

A Tale of Two Unrelated TB Cases: Mycobacteria Disease, Finally Connecting the Dots

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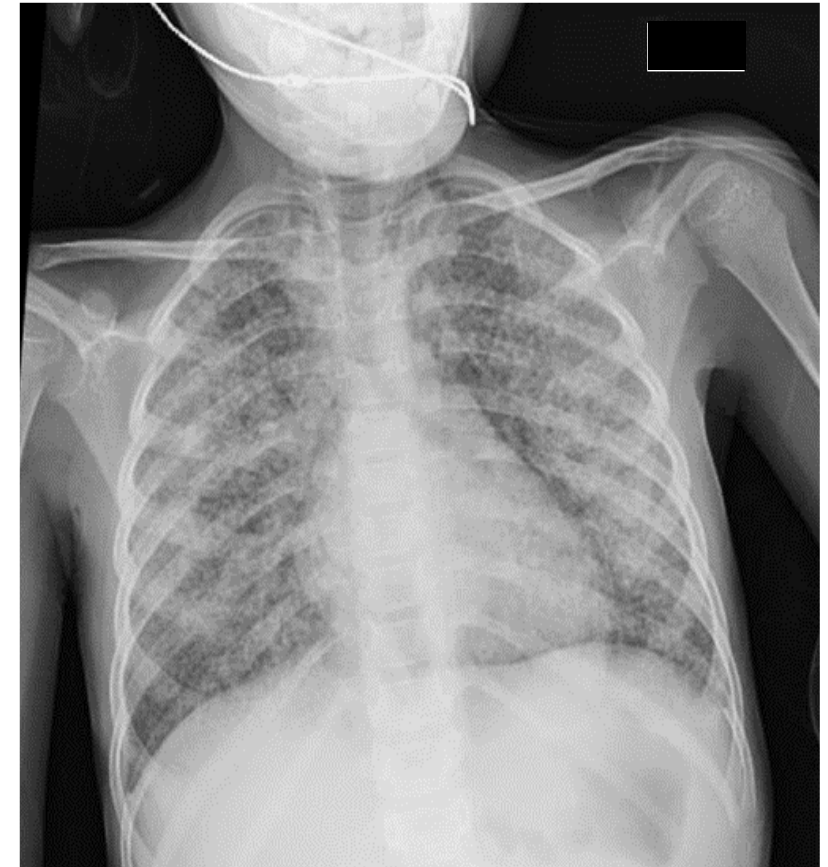
Disclosures (J Ang)

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 - **Principal Investigator on COVID-19 clinical trials supported by Eli Lilly, Roche**
- **Speakers Bureau- Pfizer, Inc**
 - **For Pneumococcal Conjugate Vaccine 20 (PCV-20)**

History...

- A 4-year-old African-American female previously healthy transferred from outside hospital (OSH) for **hypoxia (oxygen saturation 85% on room air) in 7/2023**
- At OSH, she reported following:
 - **Fever, cough, diarrhea and weight loss for 3 weeks**
 - Two weeks prior to arrival (PTA) at OSH, she was evaluated at another institution, and was diagnosed with upper respiratory infection.
- OSH Labs:
 - Rapid Strep , Influenza A/B, Respiratory syncytial virus (RSV), COVID-19, Blood Culture, Complete Blood Count (CBC), Urinalysis: Negative
 - **Hyponatremia (low sodium): 131**

OSH CXR: Diffuse Infiltrate



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History...

- At Children Hospital Michigan (CHM) mother stated :
 - Child has been **sick for 3 weeks with**
 - **Fevers daily not responding to Tylenol**
 - **Poor appetite with weight loss ~ 7 lbs**
 - **Episodic coughing**
 - **Intermittent neck pain**
 - **Night sweats**
- Labs at CHM :
 - C-Reactive Protein 74 (mg/L)
 - Complete Blood Count:
 - White blood cell count 6 (14% Lymphocyte, 80% Neutrophil)
 - Hemoglobin 10.4 ,platelet 209
 - Complete Metabolic Panel
 - NA 134, albumin 3.3, ALT 22, AST 45

CXR at CHM: Diffuse opacities



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Exposure History

- **Visited a pet store within past few months, exposed to cats and dogs**
- **No pets at home**
- **No recent sick contacts per mother at home.**
- **Native of Detroit**
- **No recent travel outside of United States**
- **Reports a friend at school sick prior to school being out for summer break 6/2023**
- **Paternal grandfather was incarcerated and released 7 month ago**
- **No history of living in homeless shelter**

Other Histories:

- Past medical history: None
- Past surgical history : None
- Meds: None
- Allergies: NKDA
- Vaccines: Up to Date per MICR
- Fhx: unremarkable
- Social History:
 - Mom is pregnant 22 week
 - Lives with mom and mom's boyfriend. Parents separated. Also stays with dad on weekend
 - No one smokes at home
 - No pets at home

Physical Examination at CHM

- **VS: Tmax 40° C, BP 97/60, Heart Rate: 128 beats/minute, Respiratory Rate: 30 breaths/minute, Oxygen Saturation : 95% on 3 liter nasal canula**
- **General: Appears in mild distress.**
- **HENT: Normocephalic, Atraumatic, Tympanic membranes are clear, Normal hearing, Oral mucosa is moist, No pharyngeal erythema, Ear canals patent, No sinus tenderness, No nasal discharge.**
- **Respiratory: Coarse breath sounds scattered throughout**
- **Cardiovascular: Regular rate, Regular rhythm, S1 auscultated, S2 auscultated, No click, No rub, No murmur, No gallop, Good pulses equal in all extremities, Normal peripheral perfusion, No edema.**
- **Gastrointestinal: Soft, Non-tender, Non-distended, Normal bowel sounds, No organomegaly.**
- **Lymphatics: No lymphadenopathy.**
- **Musculoskeletal: Normal range of motion.**
- **Integumentary: Warm. No rash**
- **Neurologic: Alert and oriented, no meningeal signs, no confusion**

Summary and Differential Diagnosis

Summary:

- A **4-year-old** previously healthy, fully immunized **African American female**, native of Detroit presented with **3 weeks history of fever, cough, diarrhea, weight loss, night sweats and neck pain.**
- On presentation, **she was hypoxic on RA requiring oxygen, febrile**, alert and oriented but looks tired on appearance, **coarse breath sound bilaterally on physical exam with CXR showing diffuse bilateral pulmonary opacities**

Differential Diagnosis:

- Miliary Tuberculosis
- Bacterial Multifocal pneumonia
- Atypical Pneumonia
- Invasive fungal disease
- Non infectious cause:
 - Malignancy

Dr. Sandhu from Health Department Consulted

Computed Tomography Thorax

- Diffuse miliary/cystic pulmonary TB with splenic involvement
- Mild soft tissue prominence in subcarinal and perihilar regions, may reflect prominent lymph nodes although no discrete lymph node enlargement is seen.



Bronchoscopy and BAL Studies:

- **AFB Stain was positive**
- **PCR for Mycobacterium Tuberculosis complex was detected**
- **AFB culture was positive for M. TB complex**

Lumbar Puncture: CSF studies

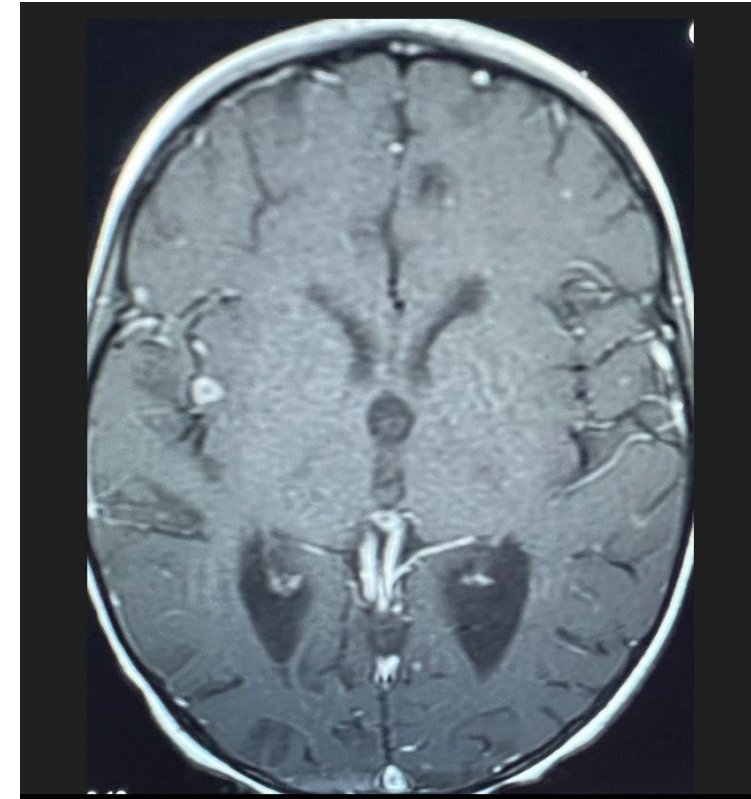
- Cell count and analysis:
 - Colorless
 - CSF Glucose 68 (serum glucose 96)
 - CSF Protein 30
 - Cell count (RBC 0, **nucleated cell 1**)
- CSF AFB stain Negative
- CSF PCR for M. TB negative
- **Culture: Mycobacterium TB complex**

Stool/Urine Studies

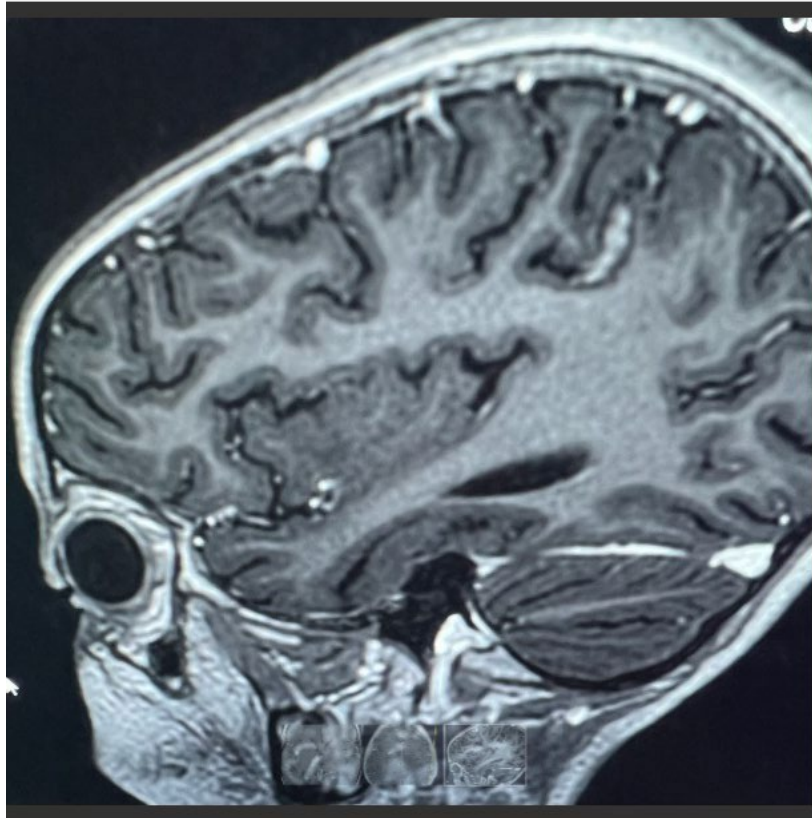
- Stool Mycobacterium culture :
 - **Mycobacterium TB complex**
- Urine Mycobacterium culture- negative

MRI Brain with Contrast

- Mild ventriculomegaly with **dilatation of the lateral ventricles and the third ventricle** and patent aqueduct
- Few areas of **abnormal T2 and FLAIR signal predominantly in the periventricular white matter** but also along the right sylvian fissure and the right parietal lobe and frontal lobe



MRI Brain with Contrast, con't



Tiny less than **2 mm nodular contrast** enhancement noted infratentorially and supratentorially and areas of ringlike contrast enhancement along the sylvian fissure and the right parietal lobe with more gyriform contrast enhancement noted in the right parietal lobe (**tuberculomas** some areas of **leptomeningeal/pachymeningeal**)

Ophthalmology Consult:

- **Baseline exam**
- **Left eye exam concerning for presumed Tuberculosis posterior uveitis**

Other Investigations

- 2D-echo: trace pericardial effusion located posteriorly, behind the heart
- Abdominal US: mild hepatomegaly, otherwise unremarkable
- PPD done: Negative
- TB QuantiFeron Gold: Negative
- TB spot: Negative
- Immune work up done essentially negative for any primary immunodeficiency

Case Summary

- 4 year-old **African-American female native of Detroit, presented with fever, fatigue, weight loss, night sweats, and diarrhea for 3 weeks**
- Admitted due to **hypoxia with CXR findings highly suspicious for miliary tuberculosis.**
- BAL specimen **positive M. TB**
- CSF and stool cx was **positive for M. TB**
- TB-spot, PPD and TB QuantiFERON Gold Plus: **Negative**
- MRI brain showing **tuberculomas with leptomeningeal enhancement**
- Ophthalmologic exam with evidence of **left uveitis.**
- Final Impression: **Disseminated TB**

Contact Tracing/ Updates/TB diagnosis and Treatment

- **Dr. Avnish Sandhu-**
 - Treatment regimen chosen for our patient along with hospital course
 - Susceptibility testing
 - MDDR testing
 - Contact tracing



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A Tale of Two Unrelated TB Cases: Mycobacteria Disease, Finally Connecting the Dots

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March 22, 2024



Disclosures

- I have no relevant financial disclosures



Pathogenesis and immune response of Disseminated TB

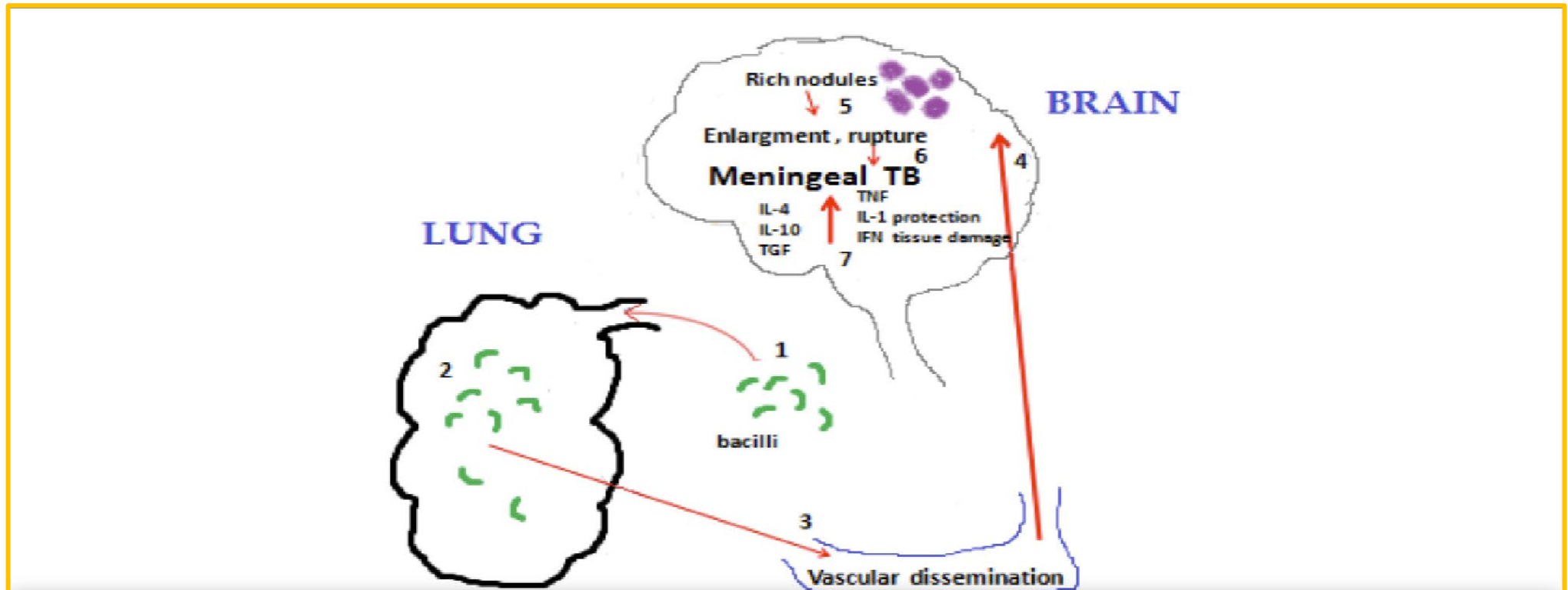


Figure 1: Pathogenesis and immune response of cerebral tuberculosis: The lung is initially infected by the aereal route (1); bacilli grow in the lungs and disseminate after blood vessels invasion (2) producing systemic infection (3) affecting the brain (4). Small groups of inflammatory cells are located in the subpial or subependymal areas (Rich nodules) after early bacteremia (5), where bacilli are content and may remain dormant for long time. Later, growth and rupture of these lesions produces meningeal tuberculosis (6). Mycobacterial infection induces the production of proinflammatory cytokines that are important for bacilli killing but they can also produce immunopathology (7). Antinflammatory cytokines are also highly produced; they protect tissue damage by excessive inflammation and induce nervous tissue regeneration (7). [Collapse](#)



Gastric Aspirate vs Bronchoscopy

Gastric Aspirate

Children should fast for at least four to eight hours before gastric aspiration.

The first aspirate of the day will have the highest bacterial yield. Approximately 50 milliliters (ml) of gastric contents are aspirated via nasogastric feeding tube during three consecutive mornings.

Children with a low platelet count or bleeding tendency should not undergo gastric aspiration.

AFB smear and mycobacterial culture are requested for testing.

NAA testing is recommended if available.

Repeat gastric aspirates are not recommended once the child is on appropriate treatment.

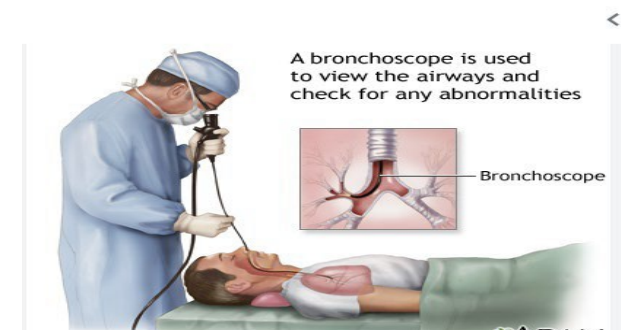


Bronchoscopy vs Gastric Aspirate

Aim of study to find out if Bronchoscopy better than gastric lavage

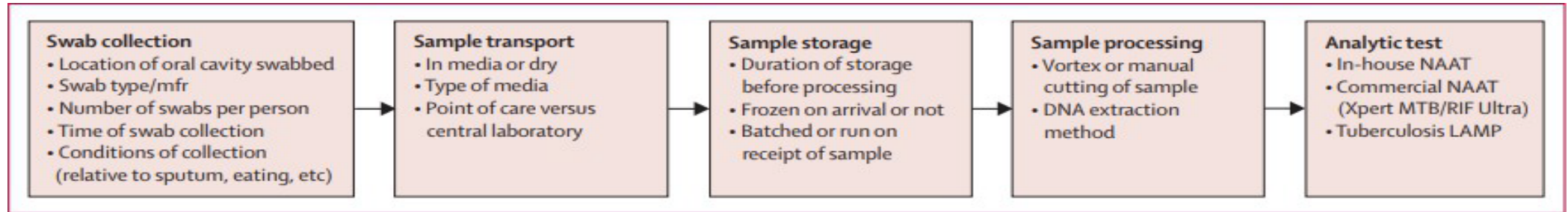
50 children with suspect pulmonary tuberculosis at mean age of 5.1

Mycobacterium tuberculosis grown in 6 (12%) bronchoscopy specimen and 16 (32%) gastric lavage sample





Oral Swabs for Pulmonary Tuberculosis in Adults and Children: A Systematic Review



- **Methods:** Systematic Review of Including 20 studies (15 adults 5 children), 3083 participants
- **Results**
 - Sensitivity on oral swabs ranged from **36% (95% CI 26–48) to 91% (80–98) in adults and 5% (1–14) to 42% (23–63) in children.**
 - Specificity ranged from 66% (95% CI 52–78) to 100% (97–100), **with most studies reporting specificity of more than 90%.**
- **Conclusion**
 - High specificity noted which means if positive you can rule in the diagnosis of tuberculosis
 - Broad sensitivity noted that means if negative you cannot confidently rule out tuberculosis. Broad sensitivity could be due to low disease burden (not enough bacterial burden to be positive), sampling site/technique, and variation in sampling storage, sample transport and processing

*CI: Confidence Interval

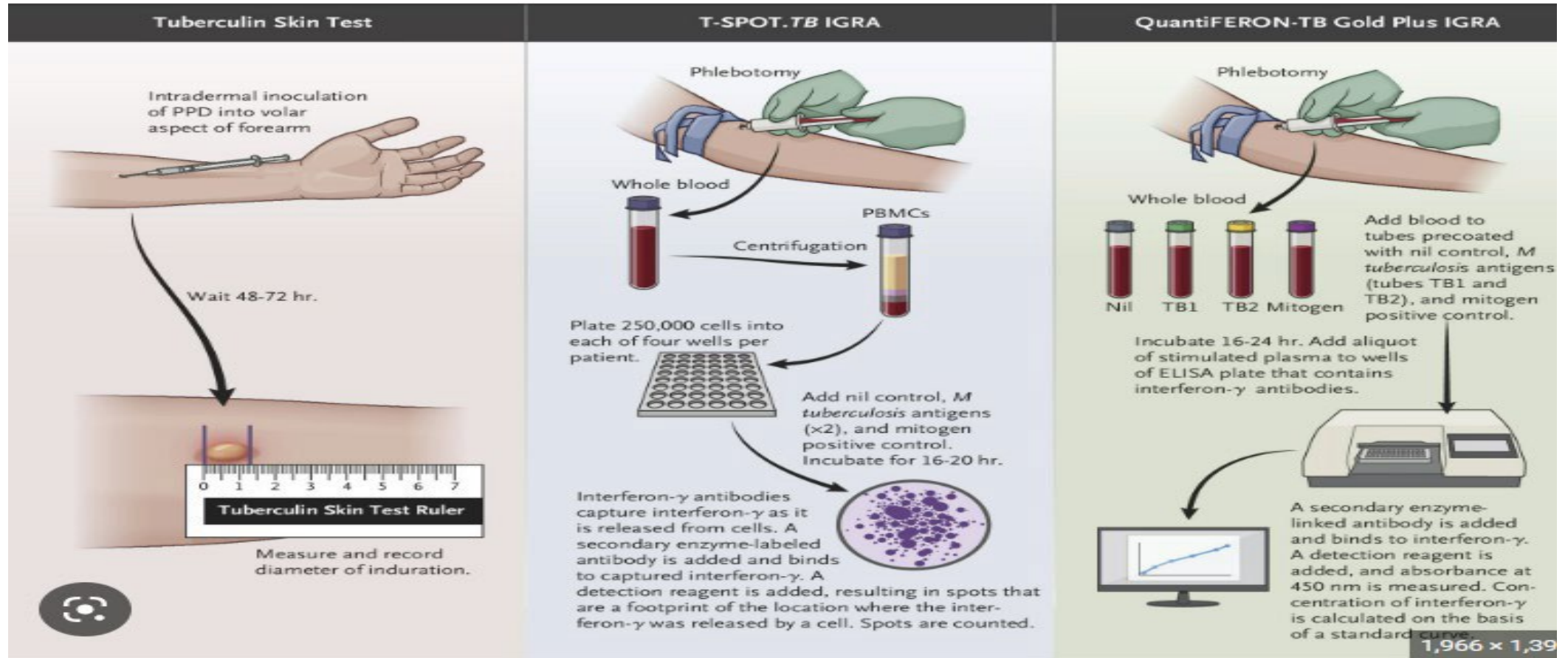


Sensitive and Feasible Specimen Collection and Testing Strategies for Diagnosing Tuberculosis in Children

- What combination of specimens, ideally minimally invasive, provide the highest yield for bacteriologic diagnosis of tuberculosis in young children?
 - **Design:** Prospective cross-sectional diagnostic study
 - **Setting:** Outpatient in Kisumu County, Kenya
 - **Time Period:** October 2013-Aug 2015
 - **Participants:** Children <5 years, who had symptoms of unexplained cough, fever, malnutrition
 - Reference standard gastric aspirate and Induced sputum
 - **Result:**
 - 300 children enrolled, 294 met criteria for analysis
 - 31 participants had confirmed tuberculosis
 - **Gastric Aspirate: 24 of 31; sensitivity 77%**
 - **Induced Sputum: 30 of 31; sensitivity 64%**
 - **2 Nasopharyngeal aspirate (NPA): 23 of 31; sensitivity 74%**
 - **1 NPA and stool sample: 22 of 31; sensitivity 71%**
 - **1 NPA and 1 urine sample: 21.5 of 31; sensitivity 69%**
 - **Combining 2 of each GA and NPA sample: 28 of 31; sensitivity of 90%**



Tuberculin Skin Test or Interferon Gamma Release Assays



*Tuberculin skin test (TST): Purified Protein Derivative (PPD) derived from tuberculin is injected into skin
*T-SPOT and TB Gold Plus: Uses *M. tuberculosis* Antigens ESAT-6 and CFP-10



Miliary Tuberculosis in Children: A Clinical Review

- Retrospective study of children with miliary TB registered from 1990-97, Dicle University Hospital, Turkey
- 23 children diagnosed as having miliary TB
- Mean age 3.7 years
- **17 of 23 (74%) of children had negative PPD.**

Our patient

- **PPD done: Negative**

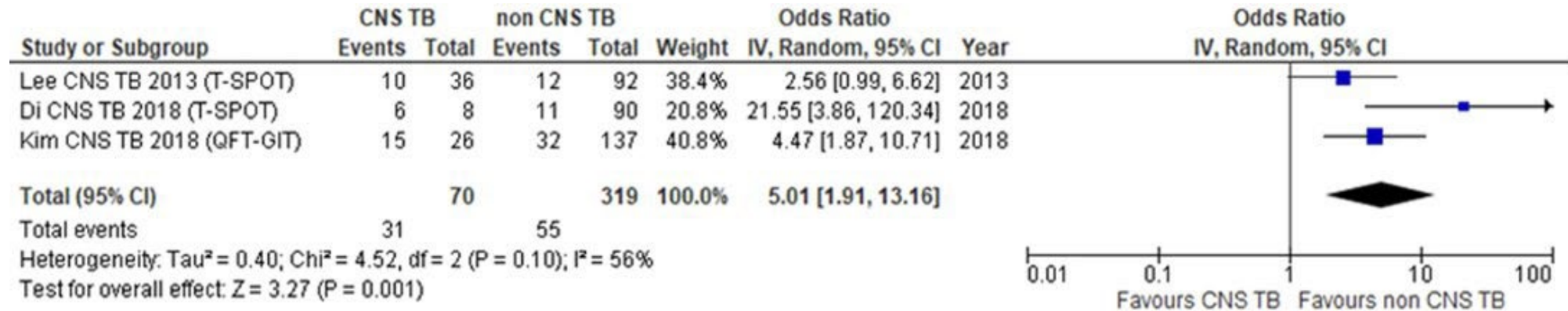


Disseminated Tuberculosis is Associated with More False Negative Interferon Gamma Release Assay

- Systematic review that compared IGRA (T SPOT or TB QuantiFERON Gold Plus test) in patients with disseminated TB (miliary/CNS TB) compared to patients with lymph node TB.
- Total 38 reports
 - Lymph node TB n= 19
 - Miliary/CNS TB n= 49
- In patients with **miliary and/or CNS TB 26.5% had a false negative IGRA result.**
 - **Our patient**
 - **TB QuantiFeron Gold: Negative**
 - **TB spot: Negative**



Factors associated with False Negative IGRA Results In Patients with TB: Systematic Review



- Methods: 14 studies evaluated
- Results: CNS TB was found to be a significant risk factor for false negative IGRA (T-SPOT or TB QuantiFERON Gold Plus test) compared to other forms of extrapulmonary TB.
- Discussion: Blood brain barrier does not allow components of TB bacilli to penetrate the CNS, the frequency of lymphocyte containing specific antigen in the CNS may be lower than that in lung leading to false negative IGRA.



Characteristic CSF finding of CNS TB

Typical CSF Finding of CNS TB

- Total white count (nucleated cell) 100-500 cells/microliter – **Lymphocytic predominant.**
- Very early in the disease, lower counts and neutrophilic predominance
- **Elevated protein levels 100-500 mg/dl**
- **Low glucose <45 mg/dl**

Conclusion: Peculiar our child had leptomeningeal enhancement on MRI but normal nucleated cell, normal protein, normal glucose but culture positive for M. TB complex, which could be explained by TB being paucibacillary

Cell count and analysis of our patient:

Colorless

CSF Glucose 68 (Normal)

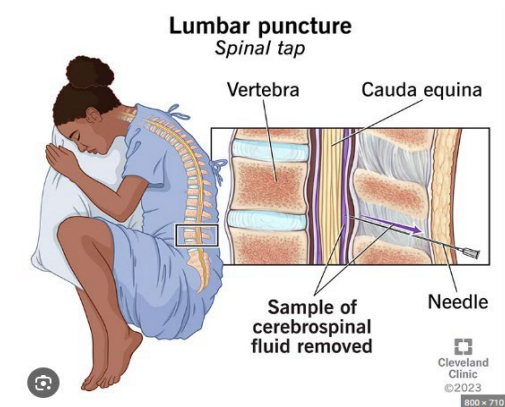
CSF Protein 30 (Normal)

Cell count **nucleated cell 1** Normal

CSF AFB stain Negative

CSF PCR for M. TB negative

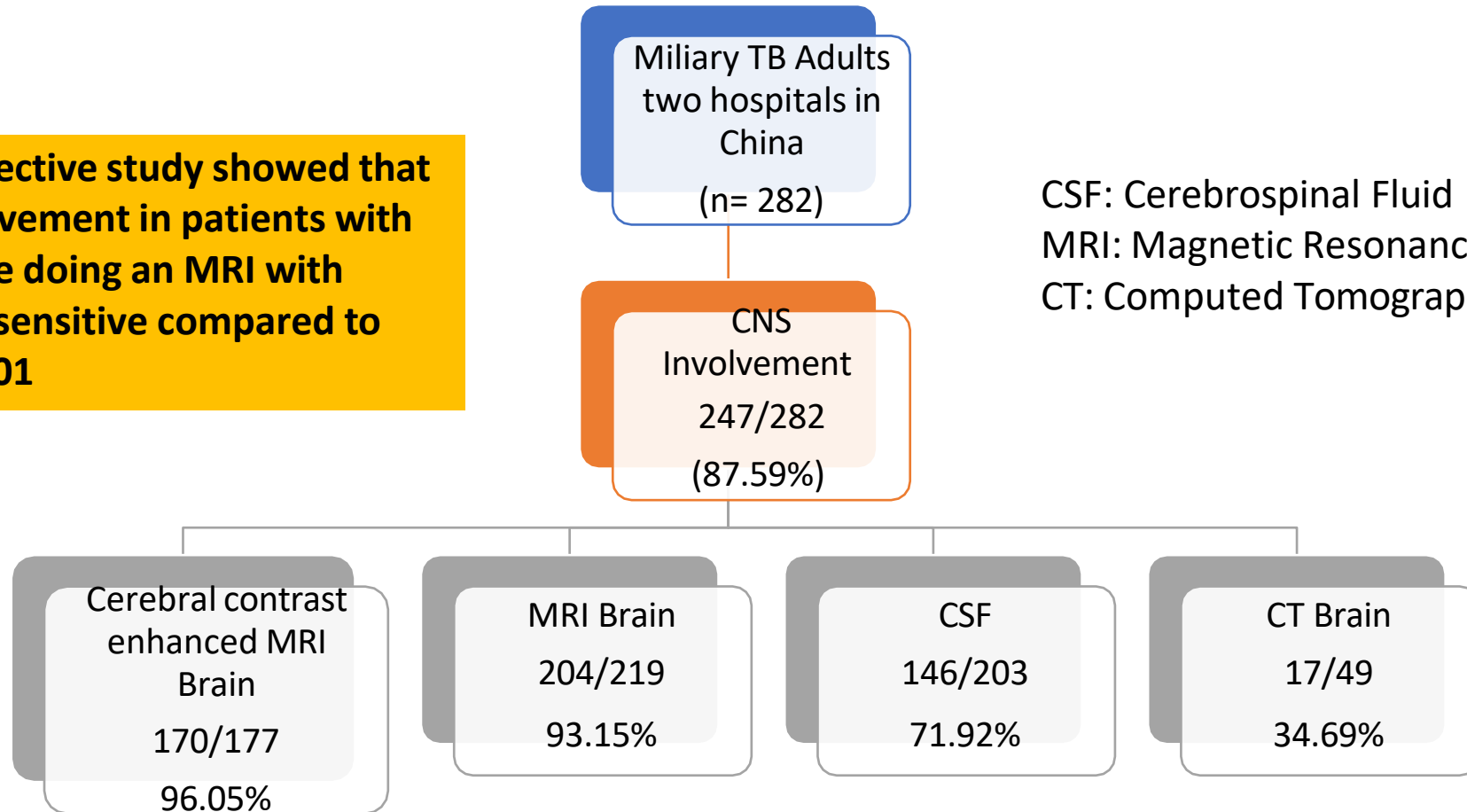
Culture: Mycobacterium TB complex





High level of CNS Involvement with Military TB

Conclusion: This retrospective study showed that assessment of CNS involvement in patients with military TB should involve doing an MRI with contrast as it was most sensitive compared to CSF and CT scan ; $p < 0.001$



CSF: Cerebrospinal Fluid
MRI: Magnetic Resonance Imaging Brain
CT: Computed Tomography of Brain



The Abnormal Rate of Cerebrospinal Fluid or Radiographic Imaging Stratified by CNS symptoms for Military TB Patient with CNS Involvement

Methods	Total	Without CNS symptoms (n = 73)	With CNS symptoms (n = 174)	P values
CSF	146/203 (71.92)	24/56 (42.86)	122/147 (82.99)	< 0.001
CT	17/49 (34.69)	5/7 (71.43)	12/42 (28.57)	0.027
MRI	204/219 (93.15)	67/70 (94.03)	137/149 (91.95)	0.303
Contrast-enhanced MRI	170/177 (96.05)	55/57 (96.43)	115/120 (95.80)	0.834

CSF: Cerebrospinal Fluid

MRI: Magnetic Resonance Imaging Brain

CT: Computed Tomography of Brain



CNS Tuberculosis Treatment Principals

Regional Prevalence of
Multi-Drug
Resistant(MDR)
Tuberculosis

Bactericidal
Activity

Least side effects

Minimal or no
drug interactions

CSF
Penetration



Criteria for Drug Resistance Testing

Concern for high risk of rifampin resistance

- Previously treated for TB
- A contact of MDR TB
- Foreign born from an area with high rate of MDR TB
- Exhibiting lack of response to clinical therapy

Known rifampin resistance by rapid test or culture based drug susceptibility testing

Result of drug resistance will have high public health impact (day care worker, nurses, school)

Adverse reaction to critical anti-TB drugs (e.g. rifampin)

Mixed or non-viable cultures

Isolates that fail to grow on drug susceptibility testing medium



Molecular Based Testing for Drug Resistance (MDDR)

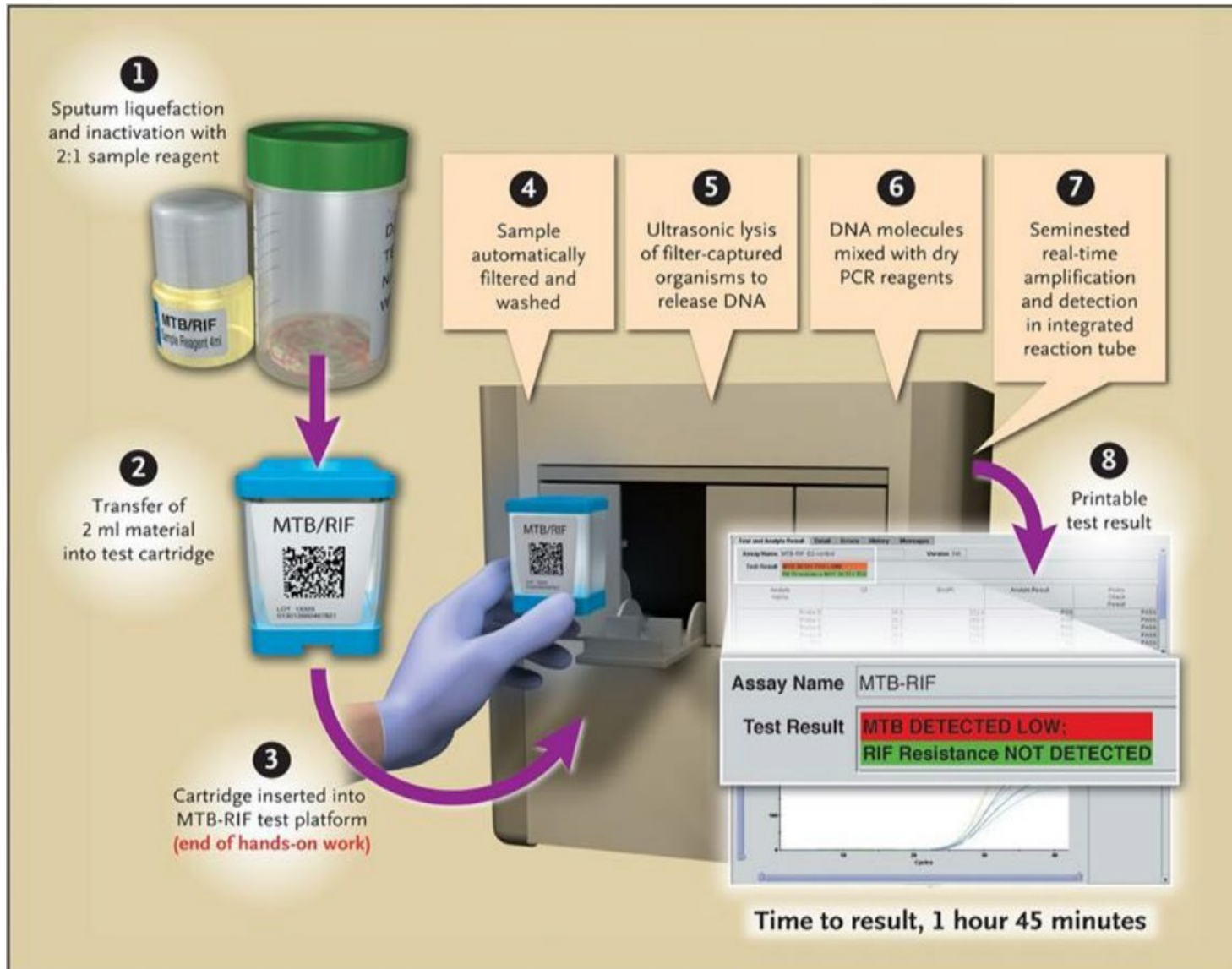
	GeneXpert MTB/RIF	Sanger Sequencing	Pyrosequencing	Next Generation Sequencing (NGS)
Company	Cepheid	N/A Laboratory developed test done at CDC	N/A Laboratory developed test done at CDC	N/A Laboratory developed test done at CDC
Detects	Rifampin Resistance	RIF, FQ, PZA, EMB, INH, AMK	INH, RIF, FQ	RIF, INH, PZA, FQ, AMK, KAN, CAP, BDQ, LNZ, CLOF
Format	Semi-automated real-time PCR	DNA sequencing	DNA sequencing	DNA sequencing
FDA approved	Yes	N/A Laboratory developed test done at CDC	N/A Laboratory developed test done at CDC	N/A Laboratory developed test done at CDC

Rifampin: RIF
 Isoniazid: INH
 PZA: Pyrazinamide
 EMB: Ethambutol
 AMK: Amikacin
 FQ: Fluoroquinolone

KAN: Kanamycin
 CAP: Capreomycin
 BDQ: Bedaquiline
 LN: Linezolid
 CLOF: Clofazamine

Core Curriculum on Tuberculosis.
<https://www.cdc.gov/tb/education/corecurr/pdf/CoreCurriculumTB-508.pdf>

GeneXpert MTB/RIF

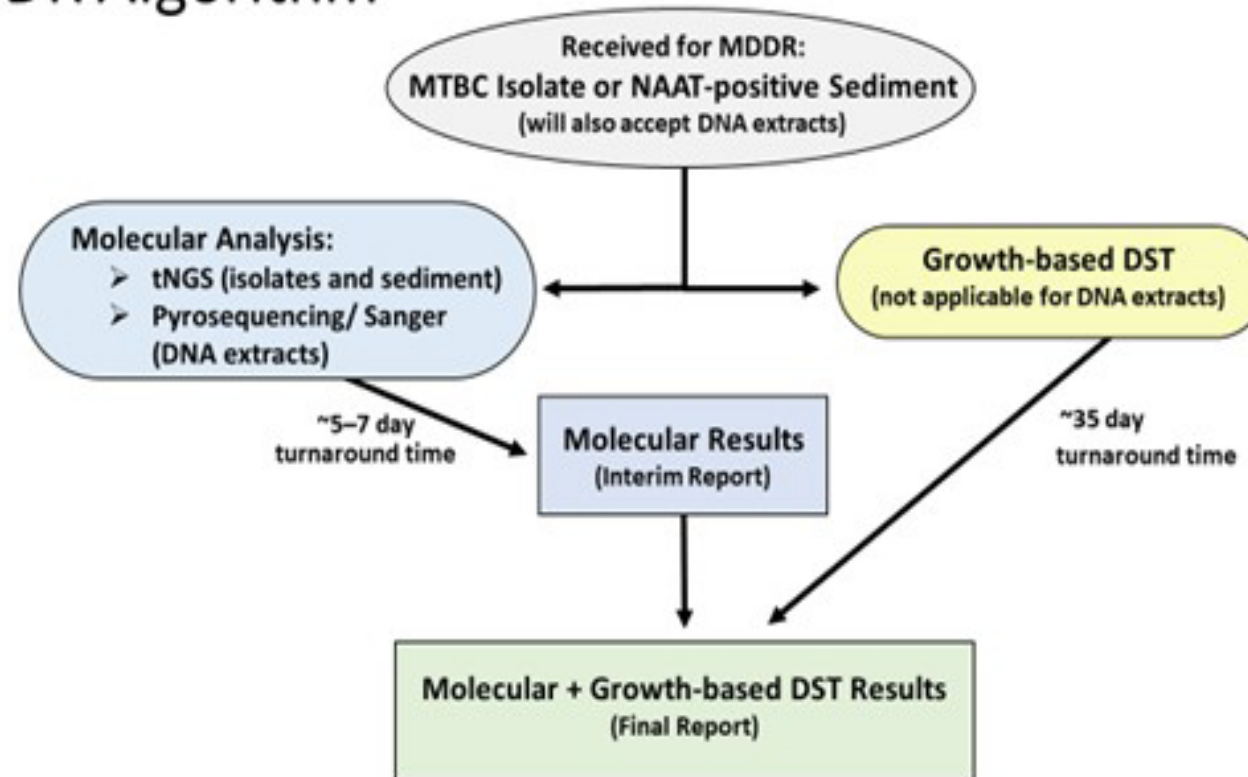


- FDA Approved in 2013
- Real time polymerase chain reaction (PCR)
- Detects Rifampin (*rpoB*) gene mutation
- Specimen: sputum only however can request to do it on other specimens [e.g. bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF)]



CDC MDDR: Update 2023

MDDR Algorithm





Main Activity of Anti-Tuberculosis Treatment (ATT)

Main Activity of ATT	
Bactericidal Activity	Sterilizing Activity
Target actively growing bacteria through the inhibition of cell processes	Ability to kill persisters and eliminate latent or dormant bacteria
Does not determine the length of treatment	Determine duration of treatment



Anti-Tuberculosis Drugs, Recommended Doses, CSF Penetration, and Activity

Drugs	Once daily dose	CSF Penetration	Activity
Isoniazid (oral)	10-15 mg/kg	Good (90-95%)	Bactericidal
Rifampin (IV/oral)	20- 30 mg/kg	Poor (5-25%)	Bactericidal
Pyrazinamide (oral)	30-40 mg/kg	Good (96-100%)	Bactericidal/ sterilizer
Ethambutol (oral)	15-25 mg/kg	Poor (10-50%)	Static
*Not recommended for TB meningitis in children			
Moxifloxacin (IV/oral)	10-20 mg/kg	Good (70-80%)	Bactericidal
Levofloxacin (IV/oral)	15-20 mg/kg	Good (60-80%)	
*For moxifloxacin use higher doses as rifampin can reduce moxifloxacin concentration			
Linezolid (IV/oral)	<15 kg: 15 mg/kg ≥15 kg: 10-12 mg/kg	Good (80-100%)	Bactericidal
Amikacin (IV)	15-20 mg/kg	Poor (10-25%) Good penetration only when CSF is inflamed	Bactericidal
Ethionamide (oral)	15-20 mg/kg	Good (80-95%)	Bactericidal

Marx, G.E., & Chan, E.D. Tuberculosis Research and Treatment, 2011

(2011):n.pag

Bhasin, H et al. The Indian Journal of Pediatrics (January 2020) 87 (1):26-33

IV=Intravenous



Drug Regimen for Pediatric Tuberculosis Meningitis

Intensive Phase		Continuation Phase	
Drugs	Interval and Duration	Drugs	Interval and Duration
Isoniazid Rifampin Pyrazinamide Ethionamide/ Amikacin	7 days/week for 8 weeks (56 doses)	Isoniazid Rifampin	7 days/week or 28-40 weeks (196-280 doses)

Corticosteroids:

- Routinely recommended when treating any patient with tuberculosis meningitis
- Experts recommend 2 mg/kg per day of prednisone or its equivalent for 4-6 weeks followed by tapering

American Academy of Pediatrics. Tuberculosis. In Kimberlin DW, Brady MT, Jackson MA, Long SS, ed. Red Book: 2018-2021 Report of the Committee on Infectious Diseases, 31st Edition. Elk Grove Village, IL: American Academy of Pediatrics; 2018: 829-853.

New York TB Guidelines 2022



Our Patient Initial Inpatient Treatment....

- Our initial regimen was IV as our patient was having diarrhea so concern was for absorption
- We also chose the regimen that will cover for drug-resistance TB.
- Rutgers TB experts were consulted

Our Patient Initial Treatment

Isoniazid oral crushed

IV Linezolid

IV Rifampin

IV Amikacin

IV Levofloxacin

IV Steroids



Our Patient Discharge Treatment....

- MDDR Testing inconclusive as unable to amplify the BAL specimen
- Phenotypic drug susceptibility testing susceptible to isoniazid, rifampin, pyrazinamide, ethambutol, moxifloxacin
- Patient was able to tolerate orals

Our Patient Discharge Treatment

Isoniazid oral crushed (280 doses)

PZA liquid (56 doses)

Rifampin liquid (280 doses)

Levofloxacin liquid (56 doses)

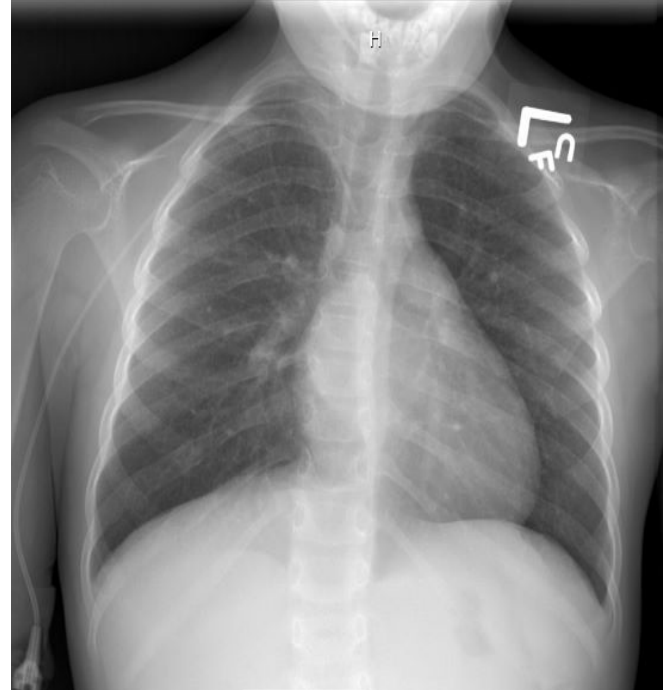
Oral Steroids (4- 6 week followed by tapering)



Serial CXR.....



July 2023
Pre-treatment



August 2023
One-Month Post treatment



Sep 2023
Two-month Post treatment



Reverse Contact (source patient) Evaluation

Who ?

Parents or caregivers for children aged <5 years.

Why?

Find the source of infection for child and protect other children in home

How?

Screen for TB symptoms
CXR
If screening positive evaluate for TB disease



Reverse Contact Investigation for Our Patient....

- **Mother: TB Quant Positive, CXR negative**
- Father: PPD negative
- **Boyfriend (mother): TB Quant Positive, CXR negative**
- Grandfather: PPD negative
- Grandmother: PPD negative
- Godparents: PPD negative
- Child school: Among classmates/teacher tested all were PPD negative
- Mother/Boyfriend and our patient live together; child also spends time with father
- Mother refused Latent TB infection treatment
- Boyfriend completed Latent TB infection treatment
- Mother worked in Casino
- Boyfriend works for large retail chain
- Mother/Father Reports no known Contact with anybody with TB



Timeline History of Events...Contact Investigation

Received an Urgent Call from Medical Examiner about a patient with Ukrainian descent noted to have lung cavities on gross pathology, specimen sent for AFB smear/culture, positive for M. TB

On 7-12-2023 4 year old child admitted. Contact investigation identified no household transmission. Patient mother and boyfriend both had positive T spot, but no signs of active TB disease .

On 8-14-23, 4 -year old child was discharged, DIS worker went to give medication and noted that child reside in a house of patient about whom medical examiner called us on 6-2-2023. They do not live together, but the source case (died) lived in basement of the house and index case lived on first floor per mom they never interacted

6-3 to 6-15 multiple attempts made to identify any contact to a patient with Ukrainian descent that passed away

On 7-21 school where our child went for academic year notified in an effort to identify a source

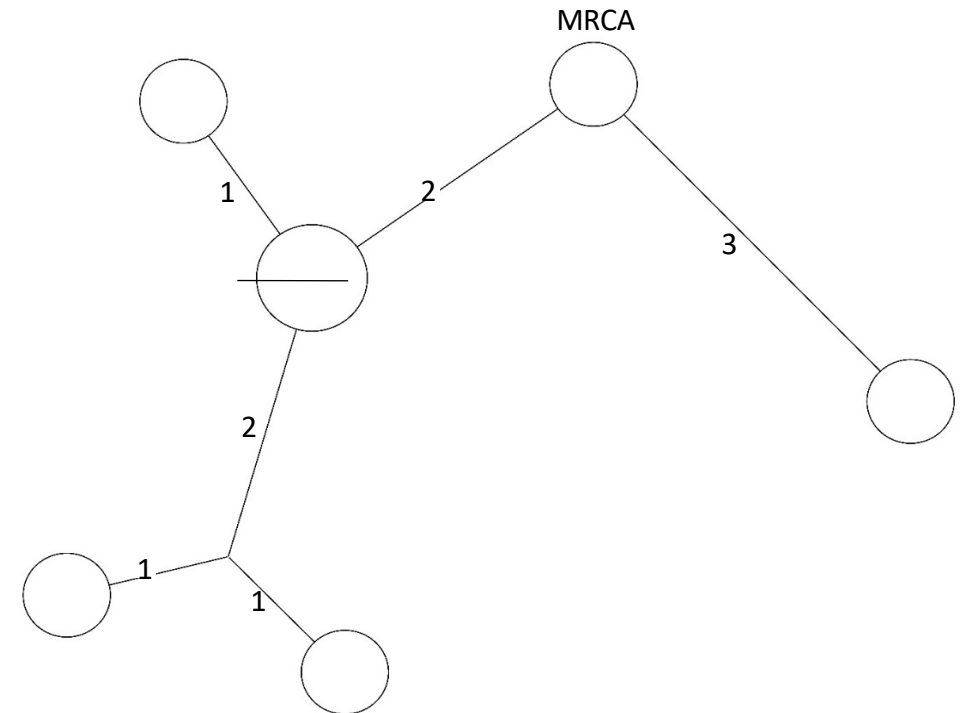


Guideline for Interpreting the Phylogenetic Tree

- Isolates are shown as circles (called nodes) and are labeled with the isolate accession number
- Isolates with the same genome type (i.e., same sequence) are displayed together in one node
- Nodes are connected by lines proportional in length to the number of SNPs that differ between the isolates
- The lines are labeled with the number of SNPs

MRCA = Most Recent Common Ancestor

- Hypothetical genome type (not an actual isolate) from which all isolates on the tree are descended
- Serves as a reference point for examining the direction of genetic change ()

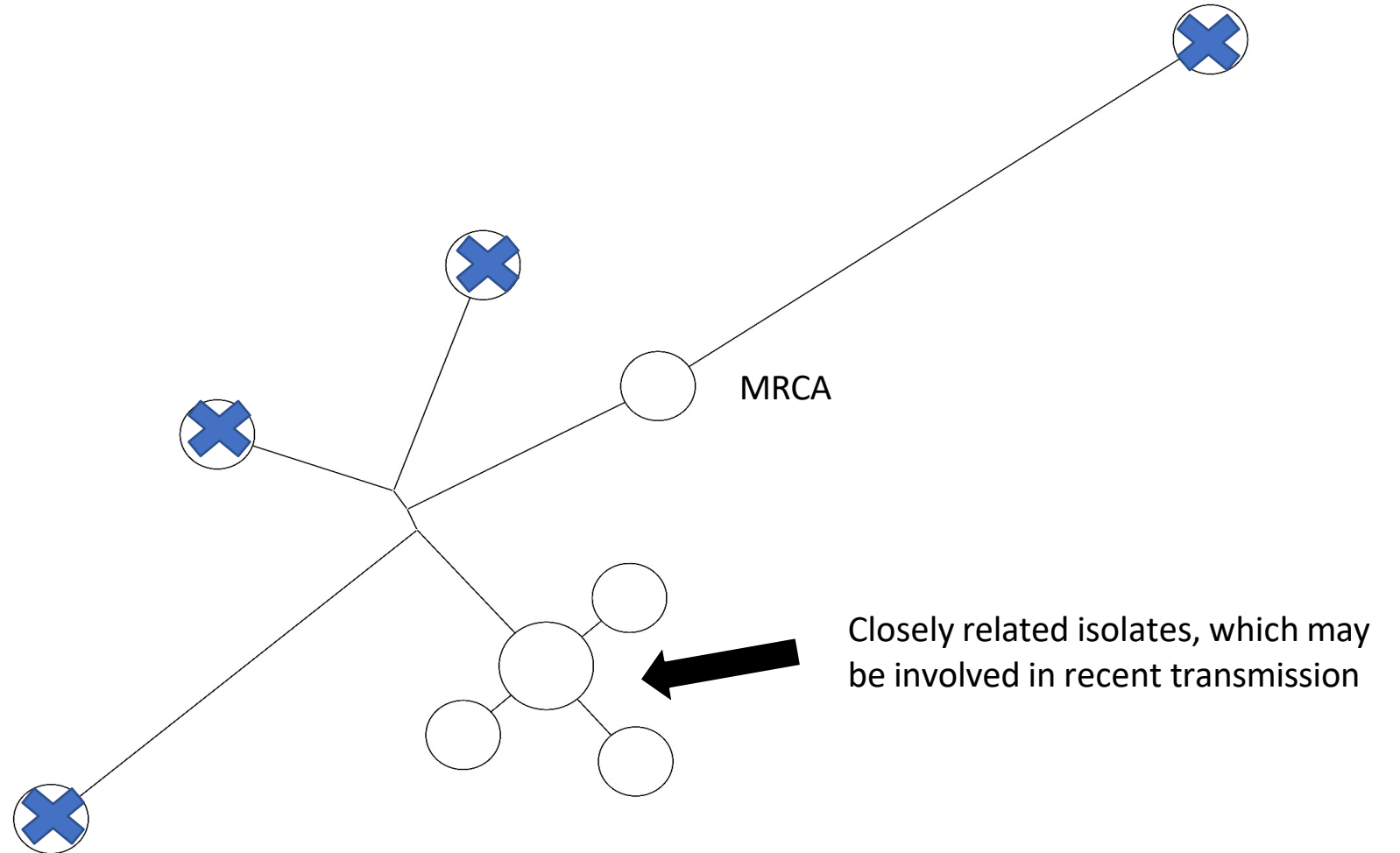




Guideline for Interpreting the Phylogenetic Tree

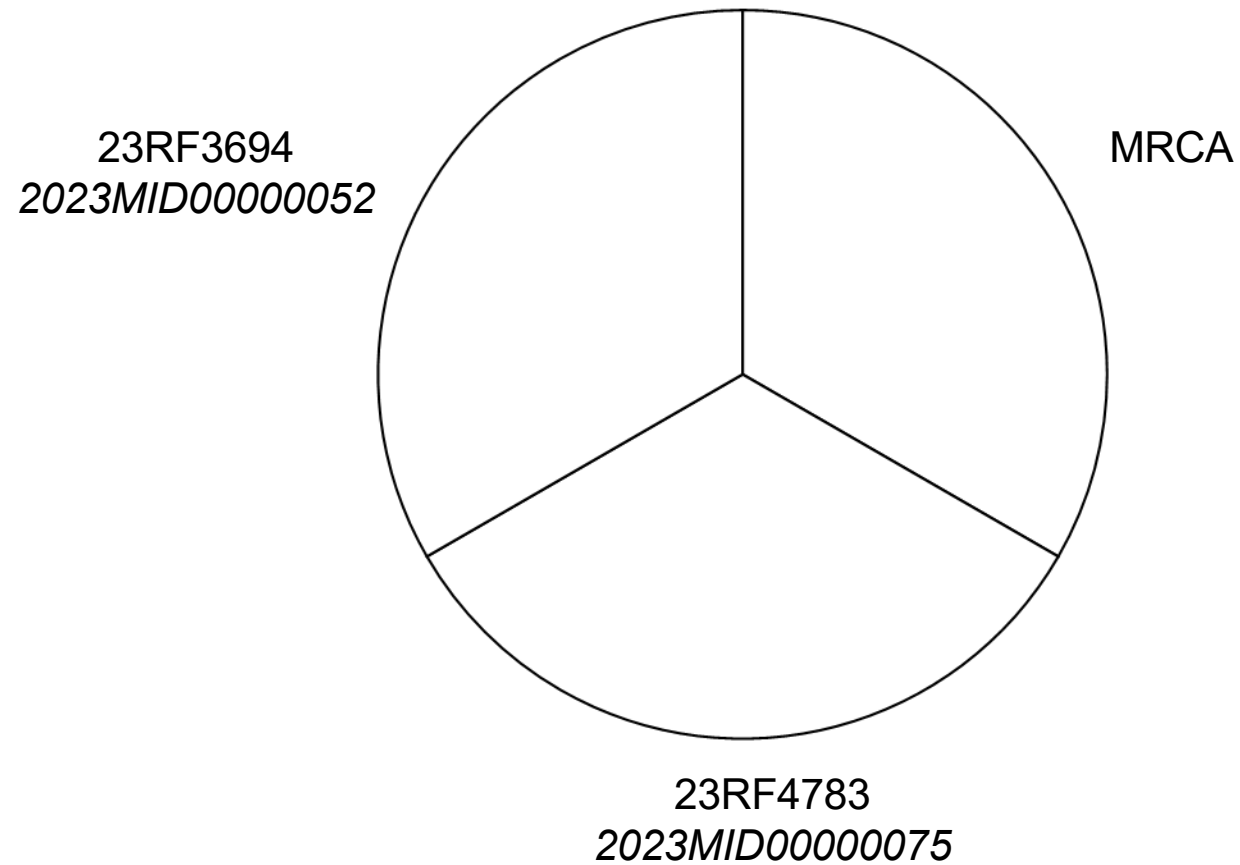


Genetically distant, and unlikely involved in recent transmission





Genotype Source of Index Case





Take Home Points.....

- Among patients (adult/pediatric) with miliary/disseminated TB, routinely screen for CNS involvement irregardless of CNS symptoms .
 - MRI with and without contrast is most sensitive
 - Lumbar Puncture if not contraindicated ---still important to do if MRI positive in effort to get culture from CSF.
- Patients with miliary/CNS TB can have negative IGRA (TB-SPOT or TB QuantiFERON Gold Plus)
- Ethambutol should not be used as part of intensive phase treatment for pediatric CNS TB
- Understand the principle of drug penetration when choosing drug for CNS TB.
- Use high dose IV rifampin 30 mg/kg for CNS TB in pediatric patients due to poor penetration of rifampin
- Understand the principle of drug absorption
 - Can do IV drugs initially if concern for drug absorption
- Evaluate if patient meets criteria to send out for molecular drug resistant TB prior to starting treatment.



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