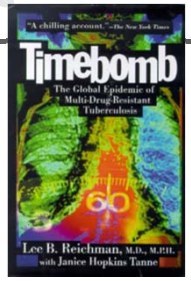
Drug Resistant Tuberculosis Disease and LTBI Contacts



Ohio World TB Day

March 26, 2019

Shu-Hua Wang, MD, PharmD, MPH&TM
Professor of Medicine, The Ohio State University
Medical Director, Ben Franklin TB Program
TB Consultant, Ohio Department of Health
TB Consultant, CDC Northeast Regional TB Training Medical Center

The Ohio State University Wexner Medical Center

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

The Ohio State University Wexner Medical Center

XDR-TB

Photojournalist James Nachtwey -

TED Prize wish come true

37 photographs in 3 minutes

Millions of lives saved: XDR TB

https://www.youtube.com/watch?v=yj8KZNI6-W8

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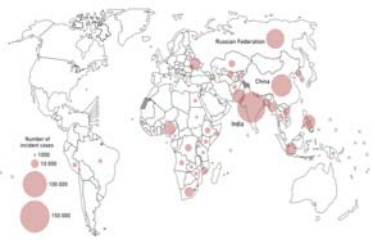
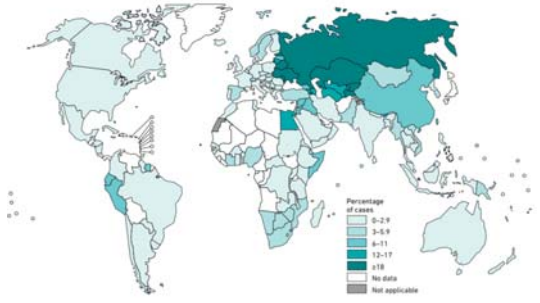
Epidemiology of Drug-Resistant Tuberculosis

- **Estimated 580,000 new RR/MDR cases occurred in 2017**
  - 43% mortality rate
- **Highest proportion of new and previously treated cases in Eastern Europe/Central Asia**
  - 37% in Belarus (2015)
  - 77% in Tajikistan (2014)
- **9.5% of MDR-TB cases resistant to fluoroquinolone or second-line injectable**
  - Classified as XDR-TB



Source: 2018 WHO Report

Percentage of New RR/MDR-TB Cases 2017



RR= Rifampin Resistance
MDR- Multidrug resistance

Source: 2018 WHO Report

Objectives

- Definition of other drug resistant (ODR), multiple drug resistant (MDR-TB) and extensive drug resistant TB (XDR TB)
- Discuss the epidemiology and pathogenesis of MDR-TB
- Discuss MDR-TB treatment regimens, including bedaquiline
- Discuss isolation issues related to MDR-TB
- Discuss contact evaluation and treatment

Clinical Case

History of Present Illness:

- 28 year old Chinese female, 32 weeks pregnant
- Presented to Emergency Room with hemoptysis
- Complaints of cough x2 days, associated with mild shortness of breath

- No fever, chills, night sweat, or chronic cough
- No appetite loss, fatigue, or weight loss
- Denies any history or contact with person with active TB
- History positive TST, did not take latent TB infection therapy
- Received BCG vaccine in China as a child

Hospital Course

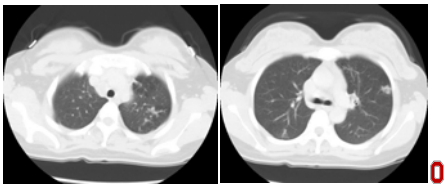
Laboratory

- WBC 6.1, Hgb 10.1gm/dL, Platelets 192, Cr. 0.5, AST 41, ALT 51, HIV negative

Radiology

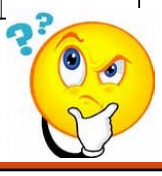
CXR: Mild asymmetric patchy opacity in the left upper lobe

CT: No pulmonary embolus, extensive diffuse nodular air-space disease with peripheral distribution



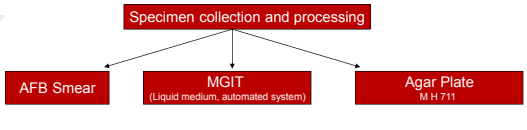
- Airborne isolation unit
- TST 17mm
- QFT Positive

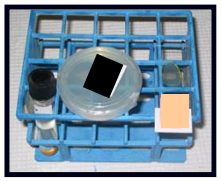
Specimen	Smear	Culture
Sputum day 1	**Negative**	
Sputum day 2	**Negative**	
Sputum day 3	**Negative**	
BAL day 4	**Negative**	



• Discharge home on INH for Latent TB infection (LTBI) treatment
• Follow up at TB Clinic

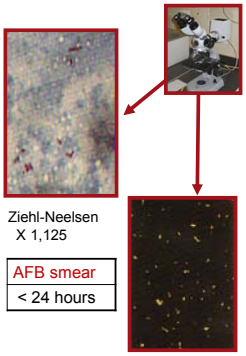
Laboratory Diagnosis – Active TB Disease





MGIT= mycobacterial growth indicator tube

AFB Smear



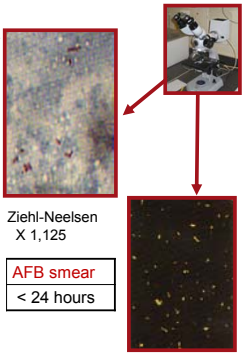
Ziehl-Neelsen
X 1,125

AFB smear
< 24 hours

X 1440

- Variable sensitivity
  - 40-70% for pulmonary TB (less in miliary TB, late HIV, children)
  - Limit of detection (LOD): $>10^4$ AFB/ml by Ziehl-Neelsen; $>10^3$/ml fluorochrome
  - Correlates with disease severity and infectiousness
- Not specific for *M.tb* complex
  - *Red snappers*
- Inexpensive and quick
  - Turnaround time (TAT) <24hr

AFB Smear and Culture



Ziehl-Neelsen
X 1,125

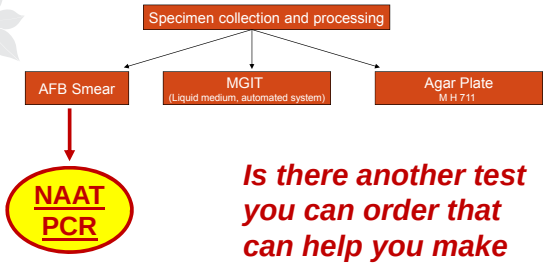
AFB smear
< 24 hours

X 1440

Liquid Culture
7 – 21 days

Solid Culture
3 – 8 weeks

Laboratory Diagnosis – Active TB Disease



NAAT: Nucleic acid amplification test
Mycobacterium tuberculosis Direct Test (MTD) or Amplicor GeneXpert

Is there another test you can order that can help you make the diagnosis?

MGIT= mycobaterial growth indicator tube

- Airborne isolation unit
- TST 17mm. QFT positive

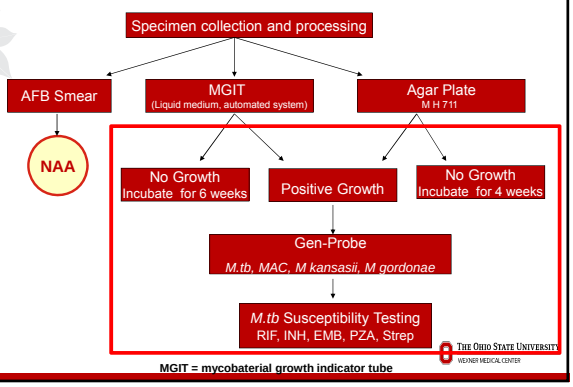
Specimen	Smear	Culture
Sputum day 1	**Negative**	
Sputum day 2	**Negative**	
Sputum day 3	**Negative**	
BAL day 4	**Negative**	

- **Add - Nucleic acid amplification test:**
  - **Positive**

Summary Hospital/Clinic Course

Tuberculin skin test IGRA (QFT or Tspot-TB	**Reactive** 17mm **Positive**
AFB sputum smear	**Smear negative**
Nucleic acid amplification test (NAAT)	**Positive *M.tb complex***
Anti-TB therapy	**Started on 4 drugs**

Laboratory Diagnosis – Active TB Disease



MGIT = mycobaterial growth indicator tube

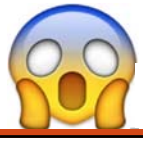
Drug Susceptibility Testing

- TST 17mm. QFT Positive
- Nucleic acid amplification test:
  - Positive for *M. tuberculosis complex*

Specimen	Smear	Culture
Sputum day 1	Negative	***M. tb***
Sputum day 2	Negative	***M. tb***
Sputum day 3	Negative	***M. tb***
BAL day 4	Negative	Negative
Sputum day 9*	Negative	Negative

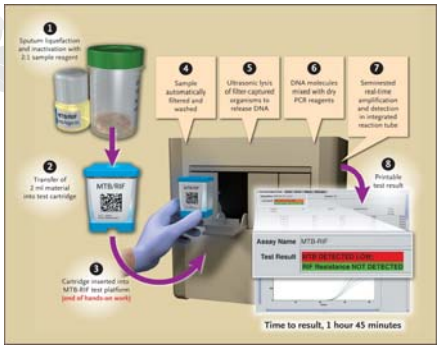
Drug susceptibility:

Resistant to Rifampin, Isoniazid, and Streptomycin



Rapid, fully-automated (less susceptible to human error), highly accurate diagnosis (TB and RIF-resistant TB)

GeneXpert Assay Procedure for the MTB/RIF Test



Boehme CC et al. N Engl J Med 2010;363:1005-1015.

Molecular Drug Susceptibility Test (DST)

- Molecular assays for INH, RIF most common
- Detect polymorphisms associated with drug resistance
- Performed on clinical specimens or culture isolates
  - In-house assays, molecular beacons - RT-PCR, whole genome sequencing (WGS)
- Commercial assays
  - HAIN and INNO-LIPA line probe assays; Cepheid GeneXpert® MTB/RIF*
- *Some issues*
  - Multiple mutations may confer resistance – not identified
  - Silent mutations – flagged but not really resistant

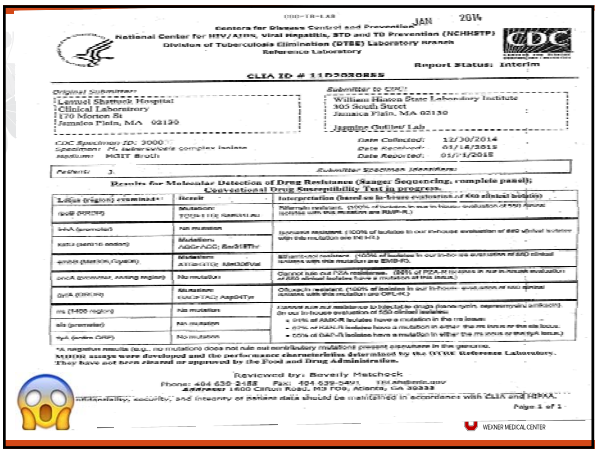
CDC Molecular detection of drug resistance (MDDR) to Rapidly Identify Drug-Resistant TB

THINK Drug Resistant TB!

- 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***

Which is NOT associated with Risk of Drug Resistant TB?

1. U.S. residents who travel to high risk areas
2. Exposure to patient on TB therapy
3. Prior treatment for TB
4. Treatment failure
5. Relapse in a patient not on DOT



CDC Molecular detection of drug resistance (MDDR) to Rapidly Identify Drug-Resistant TB

Locus	Result	Interpretation
rpoB		RIF
inhA		INH
katG		
embB		EMB
pncA		PZA
gyrA		Fluoroquinolone
rrs		Injectable Amikacin, Kanamycin, Capreomycin
Eis		
tlyA		

Using MDDR to Rapidly Identify Drug-Resistant TB

Smear- positive, cultures still pending (needed before conventional DST)

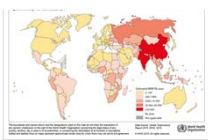
Locus	Result	Interpretation
rpoB	**Mutation**	**RIF R**
inhA	No mutation	**INH R**
katG	**Mutation**	
embB	**Mutation**	**EMB R**
pncA	**Mutation**	**Cannot rule out PZA resistance**
gyrA	No mutation	**Cannot rule out fluoroquinolone resistance**
rrs	**Mutation**	**AMK and KAN resistance, possible Capreo resistance**
eis	No mutation	
tlyA	No mutation	

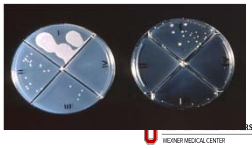
What are the risk factors for drug resistant TB?

How does drug resistant TB develop?

Treatment with second-line drugs is longer, less effective, more toxic, and costly

Danger of increasing drug resistance, given the length of drug development timelines





Transmission of Drug-Resistant TB

- Transmitted same way as drug-susceptible TB
- Drug resistance is divided into two types:
  1. Primary resistance - initially infected with resistant organisms
  2. Secondary resistance - develops during TB therapy
     a) Non-adherence to therapy
     b) Inappropriate therapy
     c) Decrease drug concentration – malabsorption, rapid metabolizer

Slide courtesy of Dr. Mase

Antimyobacterial Drugs

First-Line Drugs

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

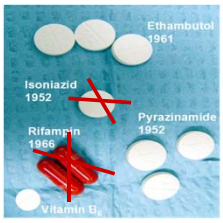
Second-Line Drugs

- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*
- Moxifloxacin*
- Gatifloxacin*
- Bedaquilline

* Not FDA approved for TB tx

MDR TB (Multidrug Resistant)

- *M. tuberculosis* isolate that is **resistant** to at least **INH and RIF**
  - Can be resistant to other drugs as well



Other Mono- or Poly- drug resistant Tuberculosis

- Resistant to **INH**, sensitive to RIF, with or without resistance to other first or second-line drugs

OR

- Resistant to **RIF**, sensitive to INH, with or without resistance to other drugs

OR

- Resistance to any (1 or more) first-line drugs (**EMB, PZA, SMN**) other than INH or RIF

If monoresistance to PZA is found, consider the specimen may be *M. bovis*

XDR TB (Extensively drug resistant)

- Resistance to at least **INH and RIF** from among the 1st -line anti-TB drugs (MDR TB)
- **Plus** resistance to any fluoroquinolone
- **And** to at least one of 3 injectable 2nd-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin

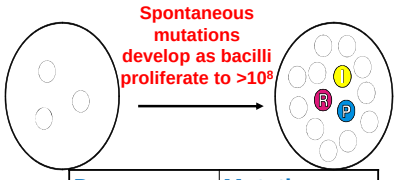
Rates of Spontaneous Resistance in *M. tuberculosis*

Isoniazid	1 in 10^6
Rifampin	1 in 10^8
Ethambutol	1 in 10^6
Streptomycin	1 in 10^5
INH & RIF	1 in 10^{14}

Number of organisms in a TB cavity = 10^9-10^{11}

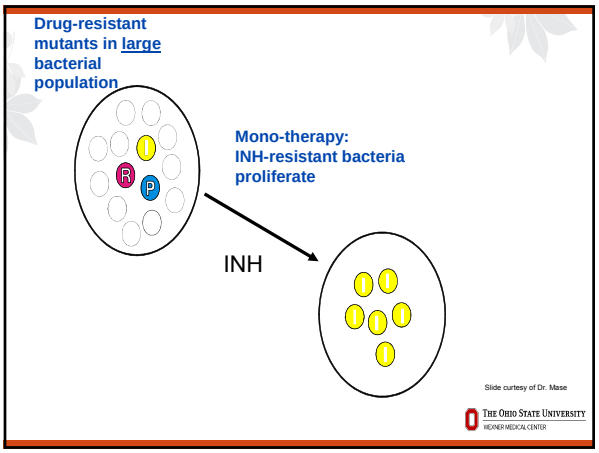
Slide courtesy of Dr. Mase

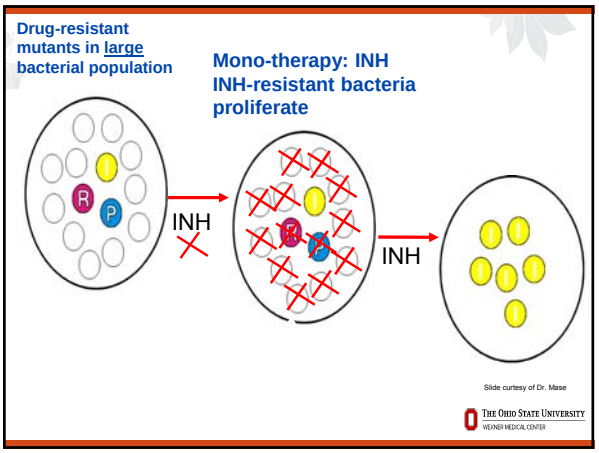
Pathogenesis of Drug Resistance

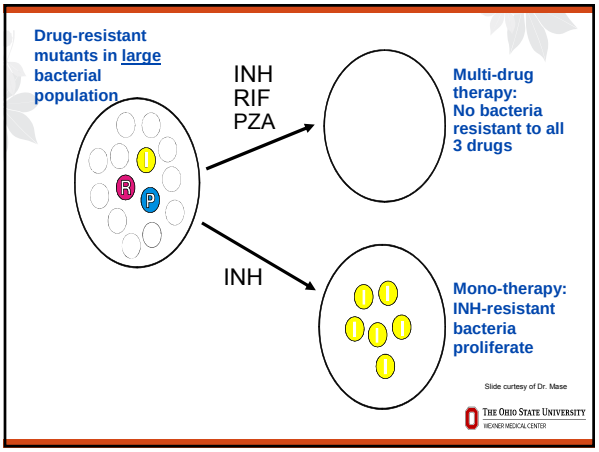


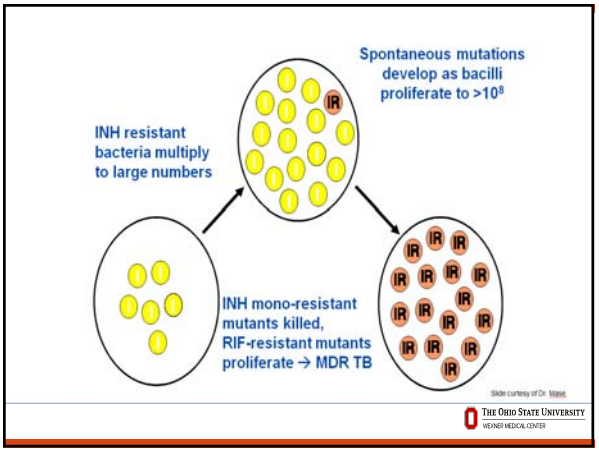
Drug	Mutation Rate
Rifampin (R)	10^{-8}
Isoniazid (I)	10^{-6}
Pyrazinamid (P)	10^{-6}

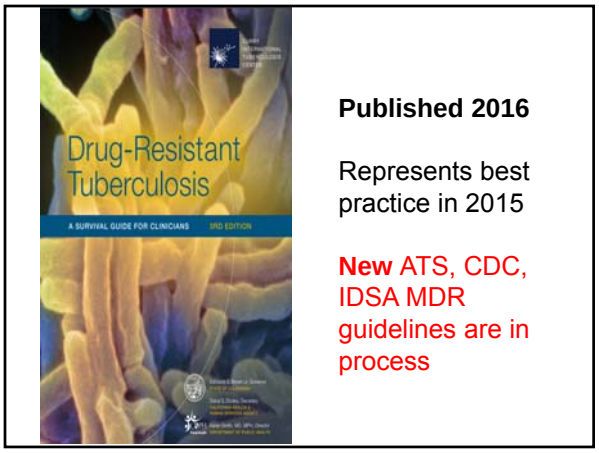
Slide courtesy of Dr. Mase











Published 2016

Represents best practice in 2015

New ATS, CDC, IDSA MDR guidelines are in process

MDR-TB Regimen

Step 1

Begin with any 1st-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 Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center

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First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

Step 2

Pick one or more of these

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Oral second-line drugs

Cycloserine
Ethionamide
PAS
Linezolid*

*Although considered a 3rd-line drug, many experts now use LZD as a 2nd-line drug option

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd Ed.*, available from Curry International Tuberculosis Center

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Ethionamide
PAS
Linezolid*

*Although considered a 3rd-line drug, many experts now use LZD as a 2nd-line drug option

Step 3

Consider use of these

If there are not 4-6 drugs available consider 3rd-line in consult with MDRTB experts

Third-line drugs

Bedaquiline Clofazimine Delamanid*
Carbapenem/Amoxicillin/Clavulanate
Macrolides High-dose isoniazid

*Awaiting FDA approval

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd Ed.*, available from Curry International Tuberculosis Center

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Rapid Communication Box 4.7 Page 109

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

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

World Health Organization

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

What Do Patients with MDR TB Need?

- Patients with MDR TB need to have
  - Accurate and prompt identification
  - Notification to the field staff and provider(s)
  - Appropriate case management
  - Appropriate treatment based on rapid molecular test results (MDDR, WGS, etc.)
  - Appropriate infection control measures instituted

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Principles for Managing MDR TB

- MDR TB should never be treated without expert consultation of a specialist in MDR TB treatment
- Patients must be treated with a regimen of at least 3-5 anti-TB medications to which the strain is likely to be susceptible (4-6 or better)

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Principles for Managing MDR TB - 2

- A single new drug should never be added to a failing regimen
- When initiating or revising therapy, always attempt to use at least 3 previously unused drugs to which there is *in vitro* susceptibility
  - One agent should be an injectable agent **(???)**
  - A good response does not justify continuation of an inadequate regimen

Principles for Managing MDR TB - 3

- Injectable agents can be given 5 days/wk initially
  - After culture conversion, dosing can be 2-3x/wk
- With extensive disease or slow conversion of sputum cultures, the injectable should be used for longer periods after culture conversion
- Streptomycin resistance may accompany INH resistance
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment

Second Line MDR Drugs Fluoroquinolones

- One of the two most important agents in MDR treatment
- Oral agents, well tolerated
- Can be given daily
- Levofloxacin/Moxifloxacin are the preferred agents of choice in adults
- Adverse Effects:
  - Nausea, vomiting, diarrhea (C. diff)
  - Hypersensitivity
  - Photosensitivity
  - Tendonitis, especially in > 60 years age & steroid use
  - Hypo/hyperglycemia
  - Prolongation of QTc interval

Third-Line MDR Drugs Linezolid

- Used as second and third line treatment for MDR TB
- Adverse effects:
  - Pancytopenia, hemolytic anemia
  - Peripheral neuropathy, optic neuropathy
    - May or may not be reversible
    - May or may not be ameliorated by vitamin B_6
  - hepatic dysfunction
  - muscle injury
  - Lactic acidosis
- Use with caution with selective serotonin reuptake inhibitors (SSRIs)
- Dosage of 600mg to 300mg QD
- Expensive

Third-Line MDR Drugs Clofazimine

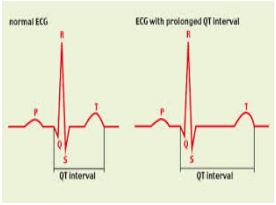
- More commonly used in patients with leprosy & MAI
- Used in patients with few other options
- Needs Investigational New Device (IND) from FDA
- Dose: 100mg daily
- Adverse effects:
  - May cause skin and body secretions to become discolored which reverse after medication stopped (Pinkish- to brownish/black)
  - Gastrointestinal intolerance, can develop intestinal obstruction
  - Photosensitivity
  - QTc prolongation

Third Line MDR Drugs Bedaquiline (SIRTURO™)

- First new TB drug since RIF (1970)
- New class of potent anti-TB drugs: diarylquinolones
  - Accumulates in the body by binding to phospholipids
- New mechanism of action: interferes with the utilization of energy in *M. tb* thereby killing it
- Part of an individualized MDR regimen for pulmonary MDR TB in adults (>18 yrs)
  - Need at least 3 drugs to which isolate susceptible
- Concerns about safety – Black Box Warning
  - ↑risk of QT interval prolongation-can cause arrhythmia
  - ↑number of deaths: 11.4% (9/79) compared to 2.5% (2/81)

Bedaquiline Dosage and Administration

- Must be given under DOT
- Should be taken with food
- 24 weeks regimen
- Oral tablets 100 mg each
  - Weeks 1-2: 400 mg once a day (4 tablets)
  - Weeks 3-24: 200 mg (2 tablets together) 3x/wk
    - At least 48 hours between doses
    - Total dose of 600 mg/week



Monitoring Patients on BDQ

- EKG at baseline and at least 2, 12, and 24 weeks after starting Bedaquiline
- Serum electrolytes, Ca and Mg
- Monitor LFTs
  - Avoid alcohol and hepatotoxic drugs
- Metabolized by CYP3A4-therapeutic effect may be reduced with inducers of CYP3A4
  - Rifamycins
  - Limited data on HIV/MDR TB co-infected patients

QT Prolongation

- Drugs used to treat TB or NTMs
  - Fluoroquinolones
  - Clofazimine
  - Delamanid
  - PA-824 (nitroimidazol-oxazine)
  - Macrolides
- Electrolyte abnormalities: ↓K, Ca, Mg
- Other drugs that prolong QT interval
- History of Torsade de Pointes
- History of congenital prolonged QT syndrome
- History of hypothyroidism, brady arrhythmias, uncompensated heart failure
- This effect can be additive

New Treatments for MDR TB Delamanid

- New mechanism: inhibits cell wall of TB but exact mode of action unclear
- Given along with background MDR regimen
  - Both regimens had sputum culture conversion at 2 months
- Mild adverse effects and few drug-drug interactions
- Had prolongation of the QTc intervals
- Dec. 2013: Approved by European Medicines Agency (EMA) for treatment of MDR TB
  - Favorable outcomes in participants who received ≥6 months vs. ≤2 months of Delamanid
  - Phase 3 trial has completed enrollment and treatment phase and full results expected in 2018

DOT for MDR-TB

- Essential that MDR TB patients be treated with Directly Observed Therapy (DOT)
  - Improved overall cure rates
  - Reduction in community prevalence of MDR
- Intermittent regimens should not be used
- All 2nd-line agents must be administered daily
- Twice/day DOT should be used when feasible, and more frequent dosing than twice daily should be avoided
- All doses must be observed for the patient to get credit

Situations Where Culture Conversion Should Be Confirmed Prior to Return to Work

- Work sites where individuals with drug susceptible TB and MDR TB should be excluded until culture conversion is confirmed:
  - Work sites where persons with HIV or other immunocompromised patients are cared for
  - Neonatal intensive care units
  - Patient care areas
  - Nursing homes
  - Congregate settings such as daycare and schools

Infection Control Issues Related to Multidrug Resistant TB Patients

- MDR TB patients should remain hospitalized or on home isolation if an outpatient until:
  - 3 sputum smears are AFB- negative
  - Clinically improved and near resolution of cough
  - Tolerating an appropriate treatment regimen
  - Patient agrees to DOT and it has been arranged
  - Proper arrangements have been made for follow-up
  - A home assessment should be done with evaluation for insertion of a HEPA filter in the residence

Returning MDR TB Patients to Work or School-Culture Conversion

- MDR TB patients should be kept from returning to work or school, or transferring to another congregate setting such as a shelter or nursing home until culture conversion is confirmed
  - 2 consecutive negative cultures at least 2 weeks apart
- Culture conversion is necessary unless the patient will be transferred to a airborne infection isolation room in the congregate setting
- Exceptions can be made for certain types of work settings, if all the conditions in previous slide are met
  - Decided in consultation w/ Office of Medical Affairs

Follow-up of MDR TB Patients after Treatment Completion

- Patients with TB resistant to INH and RIF or treated without RIF/RBT
  - Medical evaluation every 4 months during the 1st year after treatment completion
  - Then every 6 months during the 2nd year
- Months: 4, 8, 12, 18, 24 post treatment
- Educate about relapse and to return if they develop symptoms

Treatment of HIV-related MDR-TB

- Rapid diagnosis of drug resistance
- Important to treat with the most active anti-TB regimen available
- Initiate antiretroviral therapy based on CD_4 count and other individual patient variables
- Use therapeutic drug monitoring when drug interactions are possible or malabsorption is suspected

MDR TB in Pregnancy

- Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy
- PZA can be used as a main agent and is recommended by WHO & ATS
  - WHO recommends its use in pregnancy even for drug-susceptible TB patients
  - In the U.S., it is considered a category C agent

OK to use: INH, RIF, EMB, PZA, PAS, Cycloserine,
Do not use: FQ, Aminoglycoside, Ethionamide

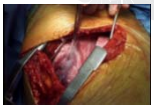
Monitoring Serum Drug Levels

- Serum drug level monitoring can be used in patients with the following medical conditions:
  - HIV positive/AIDS
  - Diabetes
  - Malabsorption syndromes
  - Renal failure
  - Failure to improve on treatment/relapse
  - MDR TB

Drug Intolerance

- In general, length of treatment for patients with drug intolerance is the same as for those who have drug resistance

Indications for Surgery - 1



- Adequate 1st and 2nd -line regimens of anti-TB medications have failed to cure or cause *M. tb* cultures to convert to negative within 4 to 6 months
- Sufficient medications are available to treat the patient postoperatively
- Disease is sufficiently localized to allow lobectomy or pneumonectomy
- Remaining lung tissue is relatively free of disease
- Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
- Even after surgery- should still complete a full course of MDR-TB treatment

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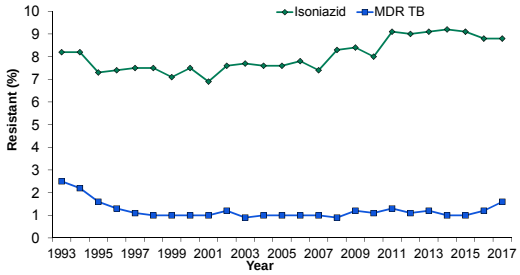
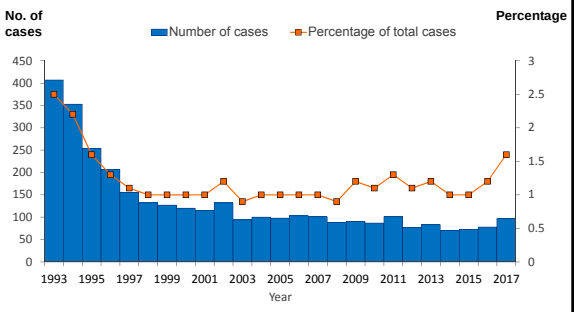
Primary Anti-TB Drug Resistance, United States, 1993–2017*



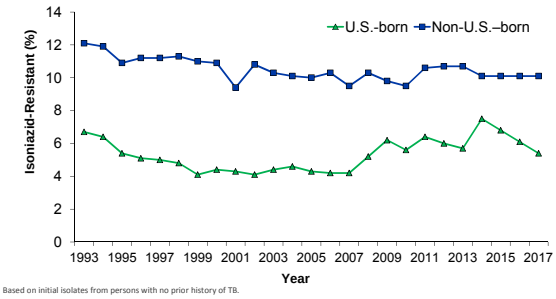
* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.

Primary MDR TB, United States, 1993–2017*



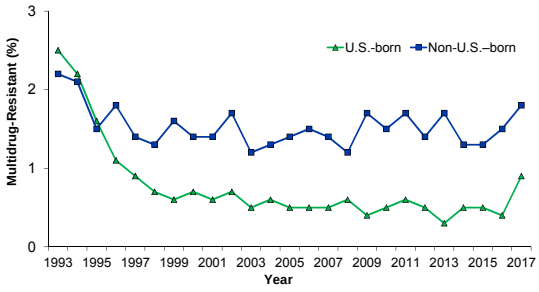
* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.

Primary Isoniazid Resistance Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2017*



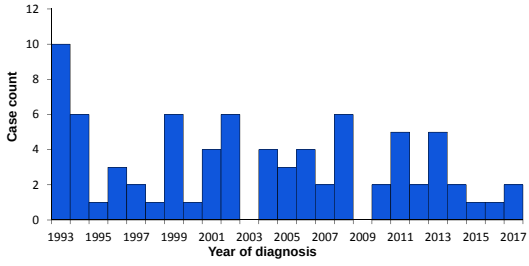
* Based on initial isolates from persons with no prior history of TB.

Primary MDR TB Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2017*



* 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.

XDR TB* Case Count, Defined on Initial DST,† by Year, 1993–2017§



* XDR TB, extensively drug-resistant TB.
† DST, drug susceptibility test.
§ XDR TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.

Impact of MDR-TB

- Enormous resource sink
- Prolonged treatment/monitoring required
- Large cost incurred (drugs, hospitalization, DOT, lab testing)
- Major impact to individual health
- Prolonged isolation, inability to work
- Pool of clinical experts diminishing
- Increasingly complex healthcare systems to navigate
- No proven therapy for contacts

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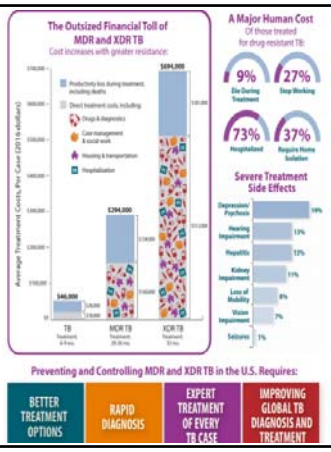
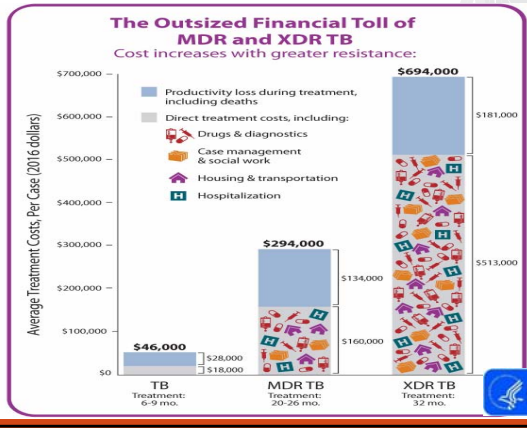
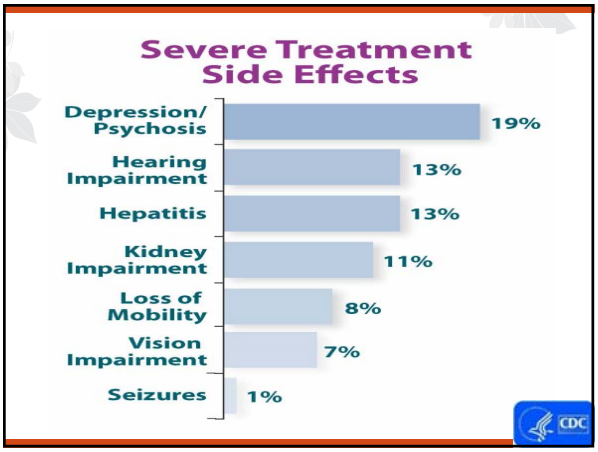
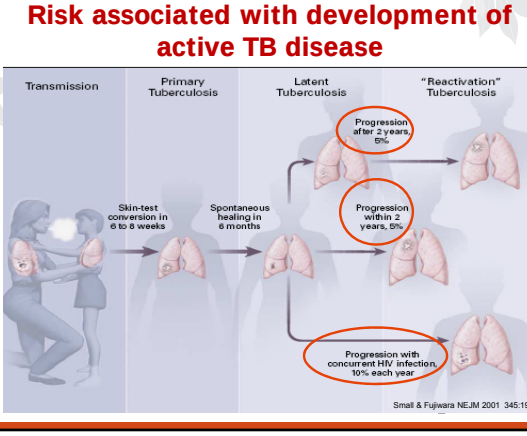
November, 2017

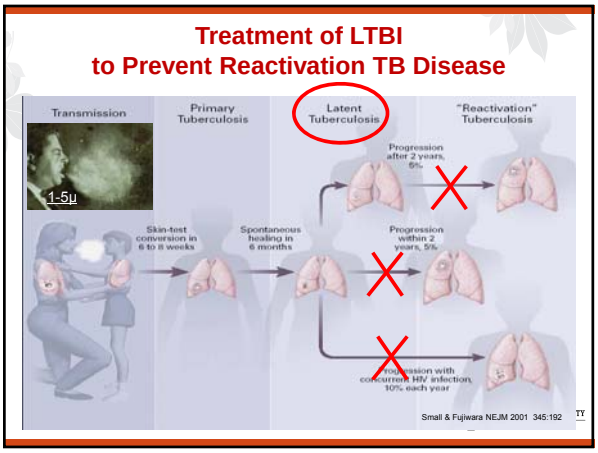
Direct costs
DS-TB $18,000
MDR-TB
$160,000
XDR-TB
$513,000



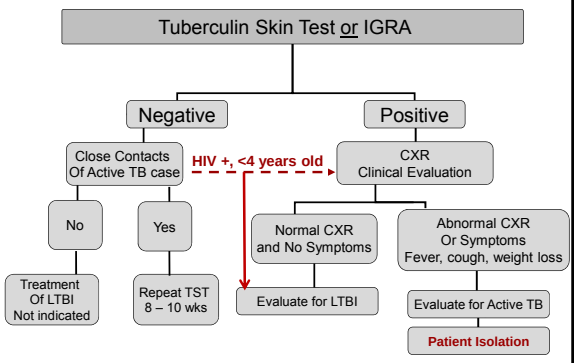




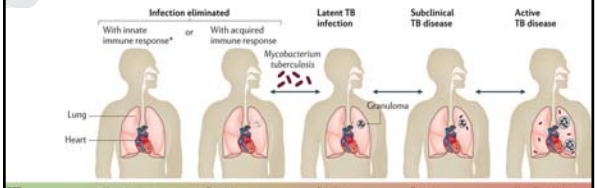




US TB Screening Flowchart



The spectrum of TB: from *M. tuberculosis* infection to active (pulmonary) TB disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai, M. et al. Nat. Rev. Dis. Primers, 2016

Treatment of Contacts is Important

- **Active Cases identified**
  - Positive or Negative TST/IGRA
  - Positive or Negative CXR
  - Positive or Negative Sign/Symptom: Fever, chill, cough, night sweat, weight loss
  - **Treat**
- **Latent TB Infection identified** –
  - Positive IGRA/TST
  - Negative CXR
  - **Treat**
- **High risk contacts: <5yo, immunocompromised**
  - Negative TST/IGRA
  - Negative CXR
  - **Treat**

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Specific treatment options dependent on susceptibility of source case isolate
The Curry Drug Resistant TB Survival Guide, 3rd Edition, 2016*

Resistance pattern	LTBI treatment options
INH (RIF-susceptible)	RIF 4 months (Adults and children)
INH and RIF	Fluoroquinolone or Fluoroquinolone + EMB
INH, RIF, EMB	Fluoroquinolone or Fluoroquinolone + ETA
INH, RIF, PZA	Fluoroquinolone or Fluoroquinolone + EMB
INH, RIF, PZA, EMB, +/-injectable	Fluoroquinolone or Fluoroquinolone + ETA
INH, RIF, PZA, EMB, injectable, ETA	Fluoroquinolone or Fluoroquinolone + cycloserine (CS)
INH, RIF, PZA, EMB, and fluoroquinolone	No treatment, clinical monitoring* (In select cases, CS + para-aminosalicylic acid [PAS] or PAS + ETA# orETA* + CS may be considered)

Thank you!

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