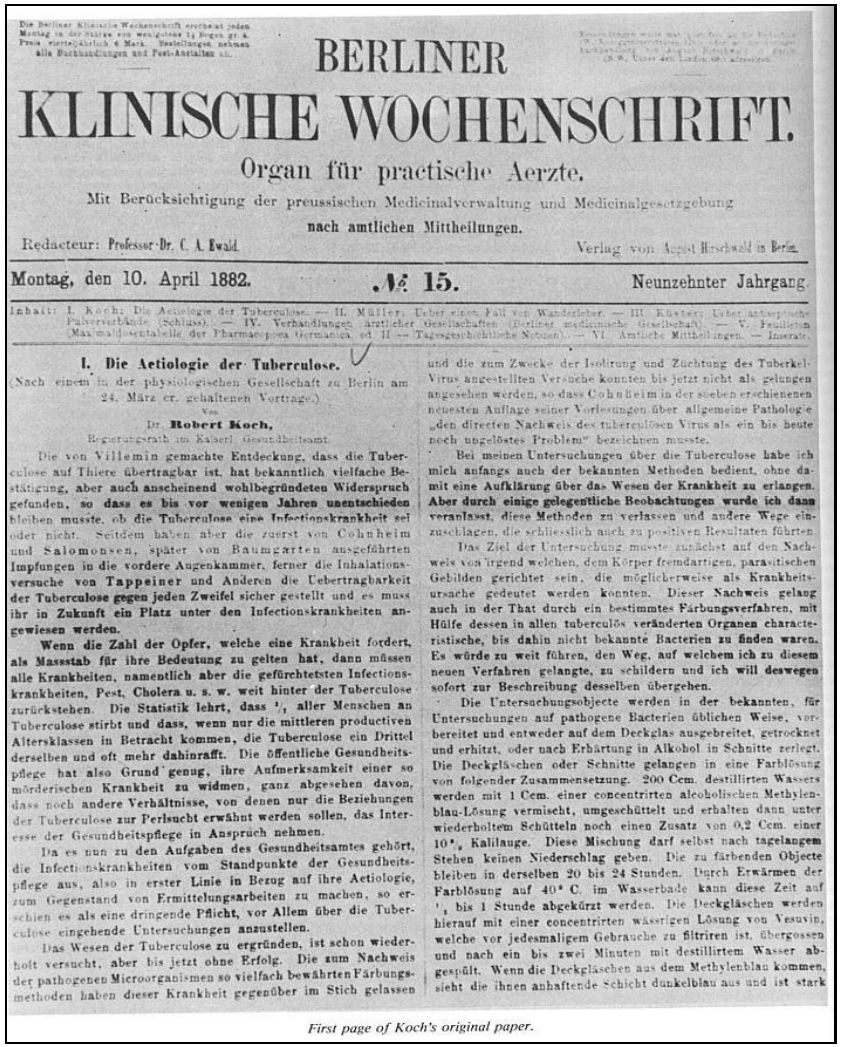
SURPRISE!!!!!!!!!!!!
It's (WORLD) TB (DAY) !!!!!!!!

David Ashkin, M.D., F.C.C.P.
Medical Director, Co-PI, Southeastern National Tuberculosis Center
Medical Director, Florida Bureau of TB and Refugee Health
Clinical Assistant Professor, Department of Medicine, University of Florida College of Medicine
Assistant Professor, Div. of Pulmonary and Critical Medicine, University of Miami

World TB Day 2018



BERLINER

KLINISCHE WOCHENSCHRIFT.

Organ für practische Aerzte.

Mit Berücksichtigung der preussischen Medicinalverwaltung und Medicinalgesetzgebung nach amtlichen Mittheilungen.

Redacteur: Professor Dr. C. A. Ewald. Verlag von August Hirschwald in Berlin.

Montag, den 10. April 1882. № 15. Neunzehnter Jahrgang.

Inhalt: I. Koch: Die Aetiologie der Tuberculose. — II. Müller: Ueber einen Fall von Wanderleber. — III. Küstner: Ueber antiseptische Pulververbände (Schluss). — IV. Verhandlungen ärztlicher Gesellschaften (Berliner medicinische Gesellschaft). — V. Feuilleton (Maximaldosentabelle der Pharmacopoea Germanica, ed. II. — Tagesgeschichtliche Notizen). — VI. Amtliche Mittheilungen. — Inserate.

I. Die Aetiologie der Tuberculose.

(Nach einem in der physiologischen Gesellschaft zu Berlin am 24. März cr. gehaltenen Vortrage.)

Von

Dr. **Robert Koch,**

Regierungsrath im Kaiserl. Gesundheitsamt.

Die von Villemin gemachte Entdeckung, dass die Tuberculose auf Thiere übertragbar ist, hat bekanntlich vielfache Bestätigung, aber auch anscheinend wohlbegründeten Widerspruch gefunden, so dass es bis vor wenigen Jahren unentschieden bleiben musste, ob die Tuberculose eine Infectionskrankheit sei oder nicht. Seitdem haben aber die zuerst von Cohnheim und Salomonsen, später von Baumgarten ausgeführten Impfungen in die vordere Augenkammer, ferner die Inhalationsversuche von Tappeiner und Anderen die Uebertragbarkeit der Tuberculose gegen jeden Zweifel sicher gestellt und es muss ihr in Zukunft ein Platz unter den Infectionskrankheiten angewiesen werden.

Wenn die Zahl der Opfer, welche eine Krankheit fordert, als Massstab für ihre Bedeutung zu gelten hat, dann müssen alle Krankheiten, namentlich aber die gefürchtetsten Infectionskrankheiten, Pest, Cholera u. s. w. weit hinter der Tuberculose zurückstehen. Die Statistik lehrt, dass $^1/_7$ aller Menschen an Tuberculose stirbt und dass, wenn nur die mittleren productiven Altersklassen in Betracht kommen, die Tuberculose ein Drittel derselben und oft mehr dahinrafft. Die öffentliche Gesundheitspflege hat also Grund genug, ihre Aufmerksamkeit einer so mörderischen Krankheit zu widmen, ganz abgesehen davon, dass noch andere Verhältnisse, von denen nur die Beziehungen der Tuberculose zur Perlsucht erwähnt werden sollen, das Interesse der Gesundheitspflege in Anspruch nehmen.

Da es nun zu den Aufgaben des Gesundheitsamtes gehört, die Infectionskrankheiten vom Standpunkte der Gesundheitspflege aus, also in erster Linie in Bezug auf ihre Aetiologie, zum Gegenstand von Ermittelungsarbeiten zu machen, so erschien es als eine dringende Pflicht, vor Allem über die Tuberculose eingehende Untersuchungen anzustellen.

Das Wesen der Tuberculose zu ergründen, ist schon wiederholt versucht, aber bis jetzt ohne Erfolg. Die zum Nachweis der pathogenen Microorganismen so vielfach bewährten Färbungsmethoden haben dieser Krankheit gegenüber im Stich gelassen und die zum Zwecke der Isolirung und Züchtung des Tuberkel-Virus angestellten Versuche konnten bis jetzt nicht als gelungen angesehen werden, so dass Cohnheim in der soeben erschienenen neuesten Auflage seiner Vorlesungen über allgemeine Pathologie „den directen Nachweis des tuberculösen Virus als ein bis heute noch ungelöstes Problem" bezeichnen musste.

Bei meinen Untersuchungen über die Tuberculose habe ich mich anfangs auch der bekannten Methoden bedient, ohne damit eine Aufklärung über das Wesen der Krankheit zu erlangen. Aber durch einige gelegentliche Beobachtungen wurde ich dann veranlasst, diese Methoden zu verlassen und andere Wege einzuschlagen, die schliesslich auch zu positiven Resultaten führten.

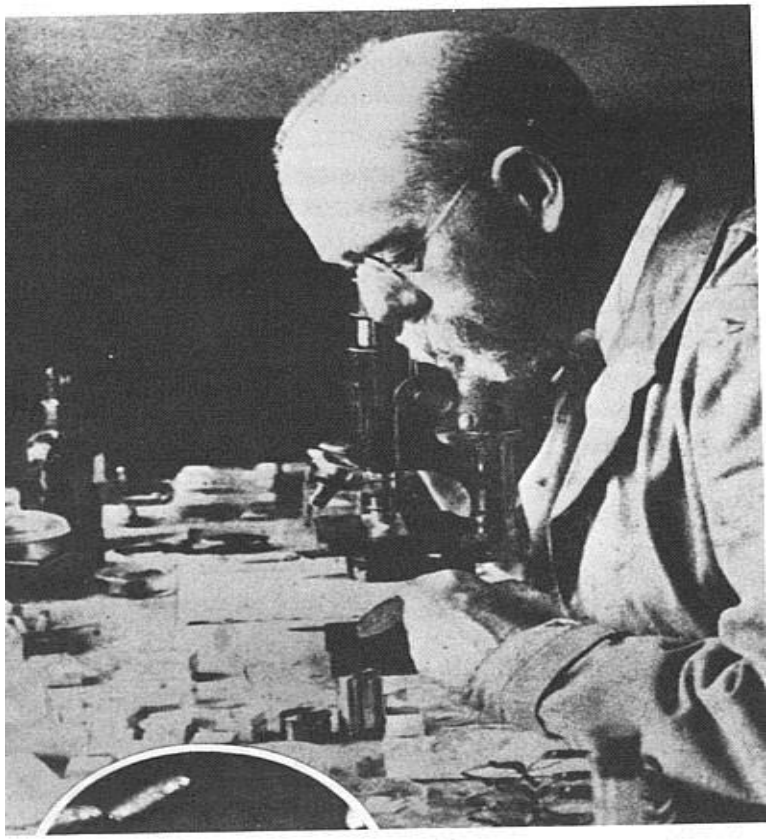
Das Ziel der Untersuchung musste zunächst auf den Nachweis von irgend welchen, dem Körper fremdartigen, parasitischen Gebilden gerichtet sein, die möglicherweise als Krankheitsursache gedeutet werden konnten. Dieser Nachweis gelang auch in der That durch ein bestimmtes Färbungsverfahren, mit Hülfe dessen in allen tuberculös veränderten Organen characteristische, bis dahin nicht bekannte Bacterien zu finden waren. Es würde zu weit führen, den Weg, auf welchem ich zu diesem neuen Verfahren gelangte, zu schildern und ich will deswegen sofort zur Beschreibung desselben übergehen.

Die Untersuchungsobjecte werden in der bekannten, für Untersuchungen auf pathogene Bacterien üblichen Weise, vorbereitet und entweder auf dem Deckglas ausgebreitet, getrocknet und erhitzt, oder nach Erhärtung in Alkohol in Schnitte zerlegt. Die Deckgläschen oder Schnitte gelangen in eine Farblösung von folgender Zusammensetzung. 200 Ccm. destillirten Wassers werden mit 1 Ccm. einer concentrirten alcoholischen Methylenblau-Lösung vermischt, umgeschüttelt und erhalten dann unter wiederholtem Schütteln noch einen Zusatz von 0,2 Ccm. einer 10%igen Kalilauge. Diese Mischung darf selbst nach tagelangem Stehen keinen Niederschlag geben. Die zu färbenden Objecte bleiben in derselben 20 bis 24 Stunden. Durch Erwärmen der Farblösung auf 40° C. im Wasserbade kann diese Zeit auf $^1/_2$ bis 1 Stunde abgekürzt werden. Die Deckgläschen werden hierauf mit einer concentrirten wässrigen Lösung von Vesuvin, welche vor jedesmaligem Gebrauche zu filtriren ist, übergossen und nach ein bis zwei Minuten mit destillirtem Wasser abgespült. Wenn die Deckgläschen aus dem Methylenblau kommen, sieht die ihnen anhaftende Schicht dunkelblau aus und ist stark

First page of Koch's original paper.

World TB Day is recognized each year on March 24, which commemorates the date in 1882 when Dr. Robert Koch announced his discovery of *Mycobacterium tuberculosis*, the bacillus that causes tuberculosis (TB). World TB Day provides an opportunity to raise awareness about TB and the measures needed to tackle this devastating disease.

World TB Day 2018

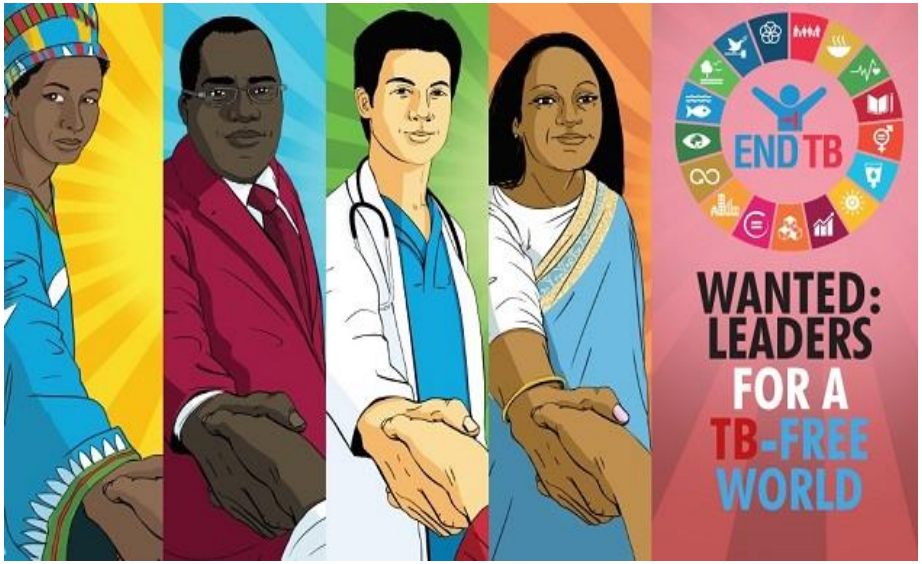


Robert Koch in his laboratory.

"If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like…If one only considers the productive middle age groups, tuberculosis carries away one third and often more of these"

Robert Koch March 24, 1882

World TB Day 2018



TB in the 20th Century

"How the Battle against TB was won... and almost Lost"

"At the midpoint of the 20th century, tuberculosis was recognized by all as the "White Plague", undeniably the most dreaded enemy of the human race by any measure. Whether measured by prevalence, cost, social consequences, sheer misery or any yardstick, I believe that any observer of the time would consider the bacillus of tuberculosis as the enemy number one of the human race. None of us-myself included- believed its control could be attained by medical means within this twentieth century."

H. Corwin Hinshaw

Thanks to Koch and Others TB Should Be The Envy Of Other Diseases

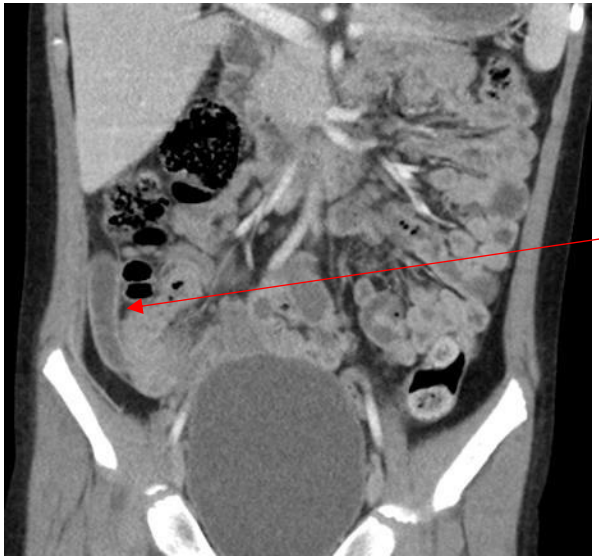
- Know the etiology of TB
- Possess very good tools for diagnosing TB
- Possess very good therapies for TB
- The therapy is relatively cheap
- Still about 1.8 million people (over 4500 deaths/day) are dying of TB world wide every year!!!-Top Infectious Killer Worldwide

Case

- 7 yo US born, Spanish speaking female without prior medical history presented to a Florida Hospital with a one day history of progressive right lower quadrant abdominal pain. Patient denied fever, emesis, constipation or diarrhea. Last bowel movement was 3pm the prior day
- Abd exam was significant for mild RLQ tenderness without rebound tenderness (eg no peritoneal signs)
- WBC 15.4

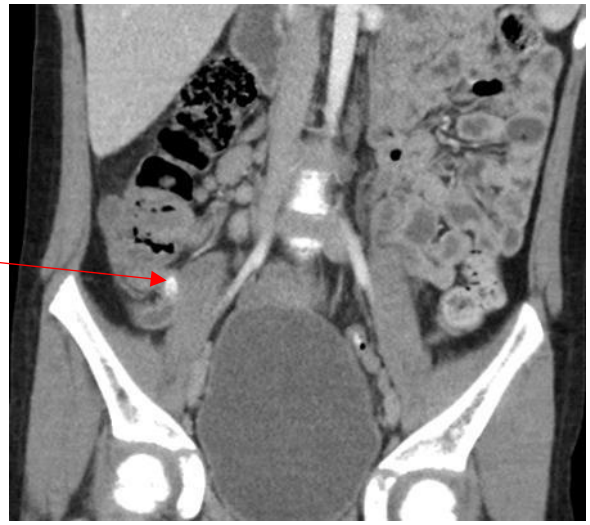
Case

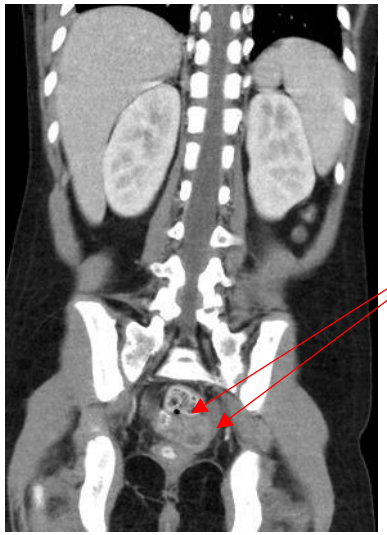
- CT of the Abdomen showed a dilated and fluid filled appendix with a 7 mm appendicolith with periappendiceal inflammatory changes consistent with acute appendicitis without perforation. Also described were enlarged bilateral ovaries with calcifications and a subsegmental pleural based atelectasis/scarring RLL
- Patient was started on Flagyl and Gentamicin



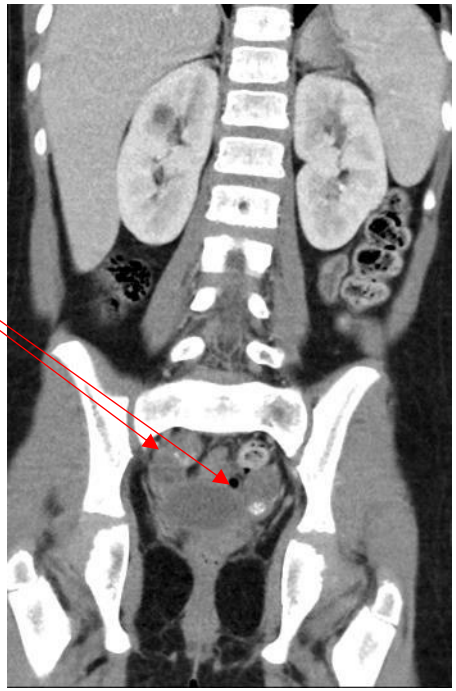
Dilated fluid filled appendix

appendocolith

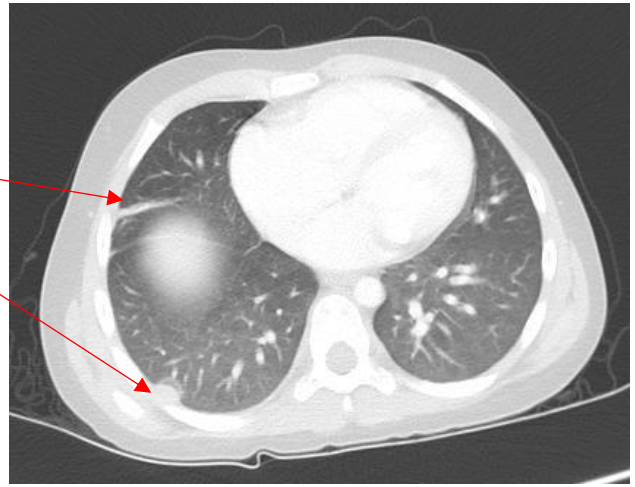




Enlarged bilateral ovaries with calcifications



Pleural based
atelectasis/infiltrate



Case

- Patient underwent a laparoscopic appendectomy
- When the surgeons entered the abdomen, they recognized that the omentum was adhered to the anterior abdominal wall extending towards the pelvis requiring an open procedure
- The laparotomy consisted of an appendectomy with excision of “bilateral ovarian inclusion cysts”

Case

- Intraoperative findings included:
  - Dilated and erythematous distal appendix with localized adhesions.
  - Diffuse adhesions from the omentum to the abdominal wall
  - Bilateral ovarian “inclusion cysts” with adhesions bilaterally
  - Inspection of the mid ileum did not have adhesions or inflammation
- Specimens sent to Pathology (in formalin) included the appendix, bilateral ovaries and omentum

Case

- The patient had an uneventful post-operative course
- Pathology revealed:
  - Acute appendicitis and periappendicitis with pinworms noted
  - Bilateral Ovaries: Multiple areas of necrotizing granulomas with occasional multinucleated giant cells with Fite staining showing positive staining bacilli
  - Omentum: fibroadipose tissue with foci of chronic inflammation
  -

Case

- Given pathologic changes an infectious disease consult was requested who found that the child was healthy without evidence of recent illness.
  - The father was a migrant worker from Mexico who traveled the US but was well as was the mother and siblings and an aunt and uncle who visited the family. Family denied recent travel to Mexico and no family visits from relatives from Mexico. Family initially denied eating unpasteurized cheese, meat or milk. The child did not have a hx of BCG vaccination
- HIV test and Brucella Antibody negative
- PPD and QFT performed

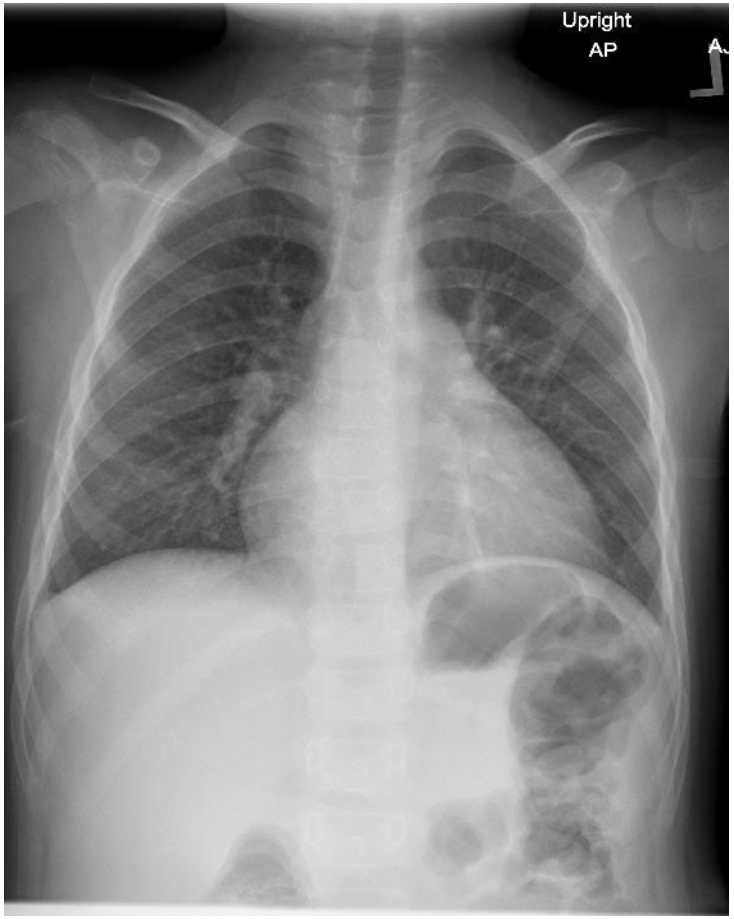


Plate-like atelectasis in RML

Case

- The patient was discharged home in good condition 2 days after the procedure with follow up with her pediatrician and infectious disease consultant
- PPD was read as “positive” and Quantiferon (TB Ag-nil 9.07 Mitogen 8.66) was also found to be positive
- CA125 49 (<35), ESR 17 CRP 2
- Mother again denies any symptoms observed in child including fevers, chills, night sweats, weight loss or cough. Last antibiotic used approx 1 year ago for otitis media

Case

- What now?
- How do we confirm the diagnosis?

Case

- Left Ovary pathology specimen (paraffin block) was sent to an outside lab which was PCR negative for TB and NTM x 2

Case

- What now?

Case

- Seen by ID consultant as outpt 2 weeks after the procedure
  - Pt in 45% percentile for height and 61% percentile for weight, BMI 68%
- Pathologist discussed Case with the State TB Medical Director
  - Probable GU TB from ? Source
  - Refer patient to Health Department for family “source case” investigation
  - Ask family again about sick family members, neighbors, visitors
  - Ask family about unpasteurized milk/meat ingestion
  - Sputum for AFB
  - Send Pathology Specimen to CDC Pathology Lab
  - Given pathologic findings and positive PPD-start 4 drugs for TB

Infectious Diseases Pathology Branch	**Pathology Report Continued** IDPB No: 2018-0049	Centers for Disease Control and Prevention

Microscopic Examination:

Left ovary: The entire ovary is extensively replaced by well-formed granulomas with multifocal regions of necrosis and abundant multinucleated giant cells of foreign body and Langhan's types. Within several macrophages and multinucleated giant cells are mineralized debris and concretions. No fungal organisms are observed using GMS special stain.

Results:

Specimen	Test	Result
Special Stains		
Lt ovary excision (12/4/17)	ZN AF	Negative
Lt ovary excision (12/4/17)	GMS	Negative
Lt ovary excision (12/4/17)	Fite	Positive
IHC		
Lt ovary excision (12/4/17)	Mycobacterium spp. (0440)	Immunostaining (See Comment)
PCR		
Lt ovary excision (12/4/17)	Mycobacterium genus 16S rRNA	Positive for Mycobacterium tuberculosis complex species

Information on the specific antibody including relevant references (as available) on primary antibody production or IHC utility is described below:

Mycobacterium spp. (D440): This rabbit polyclonal antibody reacts with several Mycobacterium spp., including M. bovis, M. ulcerans, M. tuberculosis, M. marinum and M. leprae. It also cross-reacts with fungal elements, Rhodococcus, Nocardia spp., Corynebacterium spp., and Staphylococcus spp. A negative result does not exclude the possibility of infection.

Information on the specific assay including relevant references (as available) is described below:

Mycobacterium genus 16S rRNA: DNA extracted from tissue was used as a template for a Mycobacterium genus specific nested PCR assay targeting the 16S rRNA gene. This PCR assay detects Mycobacterium species, including both tuberculous and non-tuberculous Mycobacteria. Positive amplicons (214 bp, 178 bp respectively) if obtained are sequenced to further confirm and characterize. Housekeeping genes for this assay are B-globin (300bp) and GAPDH (200bp).

Diagnosis:

Left ovary, biopsy: marked, diffuse, granulomatous oophoritis with multinucleated giant cells and mineralization

- Rare bacilliform organisms observed on Fite's stain
- Multifocal immunostaining by Mycobacterium species assay
- Molecular evidence of Mycobacterium tuberculosis complex species
- MDDR testing pending (see comments)

RLT.DR.C.0003.F02

Effective: 8/29/2016

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: Final

CLIA ID # 11D2030855

[redacted]

Specimen: DNA**

Medium: N/A

[redacted]

Results for Molecular Detection of Drug Resistance
(Pyrosequencing- INH and RMP only; Sanger Sequencing-pncA only)

Locus (region) examined*	Result	Interpretation (based on in-house evaluation of 550 clinical isolates)
rpoB (RRDR)	No mutation	Probably Rifampin susceptible. (97% of RMP-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
inhA (promoter)	No mutation	Cannot rule out INH resistance. (86% of INH-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at one or both of these loci.)
katG (ser315 codon)	No mutation	
pncA (promoter, coding region)	No MTBC amplification detected***	No result. Cannot rule out PZA resistance. *

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

**DNA received from CDC Infectious Disease Pathology Branch (IDPB #2019-0049)

*pncA subsequently with mutation His 57Asp

Case

- Patient's sputum AFB culture negative
- Mother QFT (-) (with hx of negative PPDs), Sister QFT (-)- Both healthy and asymptomatic. Aunt, Uncle and Father QFT (+)-all born in Mexico, asymptomatic, healthy, CXRs (-)
- Mother now remembers grandmother in Mexico who lives on a farm sent "white cheese" to the family about 1 year ago.
  - Child only family member who ate significant amounts of the cheese
- Child tolerating compounded TB (liquid form) well and clinically doing well-will get 9 month of Rx with INH/Rif

Tuberculosis-*"The leading cause of Death from Any Single Infectious Dx" WHO 2016*

	GLOBAL	USA
Infected cases	1.7 billion (33% population)	10 million (4% population)
Case incidence	9.6 million/year	~ 9,400/year
Case prevalence	11-14 million	~14 thousand
Deaths	**1.8 million/year**	1,000-2,000/year
MDR	**Up to 15% (Dominican Republic and Ecuador)**	**< 1%**

Mycobacterium tuberculosis

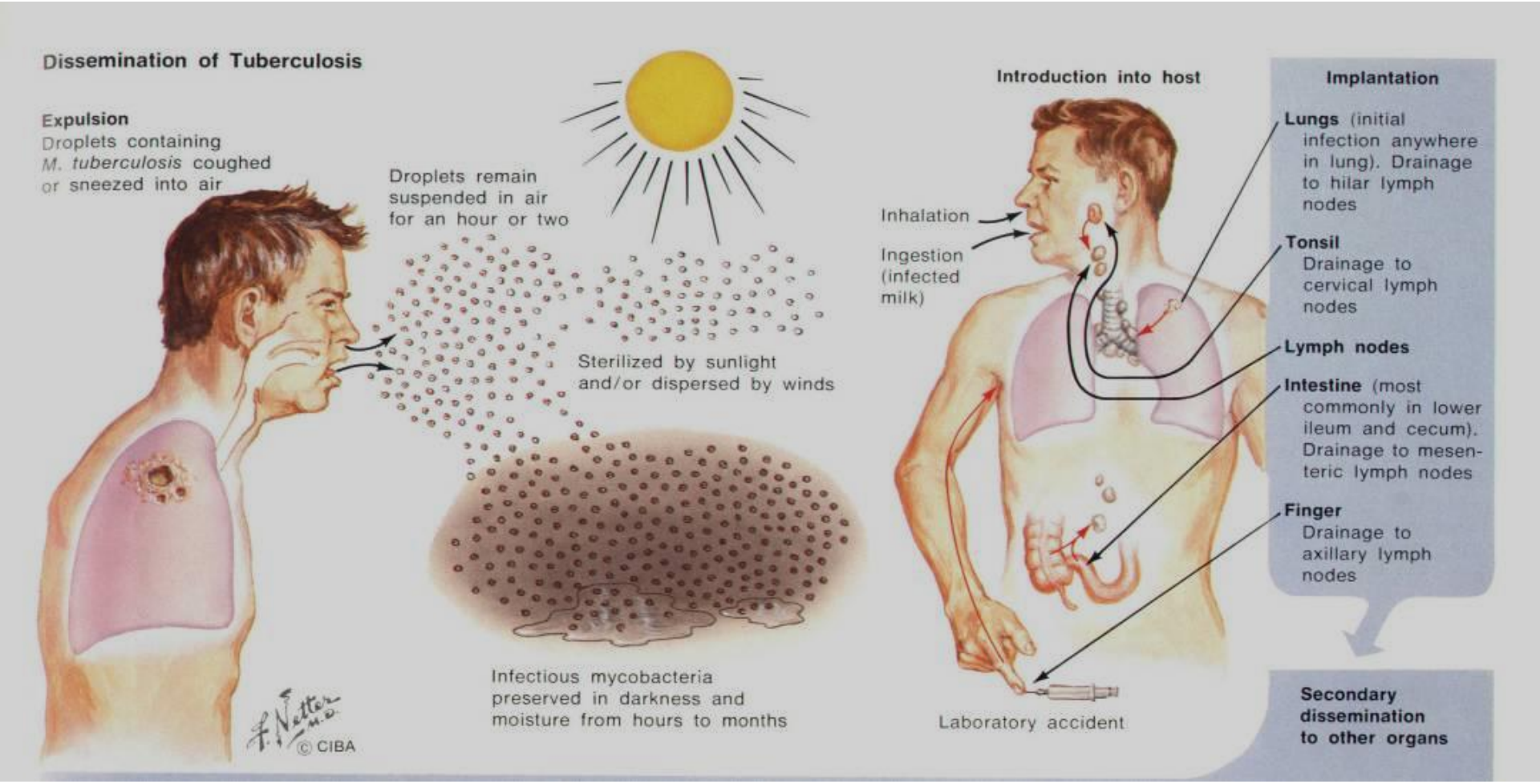
- **Mainly airborne disease caused by the bacterium *Mycobacterium tuberculosis (M. tb)***
- ***M. tb* complex (*M. tb, M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii, and M. mungi*) can cause TB disease**
- **Majority of TB cases caused by *M. tb***
- ***M. tb* organisms also called tubercle bacilli**

"Everyone knows the air is terribly infected from the numerous mortals who have died exhaling it"

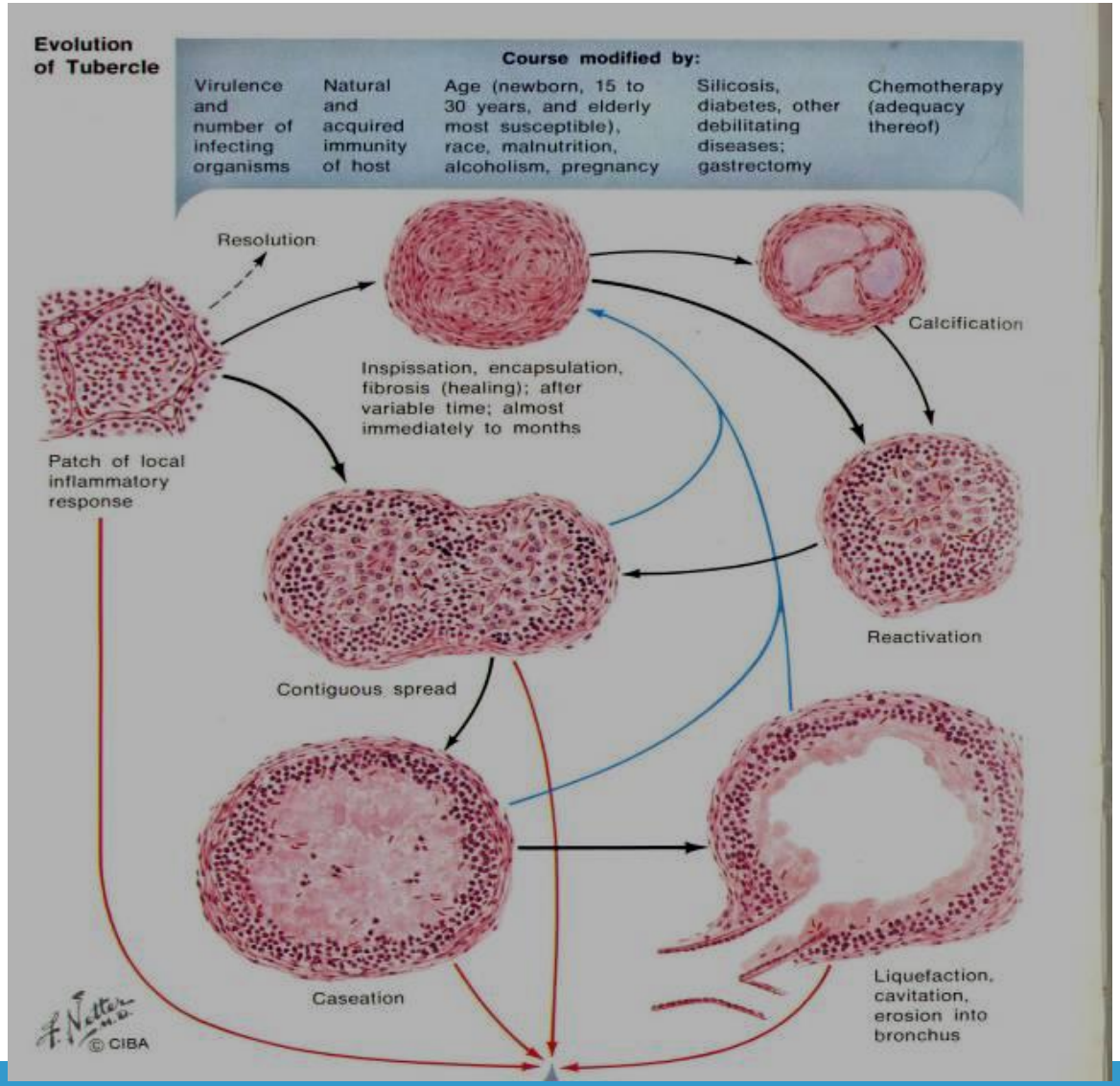
Moby Dick

Herman Melville

Transmission Of Tuberculosis



Pathogenesis of Tuberculosis



Disease Progression

- Progression from infection to disease caused by an inability to contain infection
- 5-10% of all HIV(-) will progress from infection to disease
- Up to 8% per year of PPD(+), HIV(+) pts will progress from infection to disease
- Approximately 25-30% of close contacts become infected on average
- The average patient with active TB infects 30 other individuals

M Bovis

- Majority of Cases of TB in US caused by MTB
  - ~2% of US TB cases M bovis-83% hx of eating Mexican Cheese
  - 65% Extrapulmonary involvement
- Most infected with M bovis by eating/drinking contaminated, unpasteurized dairy products-pasteurization kills organisms by rapidly heating and then cooling milk
  - Also from hunting/working with cattle, bison or cervids (e.g. deer, elk) through wounds or inhalation (rare)
- Control of M bovis in US through pasteurization and monitoring of cattle herds
- M bovis prevalent in dairy herd in some parts of Mexico
  - USDA in2005 isolated M. bovis from cheese produced in Mexico as part of its sampling program along US-Mexico border

M bovis

- TB complex may cause ulcers, strictures, colitis of GI tract-usually with involvement of lymphatics ("Peyers Patches") esp in ileum/cecal and area of physiologic stasis-most common area for TB
  - May resemble Crohn's Dx or Ulcerative Colitis
  - Issue now with use of TNF-Inhibitors

Genitourinary (GU) TB

- Second most common form of extrapulmonary TB (behind lymphatic TB)
  - Renal involvement most common
  - Usually caused by metastatic spread of organism through the blood stream during the initial infection
  - In TB of female genital tract, the bacilli reach the genital tract by three principal routes:
    - Hematogenous (90%)
    - Ascending direct spread (eg sexual activity)-rare
    - Lymphatic spread
  - 18% of infertile women in India suffer from GU TB (one of leading causes of infertility among women in India)
    - In women with GU TB: 95-100% have fallopian tube involvement, 50-60% endometrium involvement, 20-30% ovarian involvement, 5-15% cervix, 2.5% myometrium and 1% vulva/vagina

DIAGNOSIS OF TB-THINK TB!!!!
Signs and Symptoms of TB Disease

- **When you have a patient with epidemiologic risk factors (eg hx of being born or lived in area with high rate of TB, congregate living settings, immunosuppression) and have symptoms of:**
- Often of long duration
- General
  - Fatigue, malaise, weight loss, fever, night sweats
- Pulmonary
  - Prolonged cough, coughing up blood
    - Extrapulmonary
  - Depends on site
- Think TB!!-Isolate and send specimens for appropriate Mycobacterial Studies

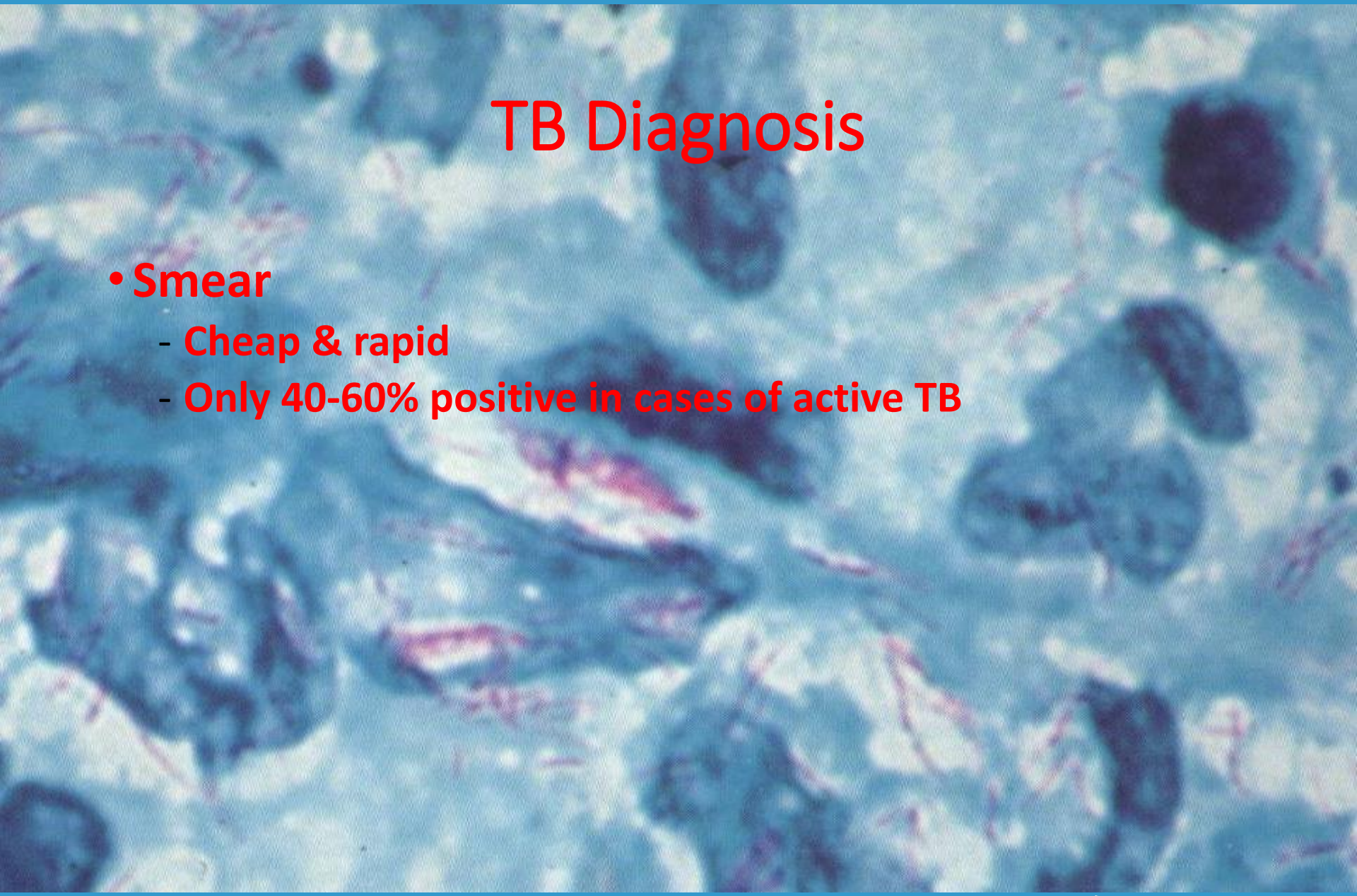
FDA Approval of GenExpert for AII

- *"In February 2015, the U.S. Food & Drug Administration (FDA) approved a change in the package insert for the Xpert to reflect expanded claims related to AII. According to this change, negative 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****"*

TB DIAGNOSIS

- Chest X-Ray
  - 95% of HIV(-) cases with upper lobe infiltrates and/or cavities

TB Diagnosis



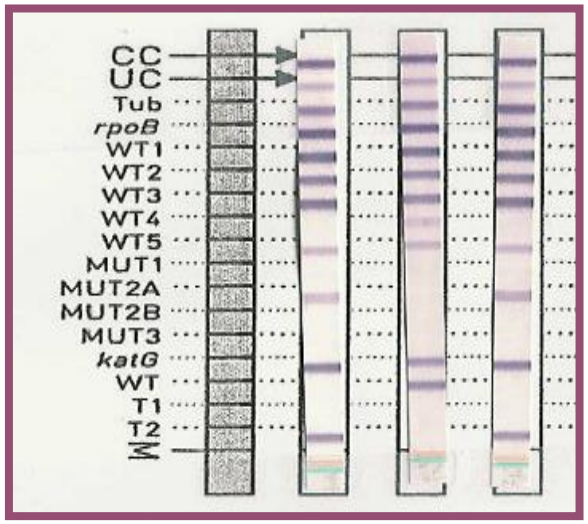
- **Smear**
  - **Cheap & rapid**
  - **Only 40-60% positive in cases of active TB**

TB Diagnosis

- Culture
  - Positive ~80% of active TB cases
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media
- Sensitivity
  - Takes 1-2 weeks after positive culture
- Nucleic Acid Amplification
  - Results available in 4-6 hours
  - Specificity ~98% on smear(+) specimens
  - Sensitivity 70-80% on multiple respiratory specimens

GenExpert

HAINS TESTING



Thanks to a partnership with the Florida State TB Lab and CDC, the SNTC offers Molecular Drug Resistance Testing when Determined to be Necessary

Pediatric Tuberculosis Clinical Presentations

Most cases of TB in children are NOT confirmed bacteriologically

"Clinical Cases"

- History of recent contact to an active case
- Positive TST or IGRA
- Abnormal CXR and/or physical exam
- No bacteriological confirmation
  - Not done or negative cultures

Pediatric TB: How cases are discovered

- Active
  - Contact investigation: 25-80%
  - Screening of high risk groups: 3-35%
- Passive
  - Symptomatic children: 15-45%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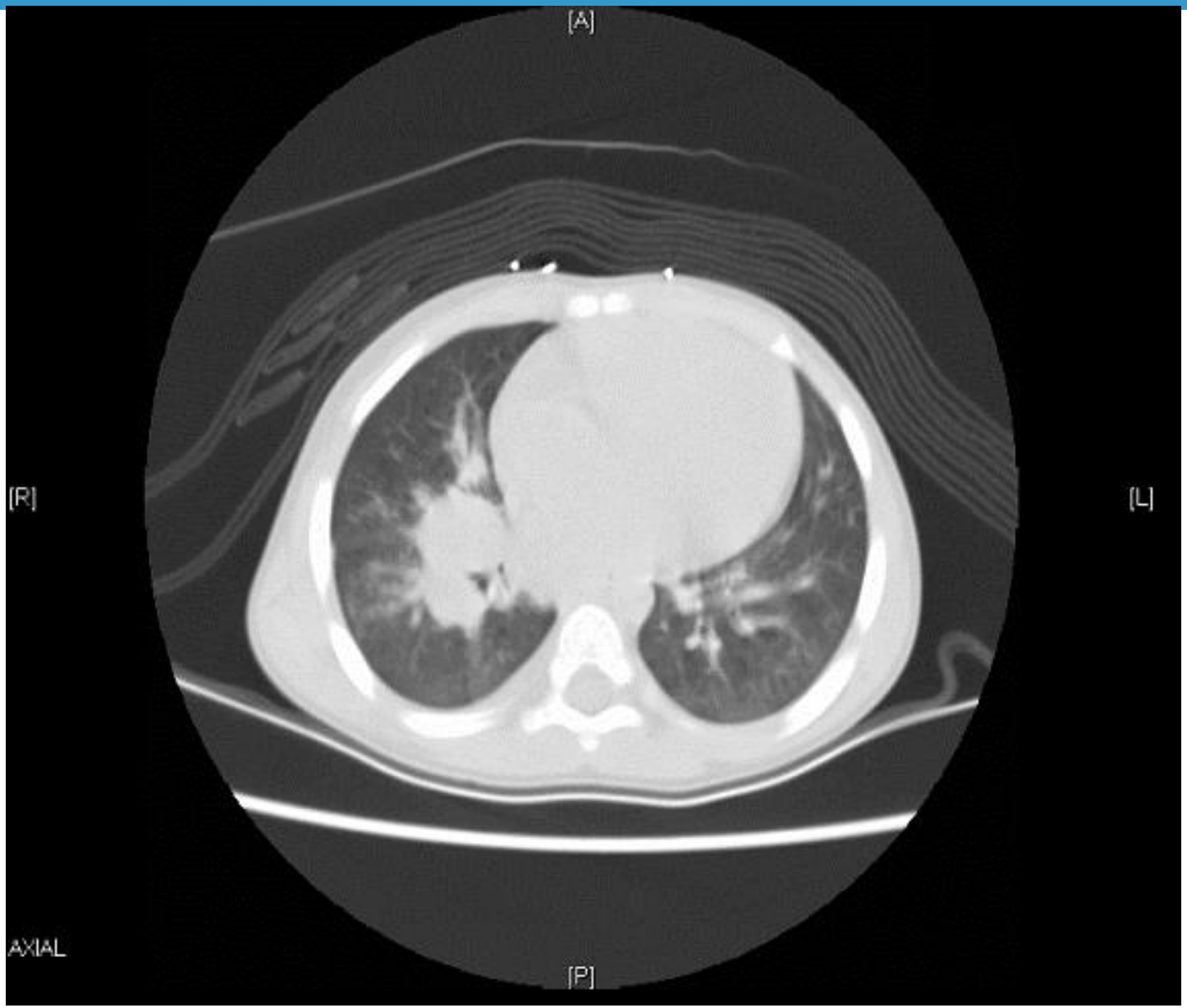
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Pediatric Cases

- Challenges
  - Harder to diagnose
    - Ana Alvarez MD-SNTC Pediatric Consultant
  - Dosing and Tolerance of Meds
    - Compounding Meds
    - TDM

TB Good News/Bad News

- Good News
  - TB rates in US and Worldwide decreasing
  - Better diagnostic Tools
  - New therapeutic options
- Bad News
  - Cases can be more complex
    - Extrapulmonary
    - Drug Resistance
  - With decreasing rates less expertise in the community
    - Complex cases may benefit from consultation (eg Pediatrics)and access to advanced resources

Summary

- THINK TB!!!!
- TB/M bovis may present in extrapulmonary forms
  - Hard to diagnose-may need advanced diagnostics
- M bovis still prevalent in resource poor countries and may be acquired by oral route
- Molecular diagnostics including resistance testing is available and may assist in cases where specimens for cultures were not obtained
- Complex cases may benefit from consultation (eg “TB Experts”, Pediatrics, Pharmacist, RNs, Program Consultants) and access to advanced resources

THANK YOU FOR ALL YOU DO!!

Southeast National TB Center Hotline

1-800-4TB-INFO