TB Treatment and Drug Resistance

James Sunstrum, M.D.
TB Consultant, Michigan Dept. of Health and Human Services
DISCLOSURES

• NONE
TB Treatment and Drug Resistance

Objectives:

• Identify the basic principles of drug-resistant TB

• Describe the current guidelines for the treatment of TB disease including the newly released CDC guidelines.

WHO GLOBAL TB REPORT 2016

Actions and investments to End TB fall far short
Tuberculosis among top 10 causes of death worldwide last year

Here are the statistics from 2015:

10.4 million people FELL ILL FROM TB

That’s 28,500 people every day

1.8 million people DIED FROM TB

including 400,000 WITH HIV + TB

That’s over 4,900 people every day

60% of TB cases worldwide occurred in just SIX COUNTRIES

More action and investment in these countries will drive down the TB burden

3 MILLION LIVES WERE SAVED BY THE GLOBAL TB RESPONSE IN 2015

ACCESS TO CARE

6.1 million people had ACCESS TO QUALITY TB CARE

4.3 million people MISSED OUT

Better reporting, diagnosis and access to care will close this gap

DRUG RESISTANCE

Only 1 in 5 people needing treatment for multidrug-resistant TB in 2015 ACTUALLY RECEIVED IT

Only half of those who started MDR-TB treatment WERE CURED

GLOBAL TARGETS* BY 2030 TO END THE TB EPIDEMIC

90% reduction IN TB DEATHS

compared to 2015

80% reduction IN TB CASES

But reaching these targets will be an uphill battle

ANNUAL GLOBAL FINANCING FOR TB NEARLY US$3BN SHORT*

Implementation

AVAILABLE: US$6.6bn

GAP: US$1.7bn

Research and development

AVAILABLE: US$0.7bn

GAP: US$1.1bn

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**Figure 1** The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease

<table>
<thead>
<tr>
<th></th>
<th>Infection eliminated</th>
<th>Latent TB infection</th>
<th>Subclinical TB disease</th>
<th>Active TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With innate immune response</td>
<td>With acquired immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TST</strong></td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td><strong>IGRA</strong></td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Intermittently positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Sputum smear</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Usually negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Sporadically</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>None</td>
<td>None</td>
<td>Mild or none</td>
<td>Mild to severe</td>
</tr>
<tr>
<td><strong>Preferred treatment</strong></td>
<td>None</td>
<td>Preventive therapy</td>
<td>Preventive therapy</td>
<td>Multidrug therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multidrug therapy</td>
</tr>
</tbody>
</table>

*Note: Infection eliminated can occur with an innate immune response or with an acquired immune response.*

*Source: Nature Reviews | Disease Primers*
Directly Observed Therapy (DOT)
Treatment of TB Disease (3)

- Initial regimen should contain the following four drugs:
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
Basic TB Treatment Regimen

INITIAL (INTENSIVE) PHASE

- 4 drugs
- 8 weeks

CONTINUATION PHASE

- Isoniazid + Rifampin
- 18 weeks

Isoniazid
Rifampin
Pyrazinamide
Ethambutol

Mayo Clinic Center for Tuberculosis
## Drug Abbreviations

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ABBREVIATION</th>
<th>USA INITIAL</th>
<th>WHO INITIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>INH</td>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>RIF</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td>PZA</td>
<td>P</td>
<td>Z</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>EMB</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>RIFAPENTINE</td>
<td>RPT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT
<table>
<thead>
<tr>
<th>DATE</th>
<th>INH 900MG</th>
<th>RIF 600MG</th>
<th>PZA 3000MG</th>
<th>EMB 2000MG</th>
<th>B6 50MG</th>
<th>Nurse Initials</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/21/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>LH</td>
<td>DOT &amp; DOT.</td>
</tr>
<tr>
<td>06/24/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>LH</td>
<td>stopped in Chicago, India. Ret. 5/3/2013 Air India from Delhi 11/2 yrs.</td>
</tr>
<tr>
<td>06/26/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CL</td>
<td>Client says has not worked in about 4 mos. Lived in North Sa. 11/2 yrs.</td>
</tr>
<tr>
<td>06/28/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CL</td>
<td>Strongly suggested wife come into clinic for QFT. CL</td>
</tr>
<tr>
<td>07/01/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CL</td>
<td>Clinic appt changed to 7/12 @ 8:00 am. Pt complained of gas and vomiting. Vomiting occurred once approx 7 hrs after taking INH/RIF/PZA/EMB/B6 on 7/5/13 and again late afternoon on 7/7. Encouraged pt to eat light diet and take meds with soda pop.</td>
</tr>
<tr>
<td>07/03/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CL</td>
<td>Client reported vomiting 1x on mornings of 7/9 and 7/10. Vomiting did not occur right after taking DOT meds. Updated Dr. Sunstrum to hv and was instructed to call Dr. S. if vomiting continues. Called clinic and spoke with Robyn Ranker RN prior to giving patient DOT meds. R. Ranker RN instructed PHN to give today's meds and have client call if vomiting continues. Dr. Sunstrum to be informed by Robyn Ranker RN and will notify PHN if wants any change in meds made. Pt took meds with Pepsi today. Strongly encouraged Pt to bring wife to clinic appt on 7/12 to be tested.</td>
</tr>
<tr>
<td>07/05/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>LH</td>
<td>Pt seen at clinic today. Isolation d/c'd today</td>
</tr>
<tr>
<td>07/10/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>LH</td>
<td>Pt complained of vomiting more than 7x. HOLD today's doses per Dr. Sunstrum.</td>
</tr>
<tr>
<td>07/12/13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CL</td>
<td>HOLD meds today per Dr. Sunstrum. Clinic appt scheduled 7/19/13 @ 8:00 am.</td>
</tr>
<tr>
<td>07/15/13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LH</td>
<td>Seen at clinic today. DOT meds on hold. Blood work done.</td>
</tr>
<tr>
<td>07/17/13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LH</td>
<td>Pt hospitalized over weekend per TB clinic. Pt to come into clinic today.</td>
</tr>
</tbody>
</table>
CDC Guidelines 2016

**Intensive Phase** 8 weeks

- Daily dosing, rather than intermittent dosing, is preferred.
- If intermittent therapy is needed, use treatment three times per week for patients with:
  - Low risk of relapse (i.e. drug-susceptible TB organisms, non-cavitary and/or smear negative) and
  - Negative HIV-infection test result
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Range of Total Doses</th>
<th>Comments&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>Regimen Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>INH, RIF</td>
<td>7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)</td>
<td>182–130</td>
<td>This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.</td>
</tr>
<tr>
<td>2</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>INH, RIF</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>110–94</td>
<td>Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.</td>
</tr>
<tr>
<td>3</td>
<td>INH, RIF, PZA, EMB</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>INH, RIF</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>78</td>
<td>Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.</td>
</tr>
<tr>
<td>4</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 d/wk for 14 doses then twice weekly for 12 doses&lt;sup&gt;e&lt;/sup&gt;</td>
<td>INH, RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>62</td>
<td>Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.</td>
</tr>
</tbody>
</table>
Baseline and follow-up evaluations for patients treated with first-line tuberculosis medications.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline</th>
<th>Month of Treatment Completed</th>
<th>End of Treatment Visit</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>MICROBIOLOGY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum smears and culture¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug susceptibility testing²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMAGING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiograph or other imaging³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLINICAL ASSESSMENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom and adherence review⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision assessment⁶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABORATORY TESTING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, ALT, bilirubin, alkaline phosphate⁷</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count⁸</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine⁸</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV⁹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B and C screen¹⁰</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Screen¹¹</td>
<td></td>
<td></td>
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</tbody>
</table>


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CDC Guidelines 2016

**Continuation Phase** 18 weeks

- Daily dosing is recommended.
- If intermittent therapy is needed, treatment three times per week is preferred.
2 month sputum very important

**INITIAL (INTENSIVE) PHASE**
- 4 drugs
- 8 weeks

**CONTINUATION PHASE**
- Isoniazid + Rifampin
- 18 weeks

Isoniazid
Rifampin
Pyrazinamide
*Ethambutol*
Why Extend Continuation-Phase Treatment for 3 more Months?

- Cavitary disease and positive sputum culture at 2 months of treatment, is associated with increased relapse in clinical trials.
- Extended continuation phase decreased relapses in silicotuberculosis (from 20% to 3%).
When DOT was not used in Detroit many years ago ……

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>STREPTOMYCIN</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>CAPREOMYCIN</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>ETHIONAMIDE</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>CYCLOSERINE</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
</tr>
</tbody>
</table>

Detroit Receiving Hospital ICU
June 2000
Basic TB Treatment Regimen

Resistance to INH and rifampin discovered at 3 weeks

Isoniazid
Rifampin
Pyrazinamide
Ethambutol

INITIAL (INTENSIVE) PHASE

4 drugs X 8 weeks

CONTINUATION PHASE

- Isoniazid + Rifampin
- 18 weeks

Mayo Clinic Center for Tuberculosis
Could the drug resistance have been identified earlier????????

• Low suspicion for MDR
• No prior TB treatment
• No known MDR exposure.
GenExpert Assay Procedure for the MTB/RIF Test.

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filter-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Seminested real-time amplification and detection in integrated reaction tube
8. Printable test result

Time to result, 1 hour 45 minutes

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

CLIA ID # 11DO658319

Report Status: Interim

Original Submitter:
Berrien County Health Department
769 Pipesone
Benton Harbor, MI 49022
Pam Quinn 269-927-5636

Submitter to CDC:
Michigan Dept of Community Health
Bureau of Lab/Micro/TB Unit
3150 N. Martin Luther King Blvd.
Lansing, MI 48906
Steve Church/Lab

CDC Specimen Id: 2013004208
Specimen: M. tuberculosis complex isolate
Medium: MGIT Broth

Date Collected: 12/17/2012
Date Received: 01/03/2013
Date Reported: 01/04/2013

Patient: [redacted]

Submitter Specimen Identifiers: CL12-305259

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel);
Conventional Drug Susceptibility Test in progress.

<table>
<thead>
<tr>
<th>Gene (region) examined*</th>
<th>Result</th>
<th>Interpretation (based on in-house evaluation of 556 clinical isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pglE (RRDR)</td>
<td>Mutation: TGG-&gt;TGC, Ser531Thr</td>
<td>- NDM resistance (100% of isolates in our in-house evaluation of 556 clinical isolates with this mutation are RMP-R)</td>
</tr>
<tr>
<td>inhA (promoter)</td>
<td>Mutation: C-18T</td>
<td>- Isopropyl resistant (100% of isolates in our in-house evaluation of 556 clinical isolates with these mutations are INH-R)</td>
</tr>
<tr>
<td>katG (ser315 coding)</td>
<td>Mutation: AGG-&gt;ACC, Ser315Thr</td>
<td>- Likely Ethambutol Resistant (87% of isolates in our in-house evaluation of 556 clinical isolates with this mutation are ETH-R)</td>
</tr>
<tr>
<td>embB (Met336,Gly406)</td>
<td>Mutation: ATG-&gt;ATA, Met306Ile</td>
<td>- Likely PAS resistant</td>
</tr>
<tr>
<td>proA (promoter, coding region)</td>
<td>Mutation: TGG-&gt;CGG, Trp20Arg</td>
<td>- Likely PAS resistant</td>
</tr>
</tbody>
</table>
| pglA (ORDR)           | No mutation | - Cannot rule out flofluquinolone resistance. (80% of FQR isolates in our in-house evaluation of 556 clinical isolates have a mutation at this locus:)

*No negative results (e.g. no mutation) does not rule out contributory mutations present elsewhere in the genome.

MIDR 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: 404-639-2432  Fax: 404-639-5491  TBlab@cdc.gov
Address: 1600 Clifton Road, MS FOS, Atlanta, GA 30333

Confidentiality, security, and integrity of patient data should be maintained in accordance with CLIA and HIPAA.
<table>
<thead>
<tr>
<th>Locus (region) examined*</th>
<th>Result</th>
<th>Interpretation (based on in-house evaluation of 550 clinical isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rpoB (RRDR)</td>
<td>Mutation: TCG&gt;TGG; Ser531Trip</td>
<td>Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)</td>
</tr>
<tr>
<td>inhA (promoter)</td>
<td>Mutation: C-15T</td>
<td>Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with these mutations are INH-R.)</td>
</tr>
<tr>
<td>katG (ser315 codon)</td>
<td>Mutation: AGC&gt;ACC; Ser315Thr</td>
<td>Likely Ethambutol Resistant (87% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.)</td>
</tr>
<tr>
<td>embB (Met306,Gly406)</td>
<td>Mutation: ATG&gt;ATA; Met306Ile</td>
<td>Likely PZA resistant.</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>Mutation: TGG&gt;CGG; Trp88Arg</td>
<td>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.)</td>
</tr>
<tr>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, am</td>
</tr>
<tr>
<td>rrs (1400 region)</td>
<td>No mutation</td>
<td>(In our in-house evaluation of 550 clinical isolates:</td>
</tr>
<tr>
<td>eis (promoter)</td>
<td>No mutation</td>
<td>• 91% of AMK-R isolates have a mutation in the rrs locus;</td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>No mutation</td>
<td>• 87% of KAN-R isolates have a mutation in either the rrs locus or the eis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 55% of CAP-R isolates have a mutation in either the rrs locus or the tly</td>
</tr>
</tbody>
</table>

*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.
Risk Factors for Drug Resistance

- **Acquired: Previous treatment**
  - Inadequate drug regimen
  - Treatment interruptions, default
  - Pharmacokinetic mismatch between drugs in regimen (?)

- **Primary: Contact of case with known drug-resistant TB**
  - Previous hospitalization or imprisonment
  - Occupational risk groups
  - Residence in high prevalence location
DEFINITIONS

- Multidrug-resistant (MDR) refers to TB that is resistant to at least isoniazid (INH) and rifampin (RIF).
- Pre-extensively drug-resistant (Pre-XDR) refers to MDR-TB that is also resistant to either a fluoroquinolone or a second-line injectable anti-TB drug (kanamycin, capreomycin, or amikacin), but not both.
- Mono-resistance: one drug
- Polydrug-resistance: i.e. INH and ethambutol
• Extensively drug-resistant (XDR) refers to MDR-TB that is *also resistant to both a fluoroquinolone* and *a second-line injectable anti-TB drug*. 
Resistance to any TB drug can occur

- First trial of streptomycin in 1952 reported resistance!
- Streptomycin 1945 \(3.8 \times 10^{-6}\) organisms
• Mutations conferring drug resistance to *M. tuberculosis* become important for the TB patient when amplified by health care system-related factors and/or patient behaviors.

• Contributors to the development of acquired resistance during treatment for TB include: *inadequate clinical management, poor adherence, drug malabsorption, and unstable drug supply.*
Management of drug-resistant TB is often complicated. Even under the best circumstances, successful treatment outcomes can be difficult to achieve compared to drug-susceptible disease.
**2\textsuperscript{ND} AND 3\textsuperscript{RD} LINE TB DRUGS**

- **2\textsuperscript{ND} LINE**
  - *Injectables*: Amikacin, capreomycin, kanamycin, (streptomycin)
  - Fluoroquinolones: Moxifloxacin, levofloxacin
  - Ethionamide, prothionamide, cycloserine, PAS, terizodone

- **3\textsuperscript{rd} LINE**
  - Bedaquiline
  - Delamanid
  - Linezolid
  - Clofazamine
  - Meropenem
  - High dose INH
  - Amoxicillin clavulanate
Empirical MDR treatment vs Individualized Regimen??

• Deferring treatment until drug-susceptibility results are available is an appropriate option only if the patient is not severely ill and can be isolated to prevent infection of contacts.
Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation).

14 Jan 2005

“A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium Tuberculosis*”

2013: First new TB drug approved in USA in over 40 years.

Only approved for MDR-TB
Janssen says the company OK'd bedaquiline R&D despite the lack of a market for MDR-TB drug.
Time to Sputum-Culture Conversion in the Modified Intention-to-Treat Population.

Prevalence of Drug-Resistant TB*

MDR TB: Resistance to at least isoniazid and rifampin
XDR TB: MDR + resistance to at least any one of the fluoroquinolones and any one of the second-line injectable drugs (kanamycin, amikacin, capreomycin).

*WHO. Multidrug and extensively drug-resistant TB, 2010 Global Report
Proportion of MDR among new TB cases
Latest available data, 1994-2011

*WHO. Global TB Control 2012 (www.who.int/tb)
Proportion of MDR among previously treated TB cases, 1994-2011
Latest available data, 1994-2011

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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*WHO. Global TB Control 2012 (www.who.int/tb)
Regimens

INH mono-resistant

- Rifampin
- Pyrazinamide
- Ethambutol
- +/- fluoroquinolone

- 6-9 months

Rifampin mono-resistant

- INH
- Pyrazinamide intensive phase 8 weeks
- Ethambutol
- Fluoroquinolone

- 12-18 months
Building an MDR regimen with 4-6 drugs

• Any available first-line agent +
• Fluoroquinolone +
• Injectable agent +
• Second-line agents +
• Third-line agents if needed
Duration of MDR Therapy

- *Intensive phase* with injectable agent for 6 months after culture conversion
- *Continuation phase* with remaining drugs for at least 18 months after culture conversion
- Monthly collection of AFB cultures for duration of course, as failure may occur.
My MDR Case…..
March 10, 2009

- 40 yr male Djibouti citizen arrived @ Detroit Metro Airport
- Flew from Yemen thru Germany to Detroit
- At Immigration noted to be nervous
- Passport in order.
- Luggage searched: bottles of ofloxacin, pyrazinamide, ethambutol, ethionamide
<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>R</td>
</tr>
<tr>
<td>Rifampin</td>
<td>R</td>
</tr>
<tr>
<td>PZA</td>
<td>R</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>R</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>S</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>S</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>S</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>S</td>
</tr>
<tr>
<td>PAS</td>
<td>S</td>
</tr>
</tbody>
</table>
- 5 weeks after admission:
- **Capreomycin** 1 gram IV daily
- **Cycloserine** 750 mg daily
- **Linezolid** 600 mg BID
- (PAS 4 grams TID)
- **Moxifloxacin** 400 mg daily

<table>
<thead>
<tr>
<th></th>
<th>AFB smear</th>
<th>AFB culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>March</td>
<td>4+</td>
<td>++</td>
</tr>
<tr>
<td>June</td>
<td>3+</td>
<td>++</td>
</tr>
<tr>
<td>July</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>September</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
MDR-TB
Boeing 747-100
Passengers and Flight Crew on Flight 4 Who Had Positive Tuberculin Skin Tests

THE SHORTER MDR-TB REGIMEN

REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-H_{high-dose}-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
H_{high-dose}= high-dose Isoniazid; E=Ethambutol

Thank You!