PREVENTION WORKS!

Drug Resistant TB:
Prevent it
Don't make it worse

Dana Kissner, M.D.
Detroit TB Program / Wayne State University School of Medicine
Tri-State TB Intensive Workshop
Columbus, Ohio
September 26, 2018

Disclosures

- Financial – none
- 10 medications are approved by the FDA for TB
  - INH, RIF, Rifapentine, PZA, EMB, Streptomycin, Cycloserine, Ethionamide, PAS, Bedaquiline
  - All other drugs discussed here are NOT FDA approved for TB

Objectives

- When you ***think TB*** you will ***think drug resistance***
- When your patient has a higher than normal chance of having drug resistant TB you will know to ***rapidly confirm*** it or rule it out
- When you suspect or know that your patient has drug resistant TB you will know how to develop a ***treatment plan***

Topics

- Introduction – uncertainties, resources, definitions
- Epidemiology / costs
- Origin of drug resistant TB – man made
- Diagnostic testing – rapid
- Building a treatment regimen
  - Mono Resistant TB
  - Poly Resistant TB
  - Multi-Drug Resistant TB

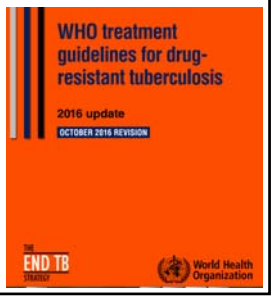
UNITED NATIONS
HIGH-LEVEL MEETING ON THE FIGHT TO END TUBERCULOSIS
26 SEPTEMBER 2018, UNHQ, NEW YORK

Uncertainties. Resources. Definitions.

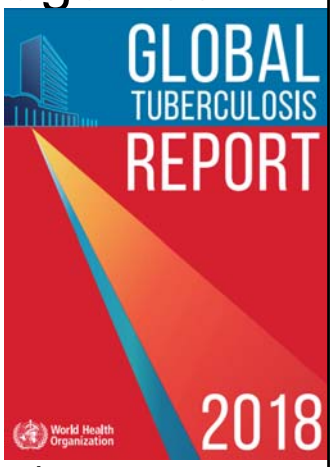
INTRODUCTION

Introductory Remarks

- Adequate data in the form of randomized controlled trials is lacking
- Recommendations for treatment are often based on expert opinion, which can vary
- Each case has its own complexities and complications should be expected, anticipated, and discussed
- This is a moving field
  - WHO Guideline Development Group convened July 16-20, 2018 to update 2016 guidelines



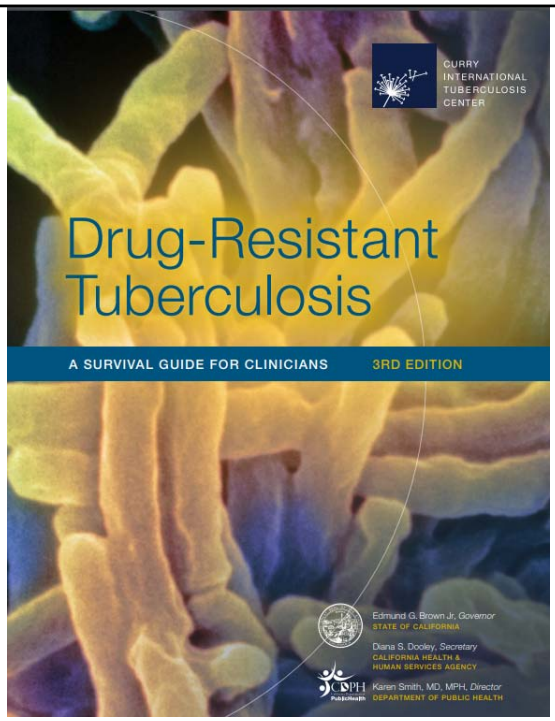
Rapid Communication Box 4.7 Page 109



- Priority 1 drugs for MDR-TB
  - Levofloxacin or Moxifloxacin
  - Bedaquiline
  - Linezolid
- "Longer" all-oral regimens are acceptable for some patients
- Inclusion of injectables is no longer required
  - Kanamycin, Capreomycin no longer recommended

The White House National Action Plan

- December 2015, 5 year plan
  - Strengthen domestic capacity to combat Multidrug-Resistant TB (MDR-TB)
  - Strengthen state & local capacity to prevent transmission of drug-resistant TB
  - Ensure that patients with drug-resistant TB receive treatment until cured



Published 2016

Represents best practice in 2015

New ATS, CDC, IDSA MDR guidelines are in process

Definitions (1)

- DR-TB: Drug-resistant TB
- MDR-TB: Multidrug-resistant TB
  - Any TB resistant to **at least** isoniazid (INH) and rifampin (RIF)
- Pre-XDR-TB: Pre-extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to either a fluoroquinolone or 1 of 3 injectables (amikacin, kanamycin, capreomycin)
- XDR-TB: Extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to both a fluoroquinolone and 1 of 3 injectables (amikacin, kanamycin, capreomycin)

Definitions (2)

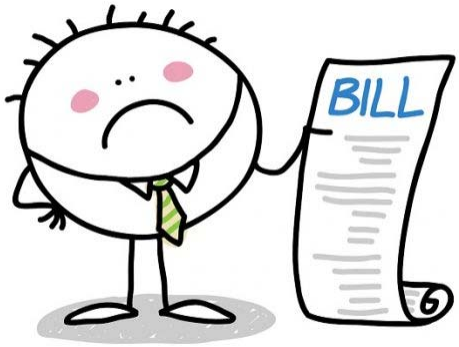
- RR-TB: Rifampin-resistant TB
- MDR/RR-TB: WHO guidelines refer to rifampin or rifampin and isoniazid resistant TB
- Transmitted drug resistance (primary): TB in a person not previously treated for TB (new* TB case)
- Acquired drug resistance (secondary): TB in a person previously treated for TB (previously treated* TB case)
  - New case* = < 1 month treatment
  - Previously treated* = treatment for ≥1 month
  - Resistance can be created by 1 month of inappropriate treatment
  - Primary & secondary are old terms

Definitions (3)

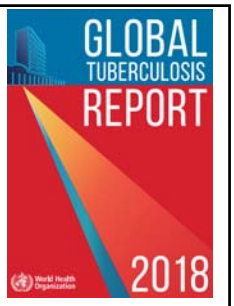
- Mono or isolated resistance – resistance to 1 drug
  - INH mono-resistance is common, rifampin less so
  - PZA mono-resistance suggests *M. bovis* (including BCG), or other mycobacteria in the TB complex (*M. canettii*)
- Poly-resistant TB – resistance to >1 drug, but not INH and RIF

Statistics. Costs.

EPIDEMIOLOGY



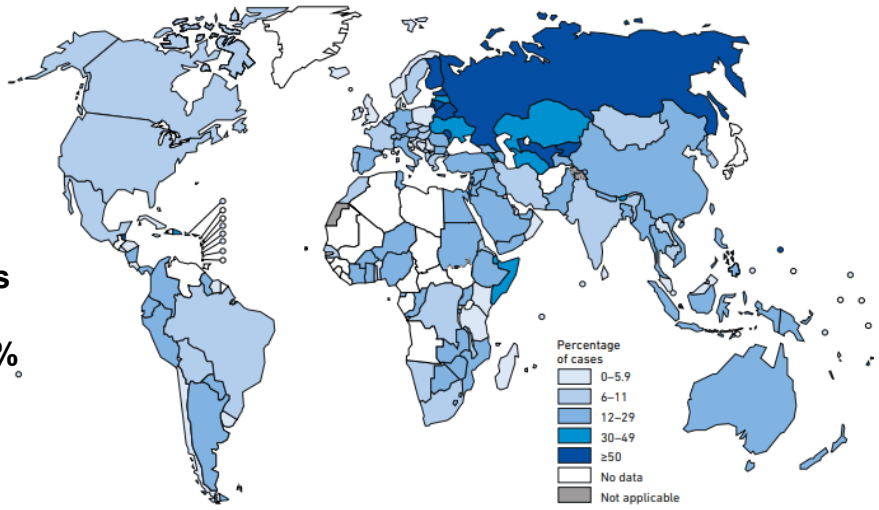
Global Epidemiology 2017



- 457,000 cases of MDR-TB
- 101,000 additional cases of RR-TB
- 47% of the MDR/RR-TB cases were from
  - India (27%), China (13%), & the Russian Federation (10%)
- 8.5% of the MDR/RR-TB cases were XDR-TB
- **3.5% new and 18% previously treated TB cases were MDR/RR**
- 240,000 (43%) MDR/RR cases died
- 139,114 (25%) MDR/RR cases started treatmen
  - 55% were successfully treated

% MDR/RR-TB in Previously Treated TB Cases 2005-2018

In new cases the darkest color is ≥18%



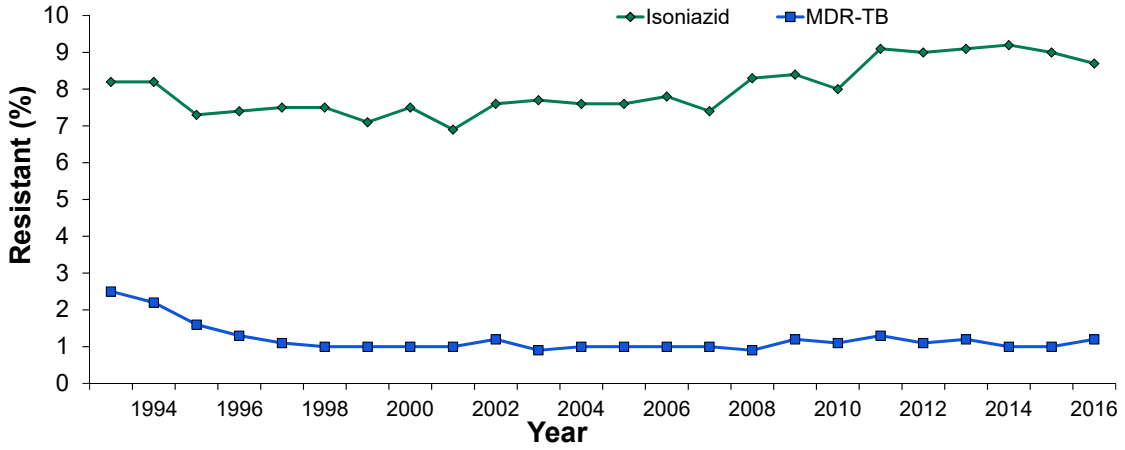
Figures are based on the most recent year for which data have been reported, which varies among countries.

World Health Organization | GLOBAL TB PROGRAMME | END TB

Epidemiology – U.S.A. 2016

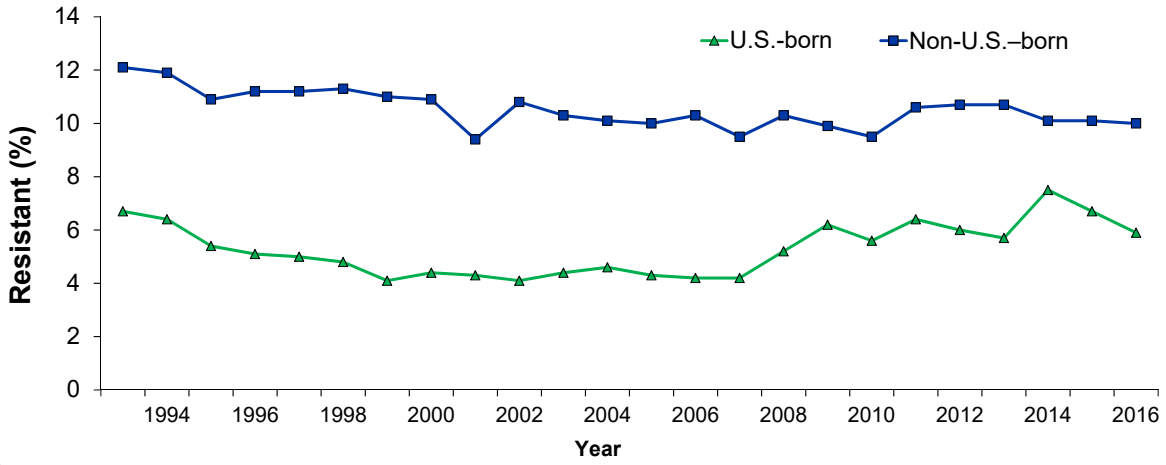
- 97 cases of MDR (including 1 XDR)
- 78 of the MDR cases were new / transmitted drug-resistant
- 18 of the MDR cases had prior TB treatment
  - 1 had unknown TB history
- 89 of the MDR cases, including the XDR one, were in non-U.S. born persons
- 1.4% of all TB cases in 2016 were MDR

Primary Anti-TB Drug Resistance, United States, 1993–2016*



* As of June 21, 2017.
Note: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.

Primary Isoniazid Resistance Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2016*



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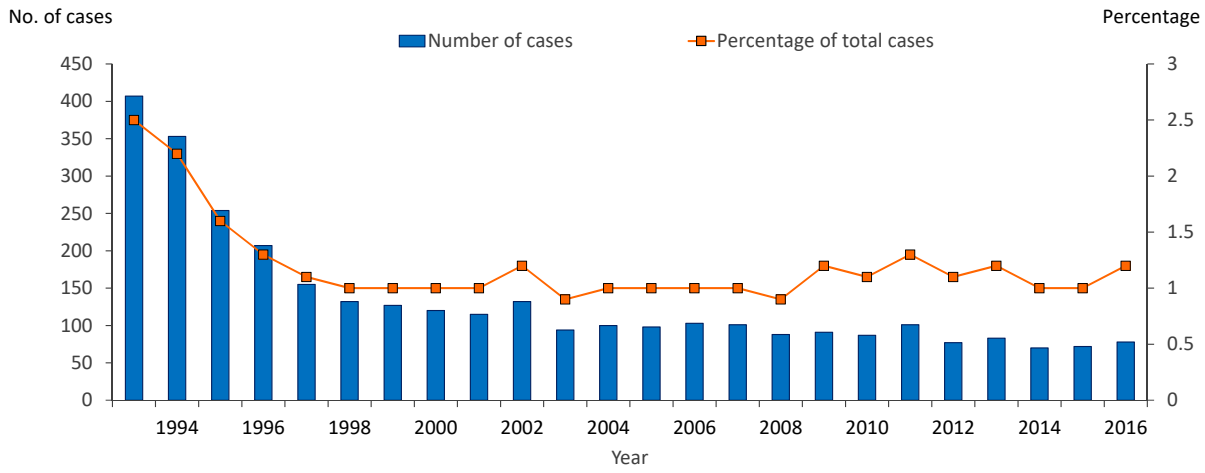
Primary MDR-TB, United States, 1993–2016*



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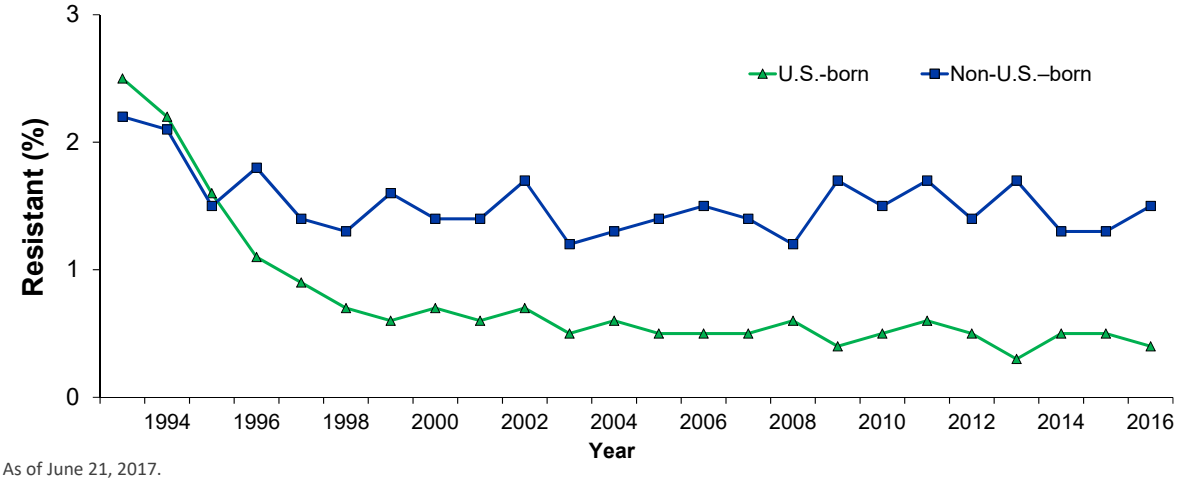

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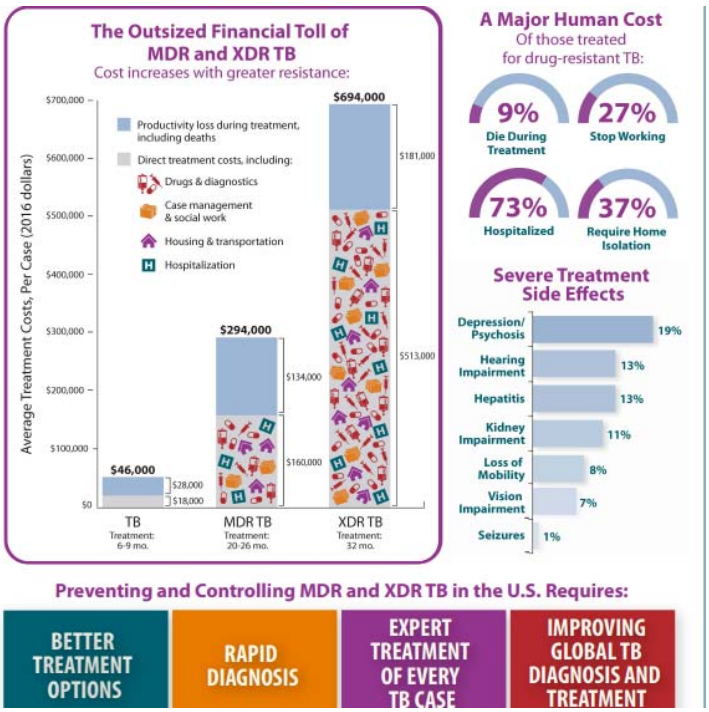
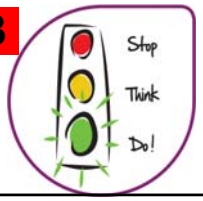
November, 2017

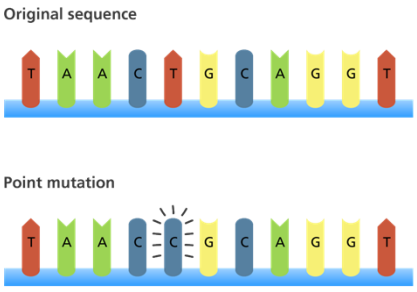
Direct costs
DS-TB $18,000
MDR-TB $160,000
XDR-TB $513,000



First Conclusions

- Rates and numbers of MDR-TB (U.S.) cases are low but costs, morbidity, and mortality are staggeringly high
- Preventing or recognizing DR should be part of initial TB management
- Estimating likelihood of DR is essential to good care
  - Country of origin and residence helps determine risk
  - Persons treated previously for TB have a higher risk
- **Consider risk of resistance before initiating TB therapy**

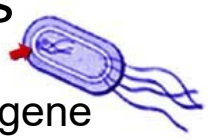




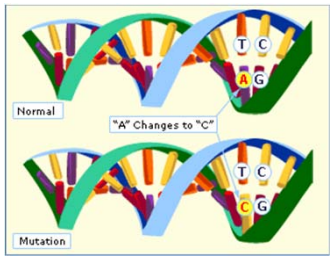
Genetic mutations. Selective pressure. Made by humans.

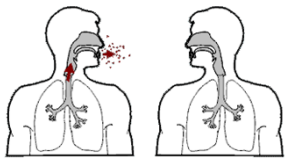
ORIGINS OF DRUG RESISTANT TB

How TB drug resistance develops



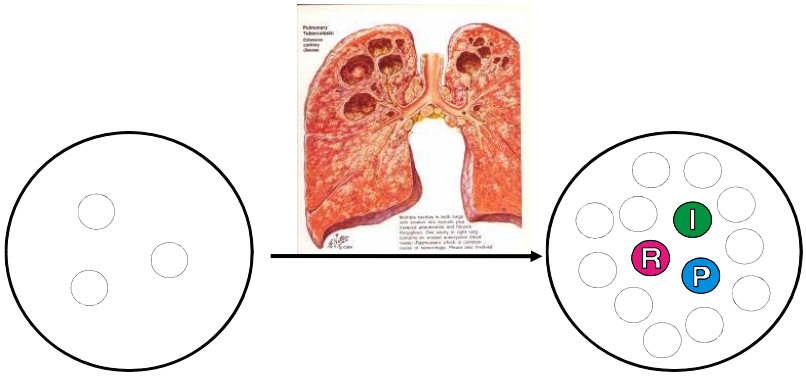
- Mechanism: Spontaneous mutations in resistance gene
  - Single nucleotide substitutions lead to mutations in a gene, conferring resistance to a specific antibiotic
- Selective pressure
  - Inappropriate treatment => acquired DR
  - Clinical drug resistance is man-made
- Transmission to contact => transmitted DR





Adenine **Thymine** **Guanine** **Cytosine**

- Spontaneous mutations develop as bacilli proliferate to >10^8 (100,000,000)
- Typical TB cavity contains 10^7 to 10^9 organisms



- Without selective pressure from inappropriate antibiotic use, a single bacillus will not be resistant to 2 antibiotics.

DRUG	PREVALENCE
ISONIAZID	3.5 X 10^{-6} .0000035
RIFAMPIN	1.2 X 10^{-8} .000000012
PYRAZINAMIDE	1.0 X 10^{-5} .00001

- The prevalence of resistance to INH and Rifampin would be 3.5 x 10^{-6} x 1.2 x 10^{-8} = 4.2 x 10^{-14}

Some Resistance Genes

- INH
  - KatG
  - inhA
  - kasA

80% of resistance

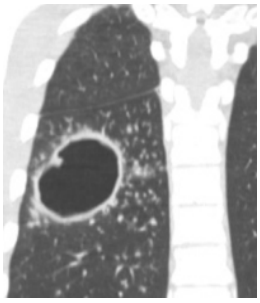
- RIF
  - rpoB

>95% of resistance

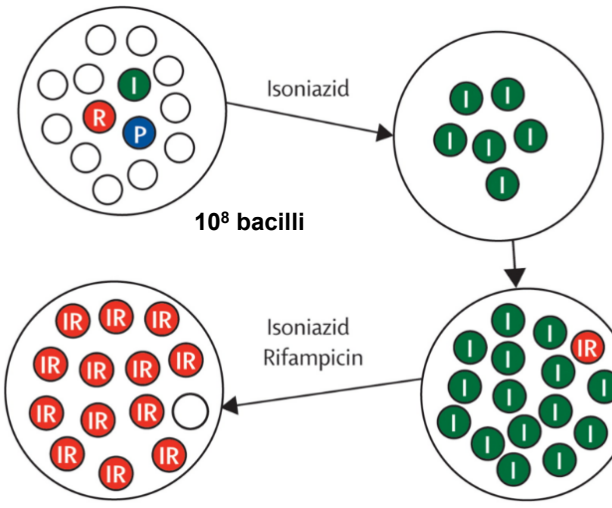
- PZA
  - pncA
- EMB
  - embB

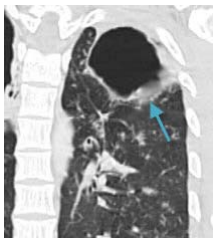
- Fluoroquinolones*
  - gyrA, gyrB
- Kanamycin*, Amikacin*
  - rrs (Kanamycin eis)
- Capreomycin
  - rrs
  - tly
- Streptomycin
  - rrs
  - rpsL
- Linezolid*
  - rplC
- Ethionamide (analog INH)
  - ethA
- PAS
  - thyA

Creation of MDR-TB
"Previously Treated" or "Acquired"



10^8 bacilli





10^8 bacilli

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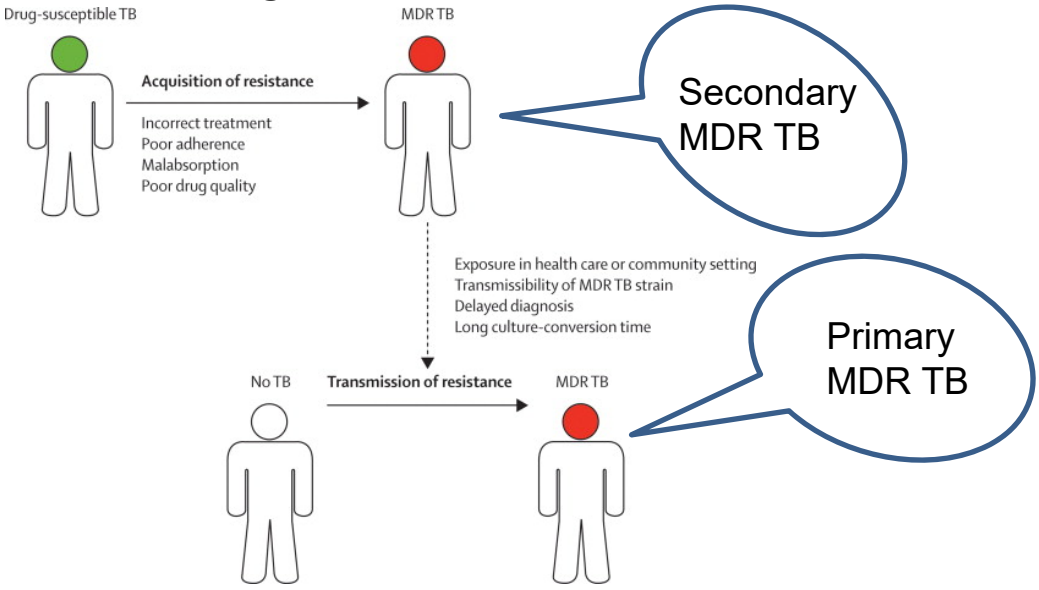
Transmission of MDR TB
"MDR in New Case" or "Transmitted MDR"



2nd Set of Conclusions (1)

- One should suspect resistance in those with prior treatment that was inappropriate
  - Wrong drugs, doses, regimens
  - Intermittent therapy with missed doses
  - Interrupted, erratic treatment
  - Noncompliance, no DOT, patient taking some medicines & not others
  - Possibility of malabsorption
    - Critically ill patient given oral medications
  - Bad medications

2nd Set of Conclusions (2)

- Consider resistance most likely in these circumstances
  - Extensive cavitary disease (more organisms)
  - Poor clinical response to therapy after 2 months
  - Positive cultures after 3 months of therapy or after conversion
  - Contact with a person with resistant disease
  - Emigration from or travel to (>1 month) region with high prevalence/incidence of DR
  - HIV – higher rates of RR-TB
- Taking a good history is essential to preventing or worsening DR and for selecting drugs for treatment

2nd Set of Conclusions (3)

- Never treat TB with a single agent
- Never add a single agent to a failing regimen (patient not improving or getting worse) unless you know the drug susceptibilities

Contact laboratory. Work with local health department / state. Consult experts, COE.

IF YOU SUSPECT RESISTANCE TEST FOR RESISTANCE

Think resistance? Test for resistance! (1)

- Conventional, growth-based DST is a gold standard, but
  - Slow
  - Growth detection and identification takes several weeks; DST an additional 1-3 weeks
- DST for 1st line drugs (INH, RIF, EMB, PZA) should be done for
  - All new TB isolates
  - Positive cultures after 3 months of therapy
  - Positive cultures after a period of negative ones

Think resistance? Test for resistance! (2)

- DST should be done for 2^{o} drugs for all cases of RIF resistance – treat as if this is MDR-TB
- Talk to lab to make sure appropriate testing for 2^{o} drugs is done

Think resistance? Test for resistance! (3)

- Xpert® MTB/RIF (FDA approved) and Xpert® MTB/RIF Ultra
  - Point of care assay to detect MTB complex and mutations of the gene *rpo*B, known to confer RIF-R
  - Does not involve gene sequencing; Molecular Beacon
  - Time to result is 1.5-2 hours
  - Ultra – better detection of MTB complex in paucibacillary specimens; more reliable detection of *rpo*B mutations that => RIF-R
  - If RIF-R is detected, confirmation should be obtained with a sequencing-based method unless patient has clear risk
    - "Silent" mutations which don't => resistance may be picked up (false positive)

MTB DETECTED VERY LOW;
Rif Resistance DETECTED

Think resistance? Test for resistance! (4)

- Line-probe assays
- Sequencing-based assays
  - Pyrosequencing
    - California Public Health Lab
  - CDC Molecular Detection of Drug Resistance (MDDR) service
    - Sanger sequencing
  - Whole Genome Sequencing
- Communicate – local lab, public health lab, local health department, state TB program, COE to make sure proper and timely testing is done!

Pyrosequencing (PSQ) for XDR TB Screening

At MDL, CA Department of Public Health

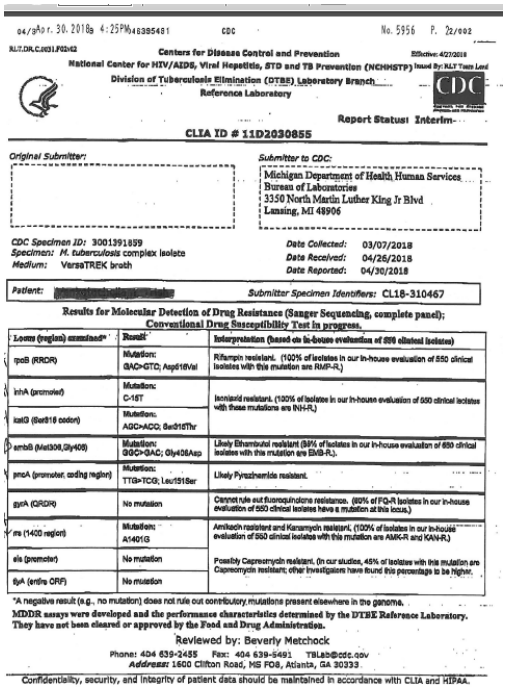
Contact: **Dr. Desmond** (**ed.desmond@cdph.ca.gov**; **510-412-3781**) or
Grace Lin (**grace.lin@cdph.ca.gov**; **510-412-3929**)

PSQ is a rapid screening technique for molecular detection of drug resistance. For confirmation of PSQ results, culture-based drug susceptibility testing should be performed.

Intended use	Pyrosequencing (PSQ) provides: • Identification of ***M. tuberculosis*** complex (MTBC). • Screening for resistance to INH, RIF, quinolones and injectable drugs.					
Date of implementation	3-26-2012					
Testing schedule	The assay is performed 3-4 times a week. If urgent, additional runs can be scheduled. Turnaround time: 1-3 days.					
Principle	The test involves two steps: 1. Use PCR to amplify the target sequences. 2. Use **pyrosequencing** technology to perform realtime sequencing. The sequencer, PyroMark Q96ID, dispenses one kind of dNTP at a time according to the order specified by the assay. If the dNTP being dispensed is complementary to the first available base in the DNA template, the dNTP will anneal to the template and pyrophosphate (ppi) will be generated. The ppi will trigger a cascade of chemical reactions and result in the emission of light. The light generated is proportional to the dNTP incorporated. The identity of dNTP incorporated represents the base(s) sequenced. The sequence grows when the incorporation of dNTP complementary to the DNA template occurs until the end of the dispensation of dNTPs.					
Specimens	**Sediments: NALC-NaOH processed specimens, at least 0.5 ml, and AFB-smear positive (1+ or greater).** Ship with cold packs. **Cultures: solid media** or **broth (0.5-1 ml)**. Ship at room temperature or with cold packs.					
Molecular targets	INH	*katG* (codon 312-316), *inhA* promoter and *ahpC-oxyR* intergenic region				
	RIF	*rpoB* core region from codons 507 to 533.				
	Quinolones	*gyrA* from codons 88 to 95.				
	Injectable drugs	*rrs*, 1397 to 1406				
Performance characterization (130 isolates + 115	DST results by MGIT 960 (KAN: by agar proportion)					
	INH (n =245) 0.1 µg/ml	RIF (n = 239) 1.0 µg/ml	Quinolones (n=125)	AMK (n =120) 1.5 µg/ml	CAP (n=119) 3.0 µg/ml	KAN (n=55) 5 µg/ml

CDC MDDR Report Drugs Tested: Gene

INH: inhA, katG
RIF: rpoB
Ethambutol: embB
PZA: pncA
Fluoroquinolones: gyrA
Amikacin: rrs
Kanamycin: rrs, eis
Capreomycin: rrs, tlyA



04/30/2018 4:25PM 48395481 CDC No. 5956 P. 02/002

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: Interim

CLIA ID # 11D2030855

Original Submitter:

Submitter to CDC:
Michigan Department of Health Human Services
Bureau of Laboratories
3350 North Martin Luther King Jr Blvd
Lansing, MI 48906

CDC Specimen ID: 3001391859
Specimen: M. tuberculosis complex isolate
Medium: VersaTREK broth

Date Collected: 03/07/2018
Date Received: 04/25/2018
Date Reported: 04/30/2018

Patient: [redacted] Submitter Specimen Identifiers: CL18-310467

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: GAC>GTC; Asp516Val	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 these mutations are INH-R.)
katG (Ser315 codon)	Mutation: AGC>ACC; Ser315Thr	
embB (Met306,Gly406)	Mutation: ATG>GAC; Gly406Asp	Likely Ethambutol resistant (88% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.)
pncA (promoter, coding region)	Mutation: TTG>TCG; Leu151Ser	Likely Pyrazinamide resistant.
gyrA (QRDR)	No mutation	Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
rrs (1400 region)	Mutation: A1401G	Amikacin resistant and Kanamycin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are AMK-R and KAN-R.)
eis (promoter)	No mutation	Possibly Capreomycin resistant. (In our studies, 45% of isolates with this mutation are Capreomycin resistant; other investigators have found this percentage to be higher.
tlyA (entire ORF)	No mutation	

*A negative result (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.
MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.

Reviewed by: Beverly Metchock
Phone: 404 639-2455 Fax: 404 639-5491 TBLab@cdc.gov
Address: 1600 Clifton Road, MS F08, Atlanta, GA 30333

Confidentiality, security, and integrity of patient data should be maintained in accordance with CLIA and HIPAA.

MDDR
New TB Patient: South African

LOCUS EXAMINED (region of gene)	RESULT	INTERPRETATION In-House Evaluation of 550 clinical isolates
rpoB (RRDR)	**Mutation**	RMP-R. 100% of our 550 isolates… were RMP-R
inhA (promoter)	**Mutation** C15T	INH-R 100% of our 550 isolates with these mutations were INH-R
katG	**Mutation**	
embB	**Mutation**	Likely EMB-R 88% of our isolates…were EMB-R (*12% were not*)
pncA	**Mutation**	Likely PZA-R
gyrA	No mutation	Cannot R/O FLQ-R 80% of our FLQ-R isolates have a mutation at this locus.(*20% don't!)*
rrs	**Mutation**	AMK-R & KAN-R. 100% of our isolates with this mutation are R
eis	No mutation	Possibly CAP-R 45% of our isolates with this mutation are CAP-R
tlyA	No mutation	

Criteria for MDDR testing (1)

1. Increased risk for drug resistance
   A. Born in / lived in for >1 month high prevalence country
   B. Contact to someone known to be or suspected to have DR
   C. Patient not responding to Rx
   D. Patient with prior Rx and relapse
2. Public or personal health consequences
   A. Congregate setting, many contacts
   B. Age <5, immune compromised
   C. Case has contacts to patients in 2B who need window prophylaxis

Criteria for MDDR testing (2)

3. Lab issues
   A. Mixed cultures unlikely to yield results
   B. AFB smear positive / culture negative
   C. Pathology specimens not sent for culture
4. Program priorities

Our patient: from S. Africa, did charity work in very poor areas, visited many homes there. She has a 1 year old child.

Principals, Classification of drugs, Mono & Poly-Resistant TB, MDR TB

BUILDING AN EFFECTIVE REGIMEN

General Considerations (1)

- Teamwork; consult experts
- Treatment should be daily DOT (5 days/week), not intermittent, with exceptions of
  - Injectables
  - Adjustments for renal failure (PZA, EMB)
  - Specific studied regimens
- Anticipate problems. Discuss with patient. Have monitoring plan
- When to start treatment? For our patient we waited.

General Considerations (2)

- While waiting for test results, what drugs to use?
  - Expanded empiric treatment regimen
    - Four 1st-line drugs plus **2 *or more*** additional ones (p. 67 in Survival Guide)
  - Avoid previously used drugs
  - Consider cross-resistance (p. 76 in Survival Guide)
- Decision to treat empirically depends on factors such as
  - How ill the patient is; how contagious
  - How long you expect it to take to get results

General Considerations (2)

- Rifampin is necessary to shorten regimen to 9 months
- PZA for 8 weeks in addition to Rifampin is essential to shorten regimen to 6 months

Mono-Resistant TB
INH

- RIF, EMB, PZA +/- later generation fluoroquinolone (Levofloxacin, Moxifloxacin, not Ciprofloxacin)
  - 6-9 months (6 months requires PZA + RIF)
  - Confirm susceptibility of fluoroquinolone (FLQ)
- RIF, EMB, + FLQ
  - 9-12 months (9 months requires RIF)
- Daily RIF, EMB, PZA, MFX 400mg X 2 months, then weekly Rifapentine 1200 mg + MFX 400 mg for 4 months

Isolated RIF Resistance

- Usually cross resistant to Rifabutin, always to Rifapentine
- Confirm Xpert result
- Preferred regimens
  - 1. INH, EMB, PZA, FLQ daily for at least 2 months
    - Then PZA can be stopped or continued
    - Duration 12-18 months or
  - 2. INH, EMB, PZA for 18 months

Isolated EMB or PZA Resistance

- EMB makes no difference
- PZA: Think *M. bovis*, including BCG, or others (*M. canettii*)
- PZA is essential for shortening Rx time to 6 months
  - INH and Rifampin for 9 months

Poly-Resistant-TB

- **INH & EMB**: RIF, PZA, FLQ 6-9 months
- **INH & PZA**: RIF, EMB, FLQ 9-12 months
- **INH, EMB, & PZA**: RIF, FLQ, oral 2nd-line agent, for 9-12 months with injectable for 1st 2-3 months
- **RIF & EMB**: INH, PZA, FLQ for 12-18 months with injectable for 1st 2-3 months
- **RIF & PZA**: INH, EMB, FLQ for 12-18 months with injectable for 1st 2-3 months

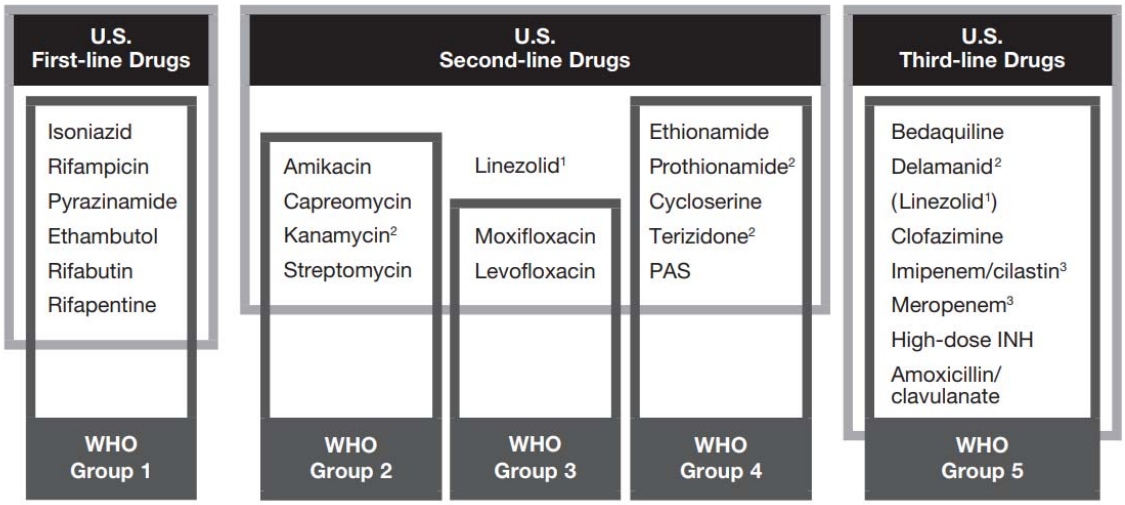
MDR-TB
Principles (1)

- Evidence weak. New guidelines are being developed
- Number of drugs: 4-6 effective ones, aim for 5
  - Consider 6 in an intensive phase, 4 in the continuation phase
  - Intensive phase is initial period with injectable
    - Aim for at least 6 months after culture conversion
  - Total duration
    - Aim for at least 18 months after culture conversion
- Better outcomes occur with less severe disease, rapid clinical response, susceptibility to FLQ and/or PZA

MDR-TB
Principles (2)

- Drug ramping
  - Cycloserine, Ethionamide, PAS should be started at low doses and increased over a 1-2 week period of time
- Therapeutic drug monitoring
  - Amikacin
  - Cycloserine (at full dose)
  - Malabsorption
  - Poor clinical response / relapse
  - Drug drug interactions

Comparison between standard U.S.-based classification and the WHO classification system for anti-tuberculosis drugs



1. **Linezolid often used as 2nd-line agent in U.S.**
2. **Not available in the U.S.**
3. **Amoxicillin/Clavulanate is used as a source of Clavulanate (adjunctive agent)**

Survival Guide

Our Patient

- Had only lymph node disease
  - Had excisional biopsy
- Was not sick
- We waited until all information was in, including standard drug susceptibilities
- We were reluctant to use IV / IM medications

Building a Treatment Regimen for MDR-TB

STEP 1

Begin with any **first-line** agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available **PLUS** One of these **PLUS** One of these

First-line drugs	Fluoroquinolones	Injectable agents
~~Pyrazinamide~~	~~Levofloxacin~~	Amikacin
Ethambutol	Moxifloxacin	Capreomycin
		Kanamycin[1]
		Streptomycin[2]

DST testing showed Rifabutin susceptibility!

STEP 2

Add **second-line** drugs until you have 4–6 drugs (optimally at least 5) to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

Oral second-line drugs
Cycloserine
~~Ethionamide~~
~~PAS~~
Linezolid[3]

STEP 3

If there are not 4–6 drugs available in the above categories, consider **third-line** drugs in consultation with an MDR-TB expert

Consider use of these

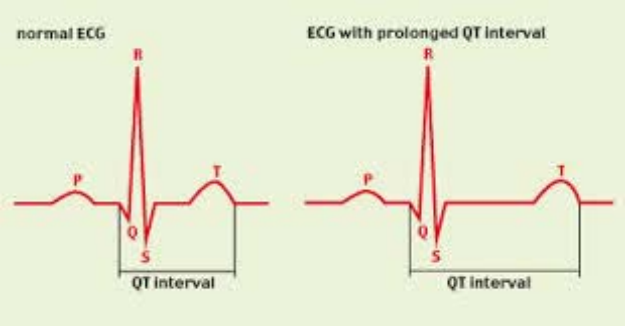
Third-line drugs	
Bedaquiline	Meropenem/Clavulanate
Delamanid[4]	Amoxicillin/Clavulanate
Clofazimine	~~Clarithromycin~~
Imipenem	High-dose INH

Bedaquiline (BDQ)

- Diarylquinoline
- FDA approved 28 December 2012
  - 1st TB drug approved since Rifampin in 1971 (except Rifapentine)
- Phase IIb studies by Diacon, et al. 2014
  - Higher mortality (12.6%) than controls (4.9%)
  - 7 patients died, median of 386 days after the last dose
- In a study in France reported by Guglielmetti, et al., 35 patients received BDQ
  - 7 (20%) had increase of ≥60 milliseconds increase in QT interval

Bedaquiline (BDQ)

- Side effects
  - Death (?)
  - QT prolongation
  - Hepatotoxicity / elevated ALT
  - Arthralgias
  - Nausea



Bedaquiline (BDQ)

- Dose: 100 mg. capsules
  - 400 mg. daily for 14 days followed by
  - 200 mg. 3 times/week for 22 weeks
- Acquired resistance can occur
- Cross reaction (both directions) with Clofazimine

XDR-TB

- Use whatever you have left
- Duration 24 months after culture conversion
- Carefully consider surgery