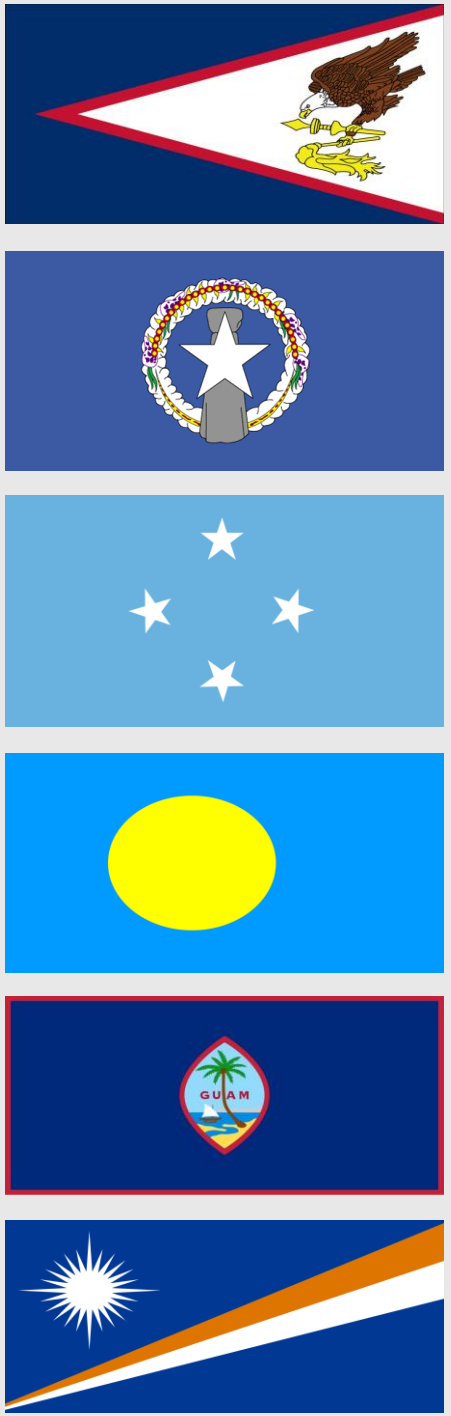
Drug Resistant TB

Samatha Malley
ARNP
Peoples Community Health Clinic, Waterloo, IA

USAPI Regional TB Training 2024



Objectives

- Review basic definitions in drug resistant TB
- Describe how drug resistance happens
- Discuss basic regimens for drug resistant TB

Definitions

- Mono-resistant TB disease: only resistant to one drug
- Poly-resistant TB disease: resistant to two drugs that are not RIF or INH
- MDR TB disease: resistant to at least INH and RIF
- Pre-XDR TB disease: resistant to INH, RIF, and a FQL **or** INH, RIF, second line injectable (amikacin, capreomycin, and kanamycin).
- XDR TB disease: resistance to INH, RIF, a FQL, and a second line injectable **or** INH, RIF, FQL, BDQ or LNZ

	Drug Classes				CDC
Resistance classification	Isoniazid & Rifampin	Fluoroquinolone (at least one)	Second-Line Injectable (at least one)	Bedaquiline	Linezolid
MDR TB	X				
Pre-XDR* TB	X		X		
	X	X			
XDR* TB	X	X	X		
	X	X		X	
	X	X			X

Resistance classifications and drug classes for MDR, pre-XDR, or XDR TB.

* Each row indicates one combination of drug resistance that meets the respective definition of pre¬ XDR or XDR TB.

The Impact of MDR TB

- WHO reported 410,000 cases in 2022
  - 160,000 deaths
- Western Pacific Region accounts for 16% of MDR TB disease globally

How can this happen?

- Primary Resistance
  - TB Disease following infection with MDR TB
  - Reactivation of latent drug-resistant TB infection

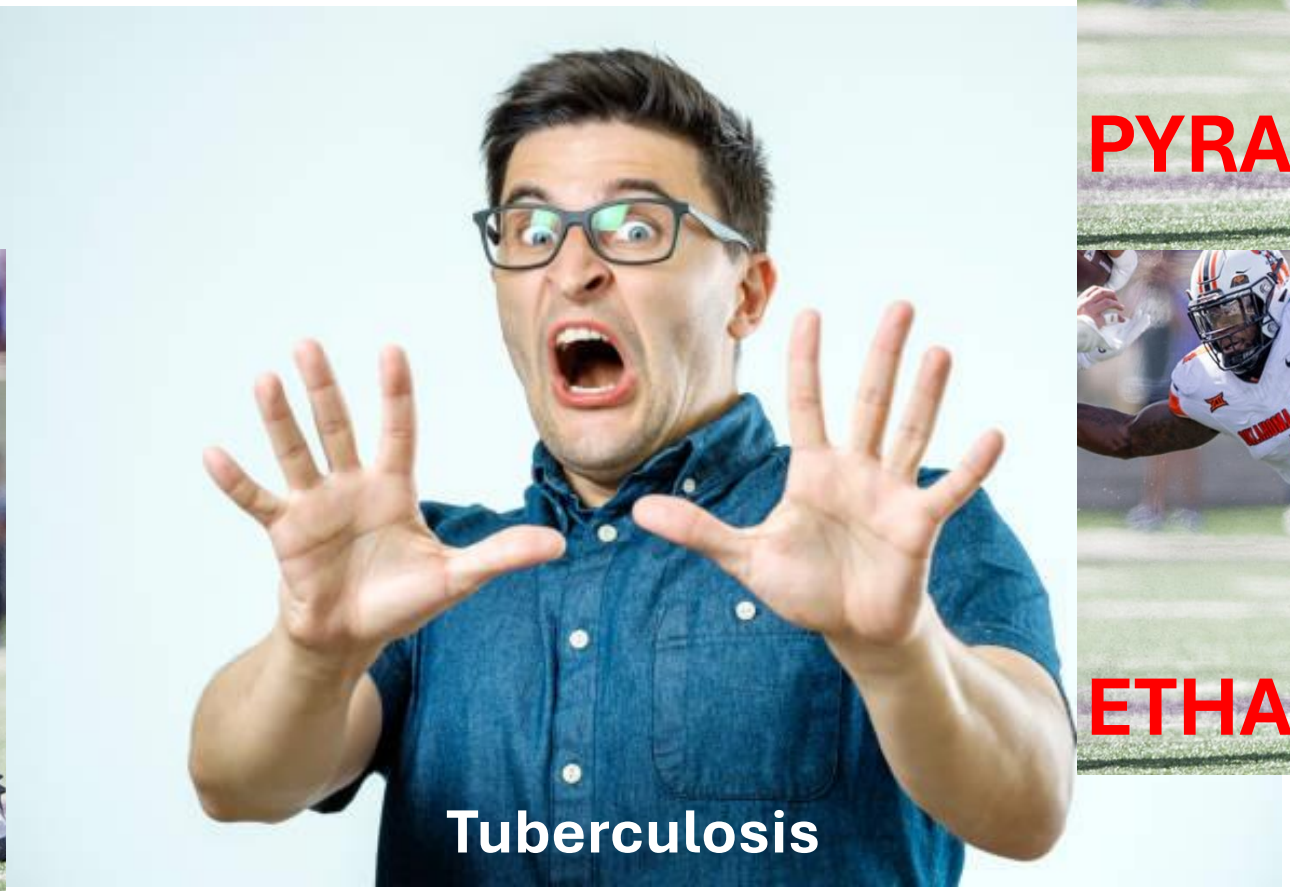
How can this happen?

- Secondary Resistance
  - Poor adherence
  - Inadequate treatment of TB disease
  - Malabsorption of ATT
  - Interrupted drug supply
  - Overuse of antibiotics

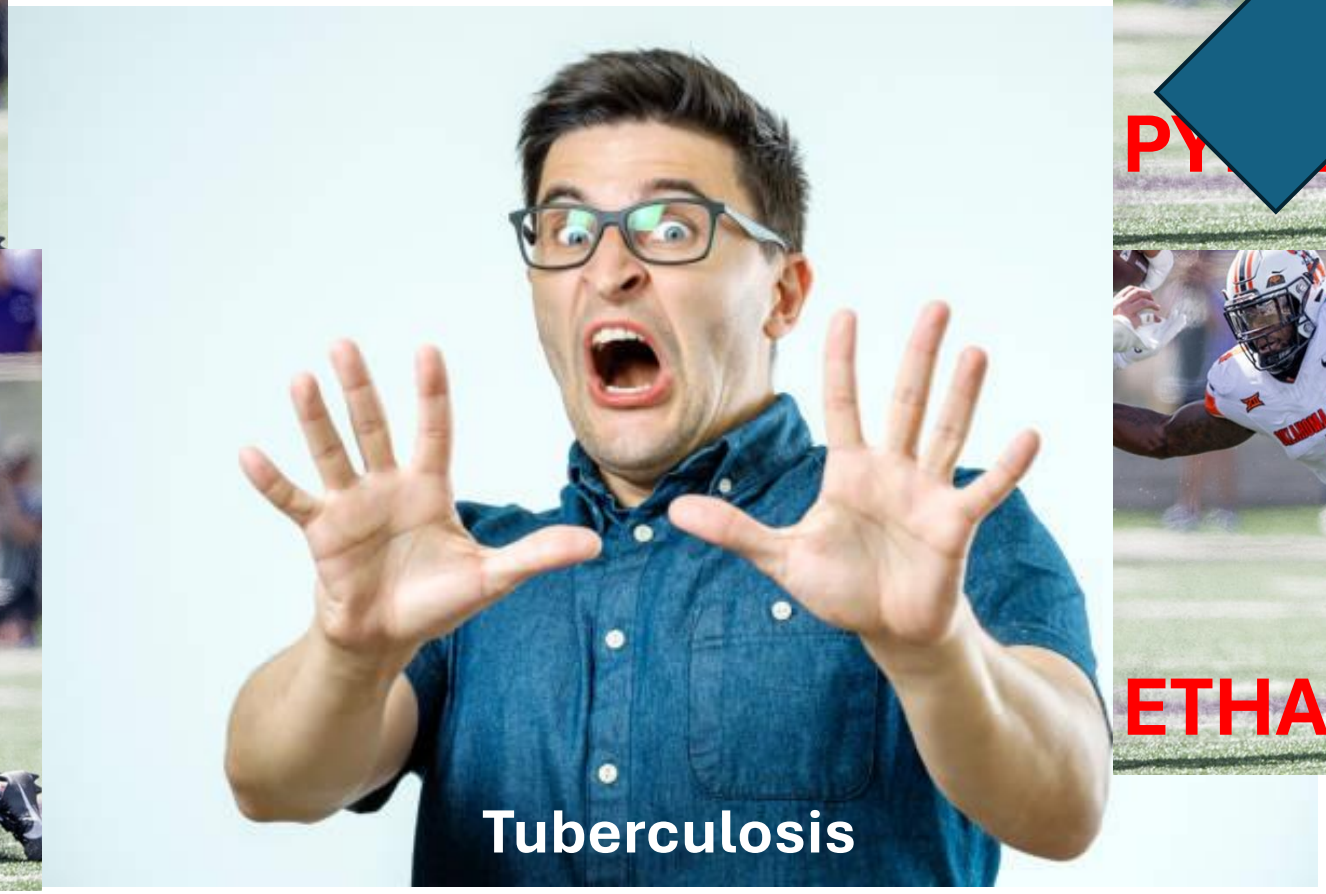
How can this happen?

- Genetic mutations confer drug resistance
  - TB is smart
- When patients have TB disease some, of the TB germs will be resistant to one of our drugs
  - Multidrug therapy

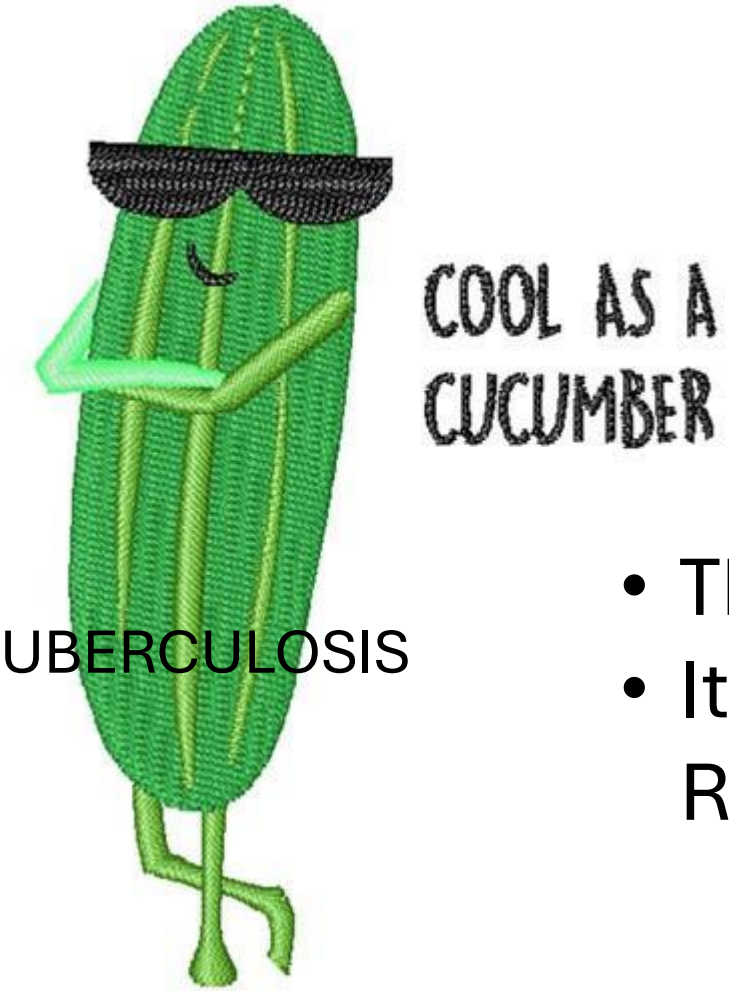
How can this happen?



How can this happen?



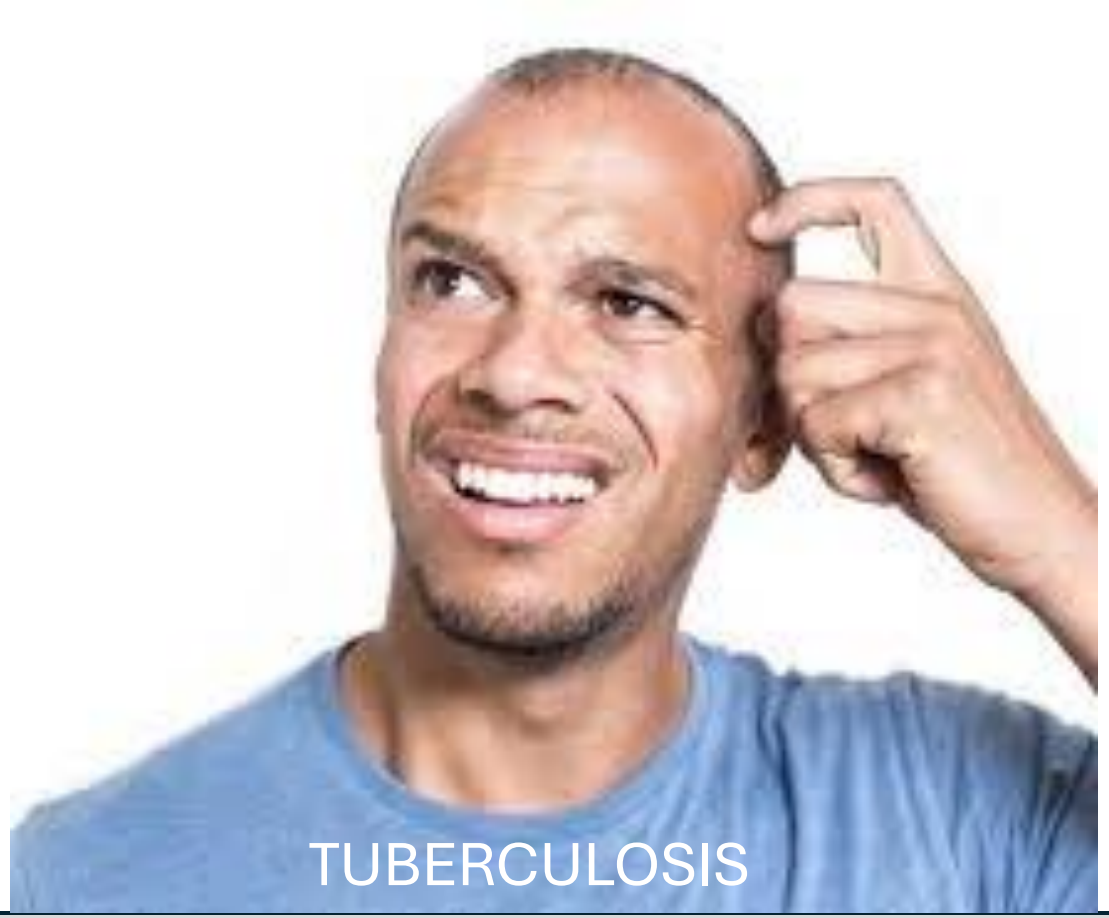
How can this happen?



TUBERCULOSIS

- TB is smart and strong
- It will learn to fight Rifampin

How can this happen?



- Patient misses DOT

How do we prevent this?

- DOT
  - Patients get all or none of their drugs
- Multi-drug therapy
  - Short periods of phased reintroduction may happen in certain scenarios
- Try our best to get a culture
- Get both genotypic and phenotypic DST when feasible

When is this happening?

- During treatment of active disease
  - Usually occurs 1-3 months into drug administration
- Following a relapse
  - Less likely with good DOT and multidrug therapy
- Immediately upon infection with an already resistant strain

Diagnosing MDR TB: Step 1: identify risk

- Risk for resistance should be assessed with all new TB disease
  - Previous TB treatment
  - Epidemiology of the patient
  - Exposure to know or suspected infectious MDR TB

Diagnosing MDR TB: Step 1: identify risk

- History of TB
  - Delayed culture conversion
  - Inadequate clinical response
  - Worsening of symptoms
  - Suboptimal adherence
  - DOT not used in first treatment course
  - Treatment failure or relapse
    - Acquired resistance is much less likely when high quality-DOT is used
  - Inappropriate treatment regimen

Diagnosing MDR TB: Step 1: identify risk

- No history of TB
  - Exposure to documented drug resistance
  - Exposure to suspected drug-resistant TB
  - Travel to an area with high prevalence of drug resistance
  - History of what sounds like TB treatment, even though the patient doesn't report previous treatment

Diagnosing MDR TB: Step 2: testing

- Initial evaluation:
  - IGRA or TST will test for infection.
  - AFB smear and culture
  - NAAT/Molecular testing
    - Xpert MTB/RIF
    - A positive rpoB mutation usually means MDR TB
      - RIF monoresistance is uncommon
      - False positives are rare but do occur
      - Reassess risk

Diagnosing MDR TB: Step 2: testing

- Sequencing-based assays
  - All first line drugs
  - Which genes have mutations
  - Get second-line drug testing when
    - RIF resistance
    - You know you need to use a second line drug (FQL for CNS disease)
    - Can’t use standard first-line regimen

Diagnosing MDR TB: Step 2: testing

- Growth based drug sensitivity testing (DST)
  - Still the gold standard
  - 4+ weeks turn round time
  - Solid or liquid media
  - Not a straightforward interpretation
    - Mycobacterium exist on a spectrum (some germs are active, others are latent)
    - Our drugs have different tissue penetrance
    - Different MIC

Diagnosing MDR TB: Step 2: testing

- Critical concentration
  - **The line between resistance and susceptible**
  - The drug “kind of” works
  - Slows down growth but doesn’t kill it
  - This concentration will be **different for every drug** but is **a fixed value** based on the test you’re using and correlates with serum drug levels (**drug in the blood).**
  - Once a specified amount of the strain’s TB germs grows at the critical concentration, we consider it resistant

Diagnosing MDR TB: Step 2: testing

- Minimum inhibitory concentration (MIC)
  - **How much drug do I need to kill this TB?**
  - Doesn't directly correlate with critical concentration
  - Usually, the critical concentration is enough to kill TB (susceptible TB)
  - Additional or add on test (not necessarily a part of the lab sequence)

- Some drugs may be tested for low and high concentrations of the drug
    - INH, FQL
    - Might be possible to consider keeping the drug on board in certain situations
    - Will the amount of drug required be safe for my patient?

Diagnosing MDR TB: Step 3: treatment

- Expert consult
- Mono RIF resistance is rare- usually BPaLM
- Mono INH resistance: generally, swap INH out for a FQL
  - Consider extending treatment depending on the circumstance
- Otherwise, BPaLM
  - 6 months of duration
  - BDQ: QTc prolongation (EKG 2, 12, 24 weeks), hepatotoxicity
  - LZD: myelosuppression, optic and peripheral neuropathy
  - MFX: rare tendon rupture, QTc prolongation
  - Pa: peripheral neuropathy

Contacts: LTBI

- If susceptible to RIF, you can do 4R
- If MDR – generally using a FQL
- Window prophylaxis: expert opinion

Thank you! Questions?