MDR TB management

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Key points

1. When to think about MDR TB
2. How to diagnose/confirm MDR TB quickly
3. How to treat MDR TB
4. Contacts, back to work, etc.

Definitions

- MDR TB
- = Multidrug resistant = resistant to Isoniazid and Rifampin
- Why important? These are the two best drugs in RIPE
- Fortunately rare in VA, ~5-10/yr, but very resource intensive

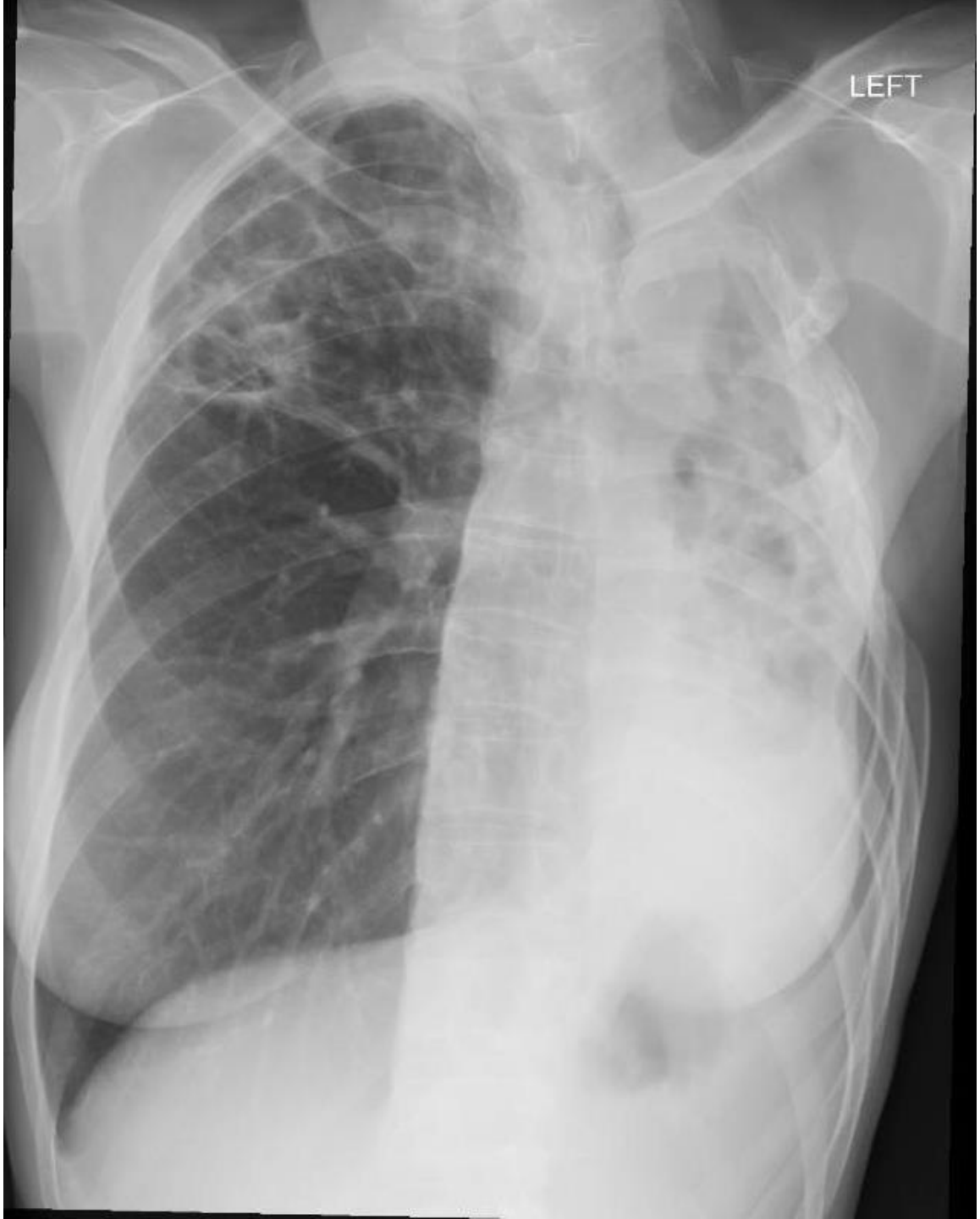
- XDR TB
- MDR + resistant to a quinolone (Levofloxacin/Moxifloxacin) and an injectable (Amikacin/Capreomycin)
- Why important? These are two of the most important drugs for treating MDR
- Very rare, in USA ~0-5/yr

Case

- 40 yo female chronic dry cough
- 50# wt loss (90#)

- PMH: recently arrived from Mongolia
- 1999: pleural effusion
- 2000: rx TB RIPE + Strep + L lobectomy
- 2001: reconstructive thoracoplasty, tiw RIP unknown duration
- 2008: rx TB with 12 mo PZA,ETH,CYC,OFL,KAN
- 2009: sputum smear and culture negative

- Fam Hx: brother dies TB 1998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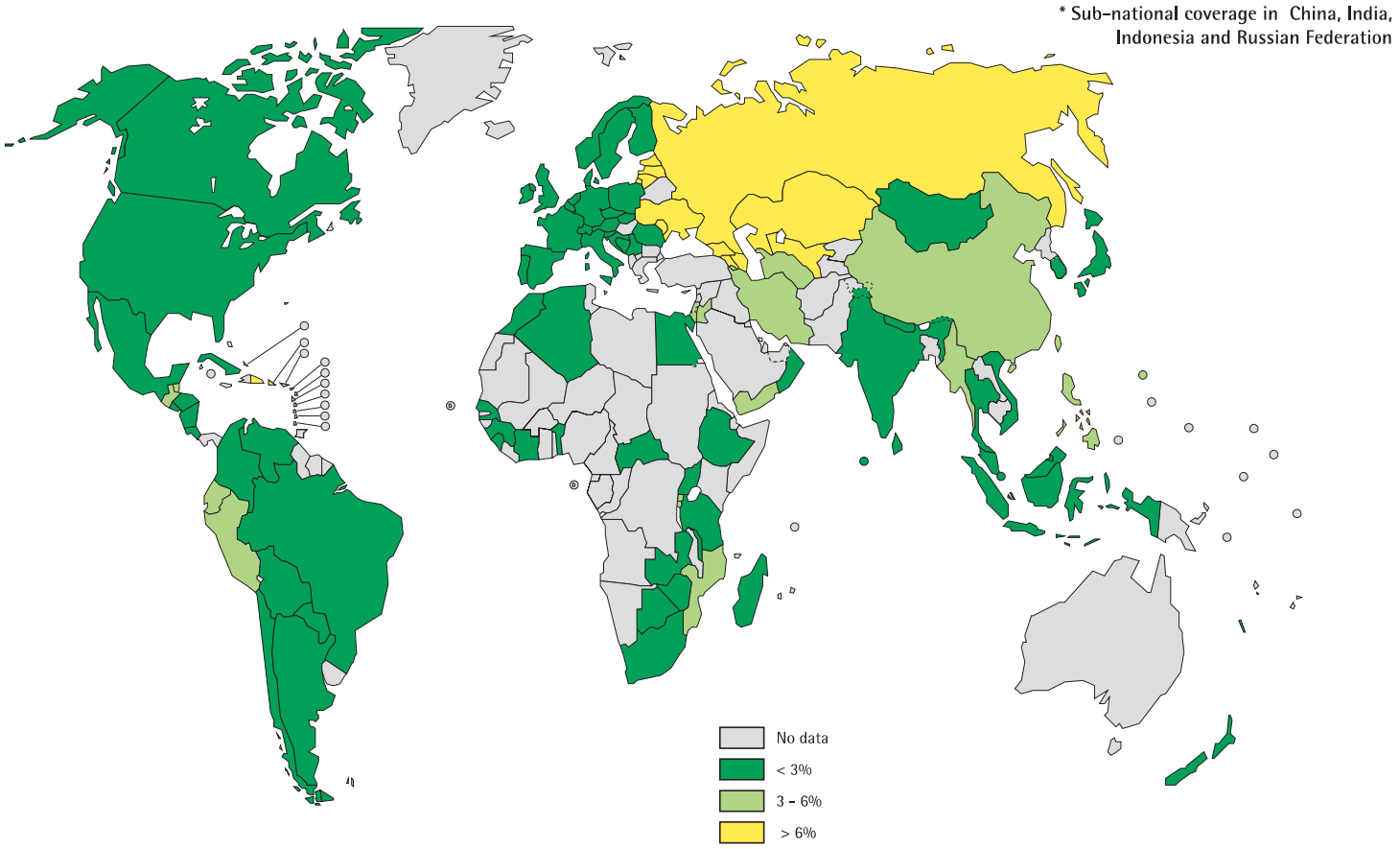
Case

- Sputum 4+AFB
- Management?

Point 1

- Think about MDR TB
- 1. patients from high risk countries
- 2. patients with prior TB treatment

MDR-TB among new cases 1994-2007



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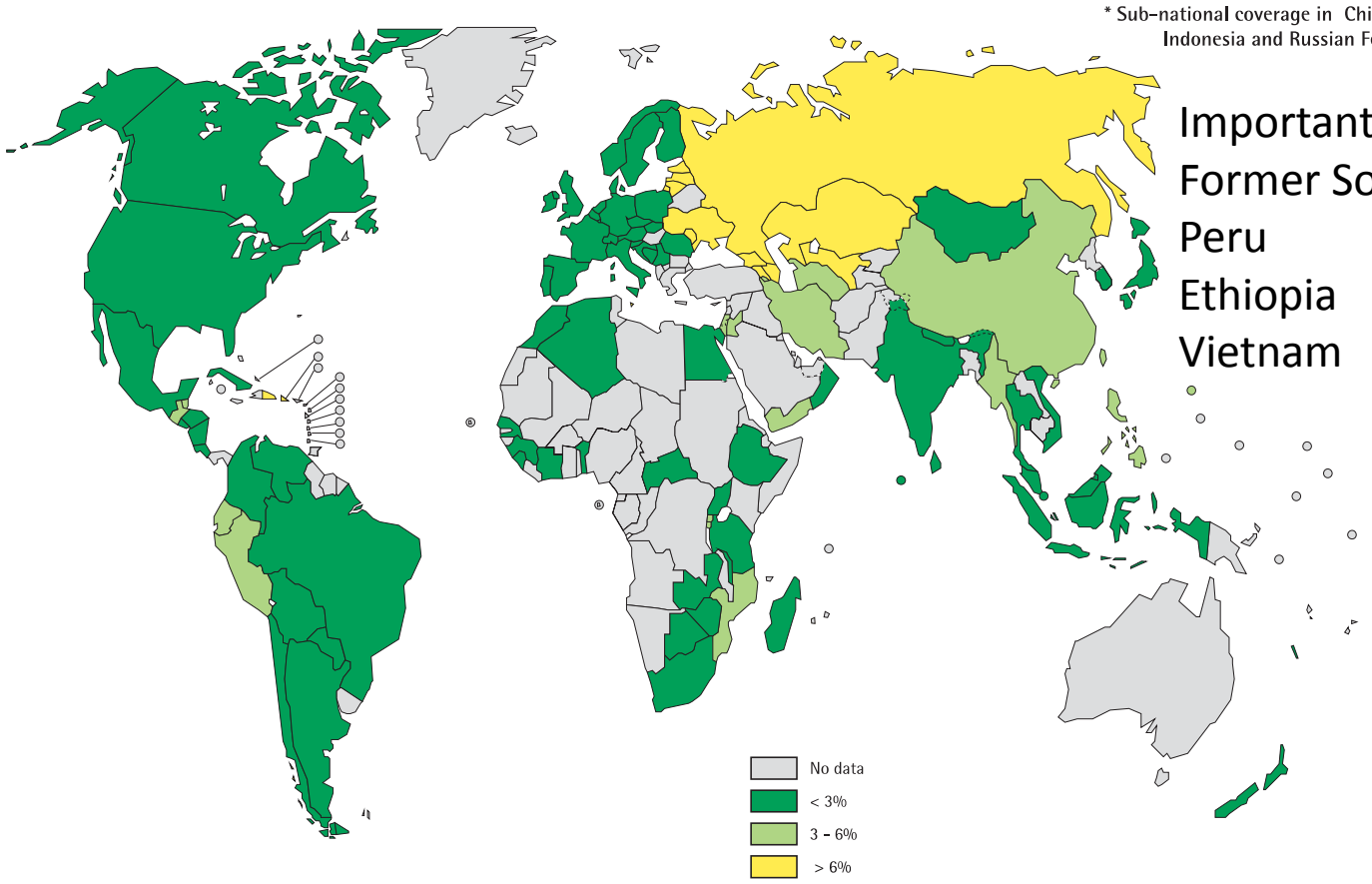
MDR-TB among new cases 1994–2007



Important areas for Virginia
Former Soviet Union
Peru
Ethiopia
Vietnam

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Point 2

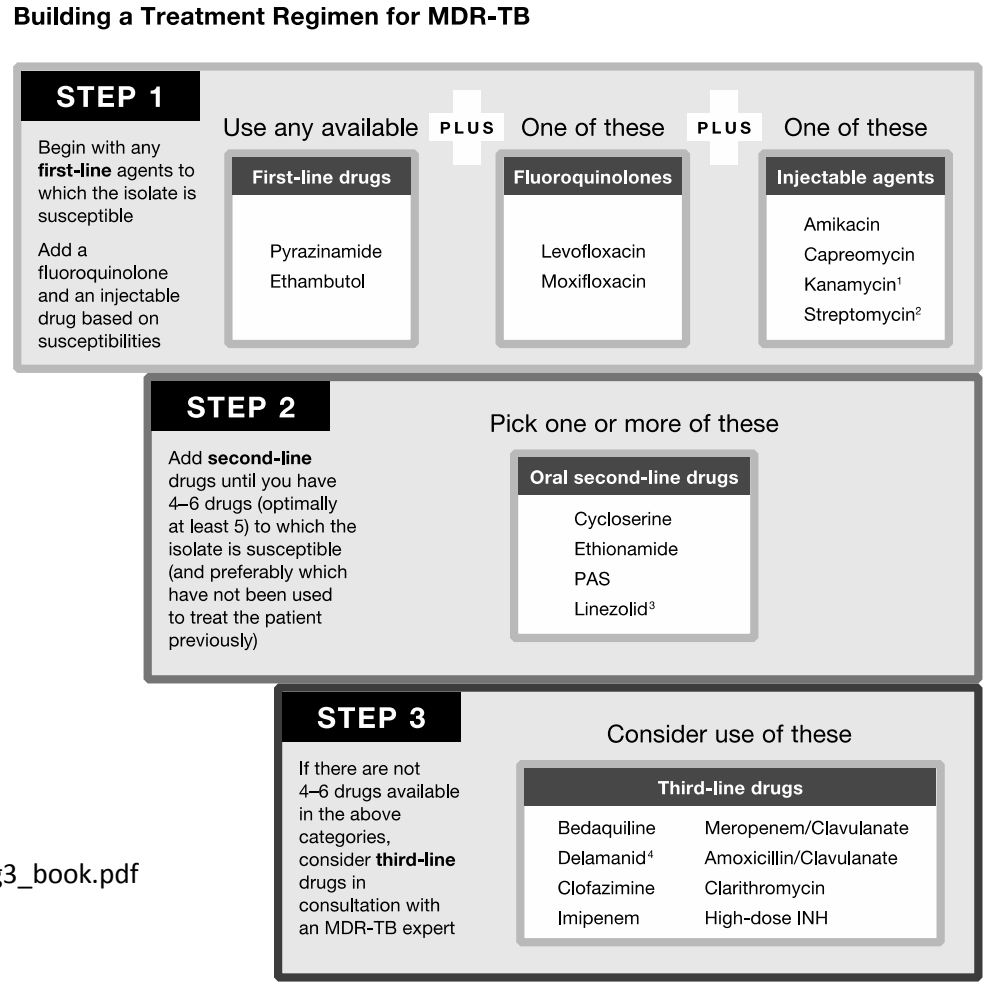
- How to diagnose/confirm MDR TB (quickly)
- GeneXpert on smear positive sputum
  - “MTB detected; RIF resistance detected”
- Send smear positive sputum to CDC for MDDR
- Molecular amplification of TB drug resistance mutations, which gives a result in 2-3 days that predicts well the final culture susceptibility result

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)	Mutation: C-15T	Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are INH-R.)
katG (Ser315 codon)	No mutation	
embB (Met306,Gly406)	Mutation: GAC>GCC; Asp354Ala	Likely Ethambutol resistant. (90% of isolates in our in-house evaluation of 550 clinical isolates with the Asp354Ala mutation are EMB-R.)
pncA (promoter, coding region)	Mutation: GCA>GAA; Ala46Glu	Effect of this mutation on Pyrazinamide resistance is unknown. This mutation has been reported to be associated with PZA resistance in the literature.
gyrA (QRDR)	Mutation: GAC>GGC; Asp94Gly	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 other than the one detected in the rrs locus; 87% of KAN-R isolates have a mutation other than the one detected in either the rrs locus or the eis locus; 99% of CAP-R isolates have a mutation other than the one detected in either the rrs locus or the tlyA locus.)
eis (promoter)	No mutation	
tlyA (entire ORF)	No mutation	

Point 3

- How we treat MDR TB
- Curry Guide
- Try to assemble 4-5 drugs



- https://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_book.pdf

Point 3

- How we treat MDR TB
- Started Capreomycin, Linezolid, PAS, Clofazimine, Bedaquiline, high dose INH
- Final susceptibility results (~2 months later)

Drug	Result	
INH 0.2 ug/ml	R	
INH 1.0 ug/ml	S	1
Rifampin	R	
Pyrazinamide	R	
Ethambutol	R	
Ofloxacin	R	
PAS	S	2
Ethionamide	R	
Capreomycin	S	3
Kanamycin	S	
Amikacin	S	
Streptomycin	R	
Linezolid	S	4
Bedaquiline	S	5
Clofazimine	S	6

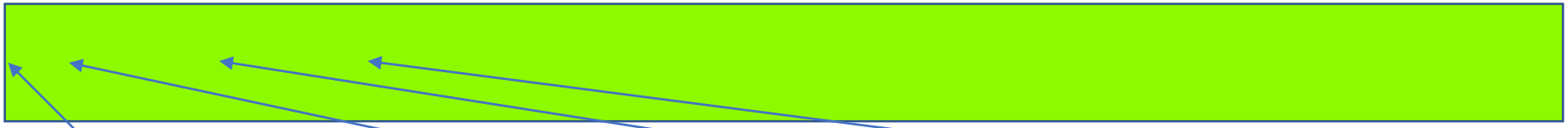
Point 3

- How we treat MDR TB
- Duration: usually 12-18 months
- Injectable often IM tiw
- Serum drug levels on all drugs to ensure OK absorption (after a couple weeks)
- Main side effects:
  - Nephrotoxicity, low Mg, hearing loss: injectables
  - Nausea: esp PAS. Zofran before meds.
  - Neuropathy: esp Linezolid
  - Myalgias: esp levo/moxi
  - EKG QT prolongation with Moxi, Clofazimine
- Clofazimine requires an FDA approval process through UVA and the client sign a special consent (Mary Marshall, Scott Heysell)

Point 4

- Contacts, back to work, etc.
- Most principles same as drug susceptible TB
- Per usual – home isolation, break transmission, window prophylaxis <5yo, screen close contacts for LTBI
- Differences
  - Maintain isolation until documented culture negative
    - Ex, if it takes 2 months to become culture negative, plus another 2 months until those cultures return negative = 4 months isolation
  - Most MDR TB is quinolone susceptible and we often use levofloxacin 500-750mg po qd for LTBI (6 mo)/window prophylaxis

Long timeline



Week 1

- Suspect MDR TB
- Confirm MDR TB on sputum with molecular testing
- Use MDDR to guide the initial regimen of ~5 drugs

Month 1

- Follow patient for response
- Serum drug levels (esp for injectable capreomycin)
- Follow cultures, set up first and second line drug susceptibilities

Month 2

- Finalize regimen

Month 4

- Confirm culture negative, stop isolation

Month 12-18

- Finish treatment
- Side effect management

INH resistant TB (~5% of VA TB cases) treatment

- Option 1: 2003 ATS/IDSA guidelines: RIF, EMB, and PZA ± a later generation quinolone (esp extensive or cavitary disease) for 6-9 months
- Option 2: WHO 2018: RIF, EMB, PZA and LFX for a duration of 6 months
  - Option 3: Curry Guide adds: Daily RIF, EMB, PZA and MFX (400 mg) for 2 months followed by once-weekly doses MFX plus high-dose RPT (1200 mg) for 4 months
- Daily/M-F therapy throughout
- Confirm quinolone susceptibility