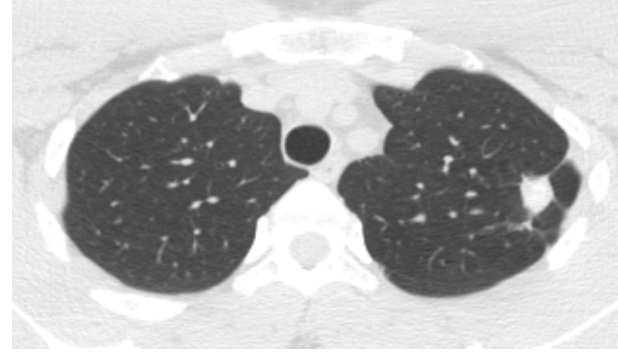
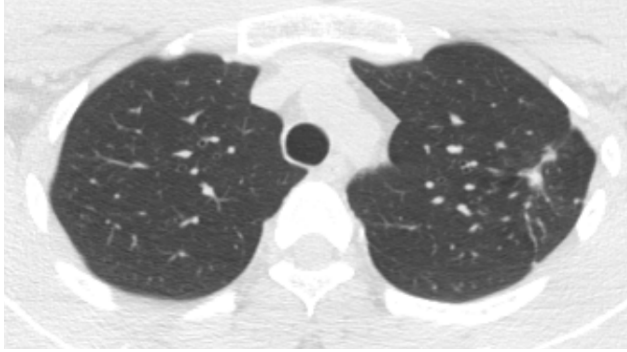


10/2017

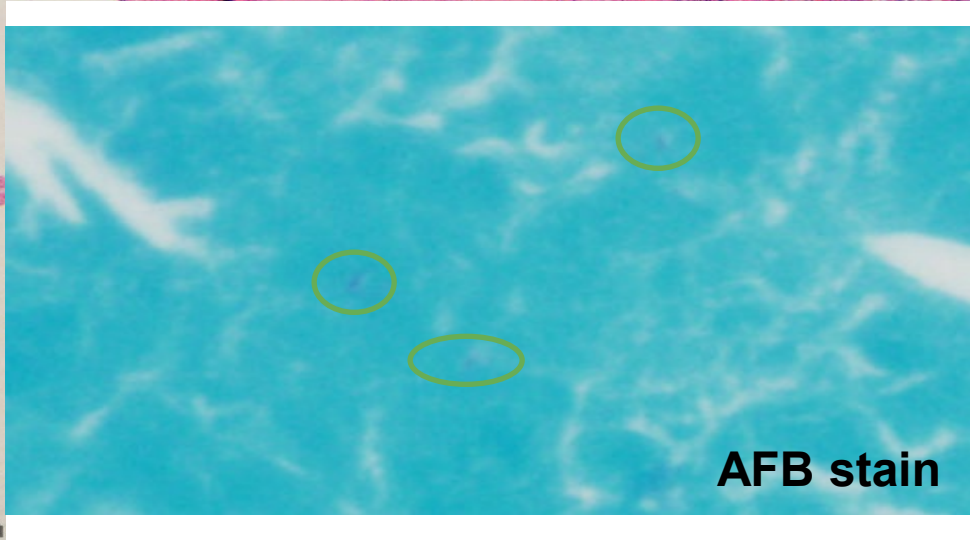
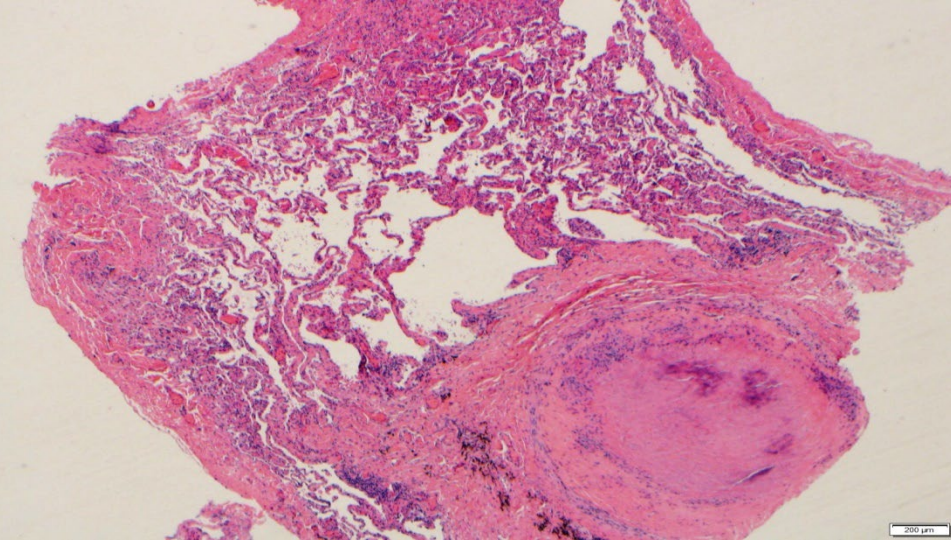
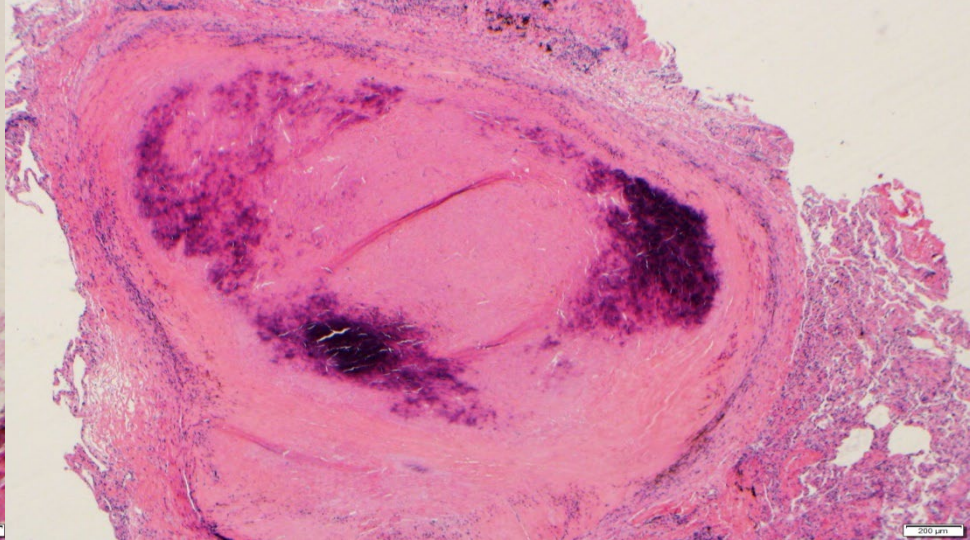
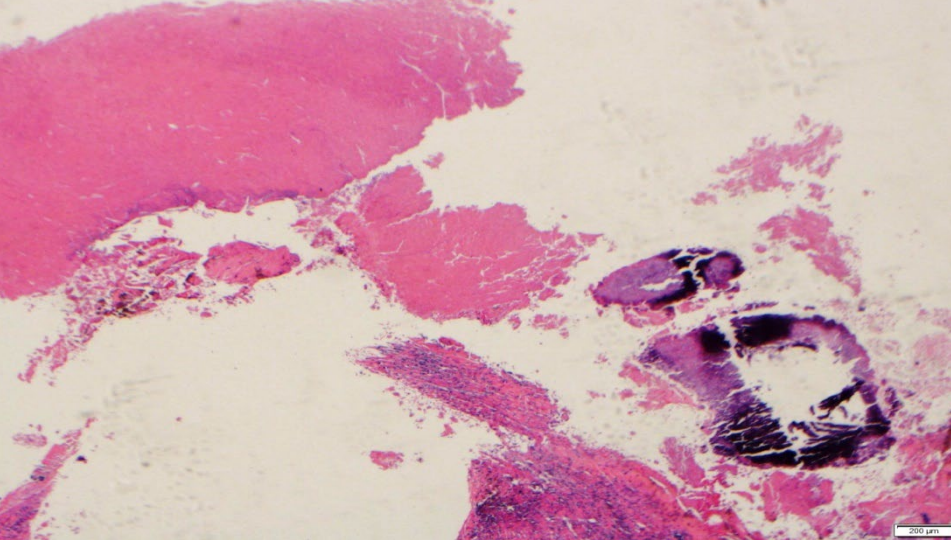


7/2018

# 45 yo M from India with prior TB treatment







# Molecular Detection of Drug Resistance (MDDR –CDC test)

Locus (Region) examined	Results	Interpretation (based on 550 clinical samples)
rpoB (RRDR)		Mutation in 97% of RIF-R isolates
inhA (promoter)		Mutation in 86% of INH-R isolates
katG (ser315thr codon)		
embB (met306, Gly406)		
pncA (promoter, coding region)		Mutation in 79% of EMB-R isolates
		Mutation in 86% of PZA-R isolates
gyrA (QRDR)		Mutation in 80% of FQ-R isolates
rrs (1400 region)		Mutation in 91% of AK-R isolates in the rrs locus; 87% of KAN-R isolates have a mutation in either rrs locus or eis locus; 55% of CAP-R isolates have mutation in either rrs locus or tlyA locus
eis (promoter)		
tlyA (entire ORF)		

# Post-Op CXR

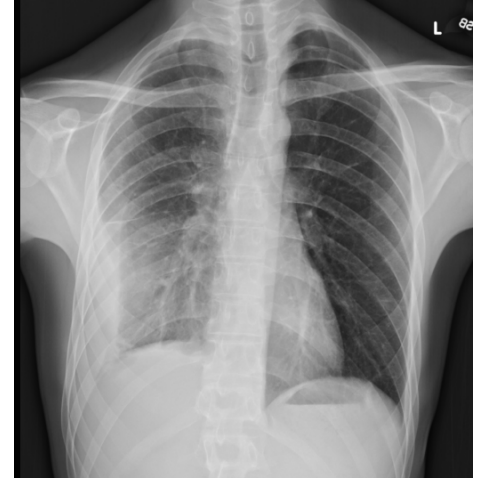


# Extrapulmonary TB



# Pleural TB

- Subpleural lesions → pleural cavity → tubercles effusion and empyema
- Pleural fluid
  - Exudate with lymphocyte predominance
  - Smear and culture is only positive in 1/3
- Needle biopsy of the pleura: granulomas in about 60% of cases
- Pleural tissue culture and granulomatous histology: diagnostic yield >70%
- Co-existing infiltrates? Check sputum/BAL



# Extrapulmonary TB

- **Renal TB**

- Insidious symptoms and often overlooked
- Microscopic painless hematuria with “sterile” pyuria
- Diagnosis: urine AFB culture and IV pyelography or CT appearance

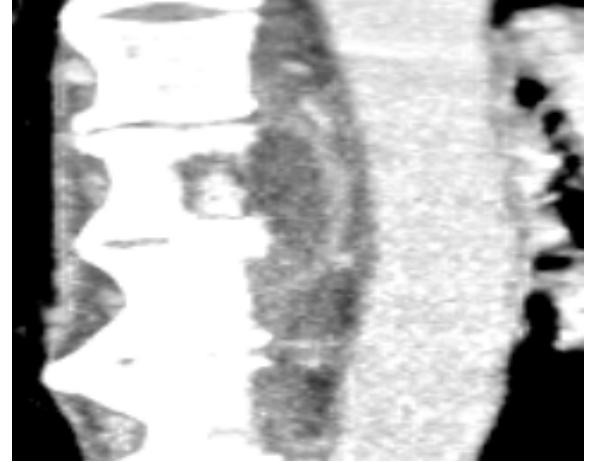
- **Genital TB**

- Epididymis, prostate, and seminal vesicles usually in men
- Fallopian tubes are usually in women
- Peritoneum can be contaminated and result in TB pelvic abscess and peritonitis

# Extrapulmonary TB

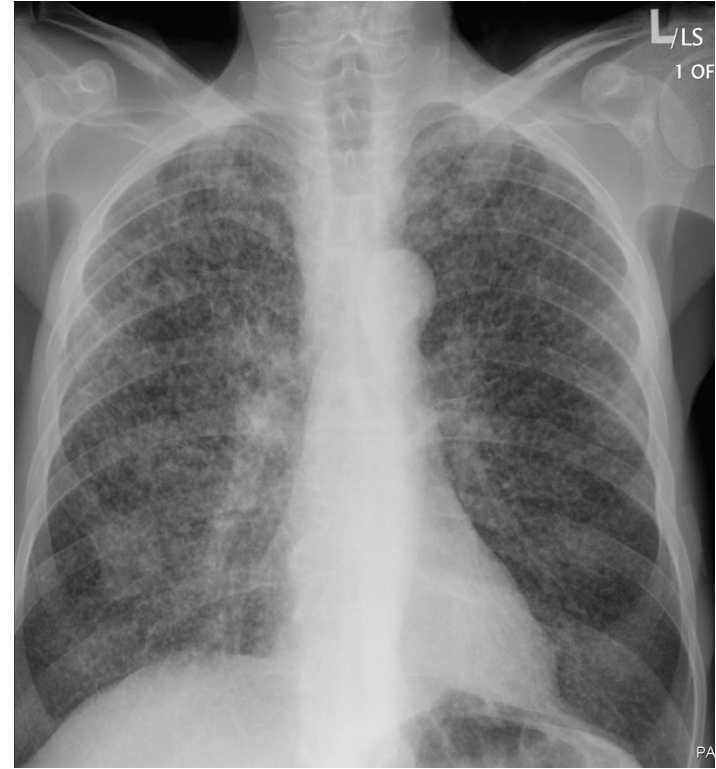
- **Skeletal and Spine TB**

- Vertebral hematogenous spread or by extension from a paraspinal draining from pleurisy and/or TB empyema
- Intervertebral disc early destruction, resulting in intervertebral disc narrowing
- Progressive destruction, fibrous ankylosis, and deformity (**Pott's disease**)
- Paraspinal TB abscess (“cold abscess”) can be the first sign of vertebral TB



# Miliary TB

- Insidious in onset: general malaise, fever, weight loss, and sweats
- Meningeal signs (common in Children)
- Retina may show choroidal tubercles
- Typical diffuse miliary pattern often appears in CXR
- Sputum smear for AFB are only positive in 30% of cases
- Liver and bone marrow can be involved in 30-60%



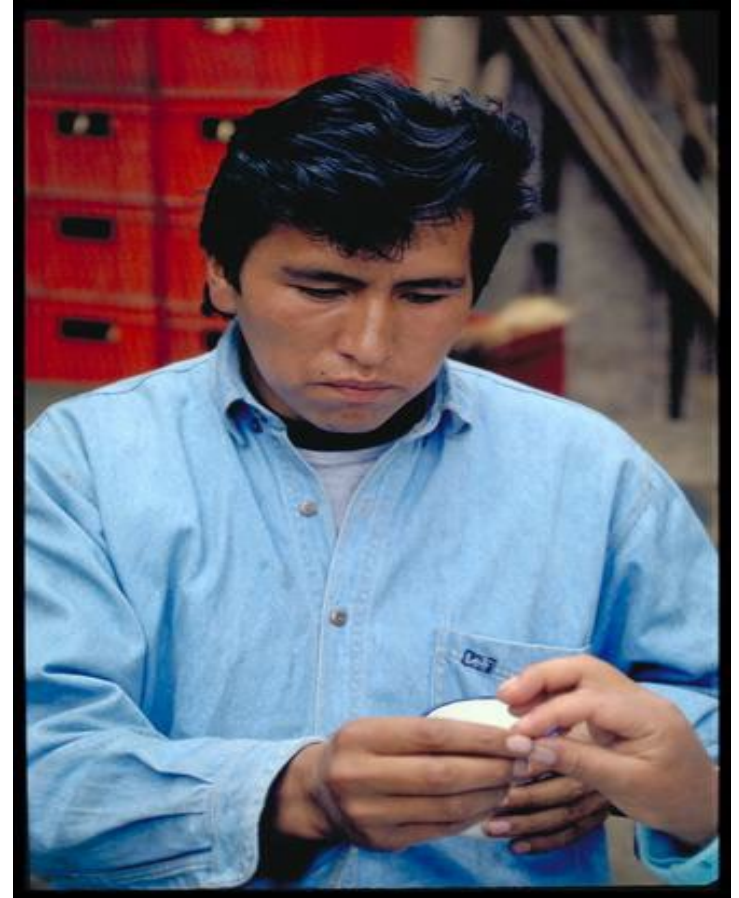


# Extrapulmonary TB Cases by Site of Disease\*, Minnesota

<u>Site of Disease</u>	<u>Cases No. ( %)</u>	
Lymphatic	284	(53)
Pleural	56	(11)
Peritoneal	45	( 8)
Bone/Joint	45	( 8)
Meningeal	18	( 3)
Genito-Urinary	13	( 2)
Miliary	5	( 1)
Other	66	(12)
<hr/> Total	<hr/> 532	<hr/> (100)

Includes TB cases with or without concurrent pulmonary disease

# Treatment for Active TB



# Treatment of Active TB

- Goal is to provide effective therapy in the shortest time
  - Usually 6-month treatment course
  - Patients with cavitary disease and +AFB culture at 2 mo require extension of Tx duration (6→9 mo)
- All treatment schemes:
  - Involve the use of multiple drugs because of spontaneous MTb genetic mutations
- Usual regimens:
  - INH, rifampin (RIF), pyrazinamide (PZA) and ethambutol (“RIPE”) in the initial 2 mo phase, and INH and RIF during the subsequent 4 mo have excellent cure rate (>95%) in compliant individuals

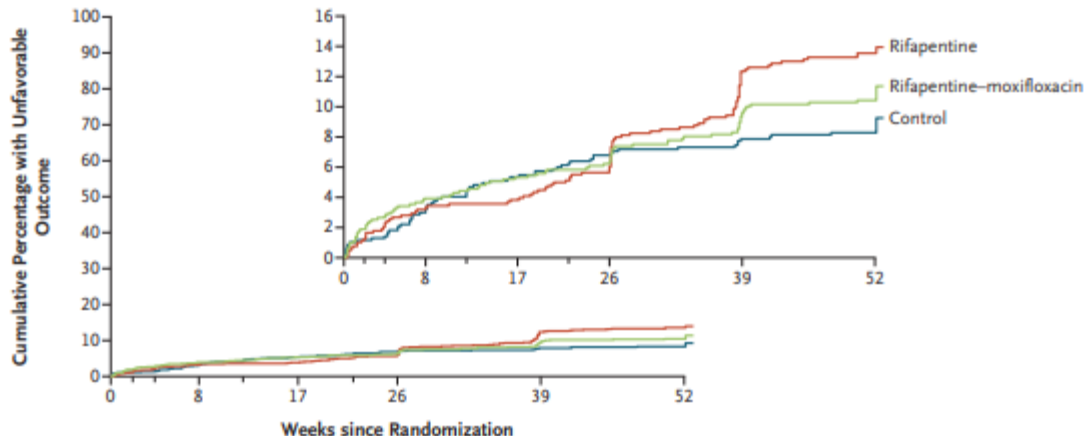
# New 4-mo treatment for active TB

The NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium



#### No. at Risk

Rifapentine	784	758	749	727	660	644
Rifapentine-moxifloxacin	791	758	747	728	686	668
Control	768	742	724	711	675	658

Centers for Disease Control and Prevention

**MMWR**

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Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

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Dorman SE, et al. NEJM 2021  
Carr W, et al. MMWR Feb 2022

# Treatment of Active TB

- Adherence to the entire treatment in TB is ensured by DOT, → successful treatment
- Development of multidrug-resistant TB (MDR-TB) is strongly associated with:
  - Poor adherence to treatment
  - Shorter duration and incomplete course of treatment
- Treatment duration for pan-susceptible MTB organisms in co-infected HIV patients on ART is usually the same as for non-HIV patients
  - ART should be initiated within the first 2 weeks of TB treatment in patients with  $CD4 \leq 50$ , and 8-12 weeks for  $CD4 \geq 50$  cells/uL
- Treatment duration for extrapulmonary = pulmonary TB (except for CNS and joint/bone/skeletal TB)

# Treatment of Active TB: side effects

- **Hepatitis:** Mostly with the use of INH, RIF and PZA
  - LFT monitor prior to start treatment in adults and high-risk individuals
  - Clinical monitoring is acceptable after baseline LFTs
- **Optic neuritis:** Mostly associated with ethambutol
  - Monitor visual fields
  - Blurred vision and decreases green and red color vision are early symptoms of optic neuritis
- **Ototoxicity and renal toxicity:** Streptomycin and other aminoglycosides
  - Monitor baseline and follow-up hearing and renal function

# Take Home Points

- Not only think about TB ...but also subclinical TB infection and MDR-TB!
- TST and IGRA testing for LTBI have limitations
- Diagnosis and management of LTBI and TB can be challenging
- Suspected drug-resistant TB requires reliable rapid testing
- New 4-mo treatment regimen and 6-mo RIPE are effective options for active pulmonary TB
- Consult with your local/regional TB experts for challenging cases



# Questions?

