Drug Resistant TB

Barbara J Seaworth, MD

June 4, 2010
Objectives for MDR/XDR TB Update

- Review the epidemiology of MDR/XDR TB
- Describe the mechanism of MDR/XDR TB
- List treatment options for MDR/XDR TB
- Describe drug susceptibility testing
- Identify infection control measures

MDR TB – Definitions

TB resistant to INH and Rifampin

- TB - No Prior Therapy
  aka
  - *Primary MDR TB*
    - Results from exposure to a patient with infectious MDR TB
- TB – Prior Therapy
  aka
  - *Acquired MDR TB*
    - Results from inadequate treatment
XDR TB

• MDR TB Plus
  – Resistance to one of the fluoroquinolones
    • Ofloxacin
    • Levofloxacin
    • Moxifloxacin
    
    AND
    
  – Resistance to one of the second line injectables
    • Amikacin
    • Capreomycin
    • Kanamycin

PRE – XDR TB

• MDR TB
  – AND either resistance to a fluoroquinolone
  – OR resistance to one of the second line injectables.

• One step away from XDR TB!

• California (1993-2004):
  – 18 % of MDR TB cases
Global Epidemiology of MDR and XDR Tuberculosis

Assessing the risk in your foreign born patients
MDR-TB and XDR-TB
The 2008 Report

- Data from 81 countries and 91,555 patients
- Highest ever recorded rates of MDR TB
- Highest rates in former Soviet Union and China
- Severely limited laboratory capacity in Africa
- Linkage of HIV and MDR in Latvia and Donetsk, Ukraine
- Decline in U.S. and Hong Kong

MDR-TB Survey Findings:
- MDR-TB, on average, in 5.3% of all TB cases
- The 14 areas with MDR-TB rates among new cases greater than 6%:
  1. Azerbaijan, Baku City (22.3%)
  2. Moldova (14.4%)
  3. Ukraine, Donetsk (10%)
  4. Russia, Tomsk (15%)
  5. Uzbekistan, Tashkent (14.8%)
  6. Estonia (13.3%)
  7. Russia, Mary El (12.5%)
  8. Latvia (10.8%)
  9. Portugal (8.1%)
  10. Armenia (7.6%)
  11. Russia, Orel (7.1%)
  12. China, Inner Mongolia (7.3%)
  13. China, Heilongjiang (7.2%)
  14. Georgia (6.8%)
MDR TB (%) Among New TB Cases 1994-2007

*Sub-national coverage in India, China, Russia, Indonesia.

MDR TB (%) Among Previously Treated TB Cases 1994-2007

*Sub-national coverage in India, China, Russia, Indonesia.

WHO 4th Global Report
Drug Resistant TB, 2008
Estimated Number of MDR TB Cases*

*Zignol et al., JID 2006

Threat of MDR in Africa

Estimated Incidence of TB/100,000 Population in African Countries in 1990 & 2005


XDR TB (%) of MDR Cases

Map 8: XDR-TB

* Sub-national averages applied to Russia

WHO estimates 40,000 cases emerge each year

49 countries
Country of Origin: Impact on TB Diagnosed in U.S.

- Drug resistance more common in recent entrants
  - MDR TB: China (6%), Peru (6%)
  - INH Resistance: Vietnam (20%), Peru (18%), Philippines (17%), China (16%)

Emergence of Totally Drug Resistant (TDR) TB

- XDR TB plus cycloserine, PAS, all injectables
- 15 TDR isolates identified in Iran
- Collected from immigrants and Iranians
- VNTR profiles and spoligotyping different
  - Not explained by transmission.

» Chest 2009; 136:420-425
XDR TB in California 1993-2006

- 12 of 18 pts were XDR at time of presentation
- 10 of 12 were foreign born
  - Disease diagnosed median 0.9 year after arrival
    - (MDR 3.7 years, TB in general 9 years)
- 7 of 18 (46.7%) born in Mexico
  - (27% of MDR born in Mexico)
  - Early in study most foreign born from Asia
  - Later in study most were from Mexico

Extensively Drug Resistant TB in California 1993-2006. CID 2008 47; 450-7

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS IN THE UNITED STATES

**Figure 1. Number of Extensively Drug-Resistant Tuberculosis (XDR-TB) Cases Reported in the United States, 1993-2007**

- Cases counts are likely to be incomplete for later years because of delays in reporting final drug susceptibility testing results, which are reported only after treatment has stopped. The duration of treatment for XDR-TB cases may be 24 months or more, so results are considered complete through 2005. A "T" trait for these trend, 2.46 (P=0.12).
Which Patients are at Risk of Drug Resistant TB?

- Birth/residence in country with high incidence of drug resistant TB
- Exposure to patient with relapse or failure
- Prior treatment for TB
- Treatment failure
- Relapse in a patient not on DOT
- Poor adherence
- Clinical deterioration during 4 drug therapy

NEW FACE OF TUBERCULOSIS

21 yr old Russian college student
Loosing weight, tired x 6 mo
Fever, cough x 4-6 weeks
Abnormal CXR,
Community acquired pneumonia
Continued to get worse

BAL + M Tuberculosis on culture, by now CXR and patient are worse

Contact Investigation
College campus
Hookah bar
Model Club
Face Book

In Egypt at least 17% of TB is transmitted Through smoking at a Hookah Bar
XDR-TB
Extensively Drug Resistant Tuberculosis

Isoniazid
Ethambutol
Rifampin

Streptomycin
Ethionamide
Ofloxacin

Rifabutin
Kanamycin
Capreomycin

---

Bad Bugs:
Are There Drugs to Treat This Patient?

- 56 yr old male, TST positive, abnormal CXR
- Cough, fever, sweats, weight loss x 4 months
  - Culture positive M TB Resistant to:
    - INH,
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Levofoxacin
    - Ethionamide
Inadequate Public Health Response from Past?

- **Contact to father who died with MDR TB in 1994**
  - Father’s culture resistant to:
    - INH,
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Ofloxacin
    - Ethionamide

- Father was drug susceptible at first diagnosis!
- Chronic, untreatable disease with transmission created by inadequate therapy, non-compliance and public health decisions
Chronic MDR TB
Extensive Drug Resistance

• 2005: Referred to Binational Project
  – Resistance: INH, Rifampin, Rifabutin, Streptomycin, PZA, EMB, Ethionamide, Levofloxacin and Imipenem
  – Susceptible: Amikacin, Capreo, Cycloserine, PAS, Linezolid
  – Intermediate: Moxifloxacin 1.0 microgram/ml

• Treatment: Amikacin, Capreo, Moxifloxin 800mg, PAS and Linezolid 600mg
  – Culture conversion at 3 months
IF YOU DIAGNOSE XDR TB -

• THIS WOULD BE A GOOD TIME TO CONSIDER MEDICAL CONSULTATION!

BUT

• ANYTIME YOU HAVE A QUESTION IS A GREAT TIME

What Factors are Responsible for High Rates of MDR TB?

• Global standard - diagnosis by smear only
  – No cultures or susceptibility tests

• Drug resistance is not recognized

• Standardized treatment regimens used
  – This allows further development of resistance
    AMPLIFICATION OF RESISTANCE
Drug Resistance:
KwaZulu-Natal Strains, South Africa

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IREI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRESI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRESII</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRESIIIF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRESIIIFa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRESIIIFe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pillay: Clin Inf Dis, 2007
Pathogenesis of Drug Resistance

How Does Drug Resistance Develop?

Pathogenesis of Drug Resistant Tuberculosis

- Genetic mutations occur spontaneously that confer resistant to an anti-tuberculosis drug
  - Are present in wild type M tuberculosis isolates.
  - Occur by chance alone
  - Do not depend on prior drug exposure
  - Not linked
  - Occur in frequency specific for each drug
    - INH: 1 in $10^6$, rifampin: 1 in $10^8$
    - INH and rifampin: 1 in $10^{14}$
      - Individual risk of each drug multiplied together
Treatment with a Single TB Drug Leads to Drug Resistance

- Due to the natural occurrence of spontaneous mutations, treatment with one drug (or one effective drug) leads to development of resistance in the whole population of mycobacteria.
  - drug susceptible bacteria will be killed
  - drug resistant bacteria will survive
    - eventually replace the susceptible population.

Increase In Streptomycin-Resistant Mutants During Monotherapy

<table>
<thead>
<tr>
<th>Weeks of treatment</th>
<th>SM-resistant mutants</th>
<th>SM-resistant mutants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (before)</td>
<td>1 / 88,750</td>
<td>0.0011</td>
</tr>
<tr>
<td>2</td>
<td>1 / 13,174</td>
<td>0.0075</td>
</tr>
<tr>
<td>3</td>
<td>1 / 817</td>
<td>0.12</td>
</tr>
<tr>
<td>4</td>
<td>1 / 588</td>
<td>0.17</td>
</tr>
<tr>
<td>5</td>
<td>1 / 367</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Pyle M. Proc Mayo Clinic 1947;22:465
Isoniazid Resistance After 2 Months of Isoniazid Monotherapy

- Retrospective analysis from isoniazid treatment trial 1952 among patients with drug-susceptible isolates before starting

<table>
<thead>
<tr>
<th>#Patients</th>
<th>Cavities</th>
<th>% Cult +</th>
<th>% resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0</td>
<td>40%</td>
<td>22%</td>
</tr>
<tr>
<td>57</td>
<td>1+</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>89</td>
<td>2+</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td>43</td>
<td>3+</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Fox W, Sutherland I. Thorax 1955;10:85-98

Protecting Rifampin

Initial therapy with standard four drug regimen (RIPE) protects rifampin if INH resistance is present

Treatment with INH, Rifampin, & PZA only
- If INH resistance is present:
  - PZA does not protect rifampin
    - is not active in cavities and rapidly growing lesions

- AND if culture and susceptibility tests not done and resistance is not detected
  - in both the initiation and continuation phase → rifampin monotherapy
Drug-resistant mutants in large bacterial population

Multidrug therapy: No bacteria are resistant to all 3 drugs

INH RIF PZA

Monotherapy: INH-resistant bacteria proliferate

INH

Spontaneous mutations develop as bacilli proliferate to $>10^8$

INH resistant bacteria multiply to large numbers

INH mono-resist. mutants killed, RIF-resist. mutants proliferate $\rightarrow$ MDR TB
"Fall and Rise" phenomenon

Fluoroquinolone Resistance

  - MDR TB 8.5%
  - XDR TB: 89%

  - MDR TB 8%
  - XDR TB 100%

  - MDR and XDR TB 42%
Empirical Rx of CAP and Development of FQN-Resistant TB

- Case control study 428 pts with pulmonary TB who were enrolled in drug benefit plan
  - 74 (17%) received ≥ 1 FQN prescription
    - FQN more likely in older pts, those without cavity
  - Only those with > 1 FQN prescription developed FQN resistance
  - 54 single prescriptions 20 multiple scripts
    0 FQN resistant 3 (15%) FQN resistant

Prevalence of 2nd Line Drug Resistance in MDR TB Patients

- PETTS Study in 7 of 8 countries*
  - 522 MDR isolate
    - 109 (20%) had resistance to either an injectable second line drug (SLD) or FQN
    - 30 XDR
    - 285 resistant to all 1st line drugs

Preserving Effective TB Treatment Study; *Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand
Principles of Treatment and Management of MDR TB

• Treat patients with likely drug resistant disease with an adequate number of drugs to prevent emergence of further resistance (amplification of resistance).
  – Use more drugs if susceptibility tests pending
    • Often will start with at least 5 - 6 drugs
Principles of Treatment and Management of MDR TB

• Drug selection
  – **At least 3 New drugs** not previously used
  – Those with **proven or suspected** susceptibility
  – **As many bactericidal** drugs as possible
  – Any first line drugs with proven susceptibility
    • Even if part of prior failing regimens
• Limit toxicity as much as possible
Principles of Treatment and Management of MDR TB

• Treat at least **18-24 months after conversion of the culture to negative**
• Continue **injectable at least 6 - 12 months after conversion of culture to negative**
• Shorter therapy for limited, primary or early disease
  – Consistent with the International Standards for TB Control released 3-24-06

Principles of Treatment and Management of MDR TB

• Never add a single drug to a failing regimen
• However a single drug can be added;
  – To augment a weak regimen in the first 2 – 3 wks
  – After conversion of cultures
  – To augment an oral regimen after stopping an injectable or another drug if patient is responding and cultures are negative
• If culture still positive, add 2 drugs
Case Study: Immigrant from Nepal

• History of TB treated for one year
  – Reported normal exit CXR and cleared
• Coughing during flight
• Weight loss, malnutrition, (76 lbs)
• Sputum + for AFB
• Treatment: RIPE plus Moxifloxacin

Was this a good idea?

Recent Immigrant from Nepal
Recent Immigrant From Nepal

• Culture positive for M TB
  – Initial: resistant to INH, rifampin, ethambutol (5.0 ug/ml), rifabutin, and PZA
  – Several weeks later treatment: Amikacin, Moxi, EMB, Cycloserine
  – Susceptible to ethionamide, levofloxacin, amikacin

Should we worry about fluoroquinolone resistance?

Recent Immigrant from Nepal

• Patient improves clinically
  – Gains 25 pounds
  – Cough and fever resolve, night sweats gone
  – Smears and cultures convert at 12 weeks
  – Last positive culture now Moxifloxacin resistant

Repeat sensitivity on last positive culture to look for further resistance!
When Do You Start Treatment for MDR TB?

- Stable patient: Wait to identify enough drugs to constitute a regimen with a chance of cure

- If patient seriously ill or HIV positive: start now
  - At all costs avoid creating an untreatable patient who can transmit this bug
  - If empiric treatment needed pending susceptibility - use enough drugs to cover for unsuspected resistance
  - HIV TB always treated now – there is no time to wait
    - If suspect MDR TB augment regimen and back off later

- Must also consider risk to community

MDR (PRE-XDR) TB

- 24 yr old Indian graduate student
  - Flies to Texas to visit boyfriend
  - Sick on flight and goes right to the hospital

- BAL positive smears for TB

- Treatment started but patient is getting worse

- Culture shows MDR TB
  - With resistance to everything but ethionamide and injectables

- Pulse 150, respiratory rate 35

- SOB at rest, 84 pounds, albumin 1.6, fever 103, Extensive cavitary TB on CXR
Repeat Susceptibility Tests

- Always repeat susceptibility at least every two months if culture is still positive
- At the time MDR TB is identified and standard regimen stopped
- Anytime new resistance is identified and there is a question as to whether treatment is effective
- Try not to chase the culture/susceptibility

Case Study

- 26 year old Vietnamese female diagnosed with smear and culture + M TB June 2008
  - Weight loss, bloody sputum, fever, short of breath, rapid heart rate
  - Extensive bilateral cavitary infiltrates
  - Started on standard TB treatment “RIPE”
    - Cough, fever, and shortness of breath worsen
    - Admitted to ICU end of July
Case Study  
Patient deteriorating  

• Impending respiratory failure  
• From an area of the world with not only MDR TB but XDR TB  
• Physician adds moxifloxacin alone 7/27/08  
• 8/1/08 nurse calls lab and they report possible “resistance to everything”  
  – I asked her to clarify what that meant  

No Time to Wait For Lab Results  

• “We have preliminary MTB drug susceptibility test results for patient - -. specimen # - -, DOC=06-13-08. We have repeated the test a second time. The test results indicate MDR TB to include resistance to INH, Streptomycin, Ethambutol and Rifampin. We are checking to determine if the culture is pure before we report out a preliminary report. The culture will be sent to - - this week for extended susceptibility testing and genotyping”  

Sent 8/4/08
The healthcare providers knew the patient was getting worse

The laboratory knew the specimen did not look like drug susceptible TB

Drug Susceptibility Tests

• All cultures should get INH, rifampin, ethambutol, and PZA in liquid media
  – Expect results by 14 – 21 days
  – If lab sends out after growth – send culture
    • Do not wait for a new culture to grow to send

• If any resistance detected
  – Second line susceptibility tests to include:
    • Ethionamide, Ofloxacin, Kanamycin, Capreomycin, Streptomycin,
  – Third line tests: PAS, Linezolid, +/- cycloserine
A Fluroquinolone Should Be Part of the Initial Panel

- They are increasingly used to treat a variety of respiratory infections
  - Resistance can develop after several weeks

- It is the most important drug in the treatment of MDR TB or treatment failure

- A fluoroquinolone is the primary substitute drug for toxicity, intolerance & INH resistance

Counting on a drug that is not susceptible is a grave mistake but many don’t think to test for resistance.

Molecular Tests for Drug Resistance

- Primarily available for Rifampin and INH
  - Results show good sensitivity and specificity
    - Especially for rifampin (>96%)
    - INH also good but (>90%)

- Several sites run tests on sputums that are smear +

- CDC offers on positive cultures

- More drugs soon will be tested (FQN, injectables)
### Discontinuation of Airborne Infection Isolation: MDR-TB

<table>
<thead>
<tr>
<th>Organization</th>
<th>Title</th>
<th>Smear/Culture</th>
<th>Min days Tx</th>
<th>Lab results</th>
<th>Type</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC</td>
<td>all</td>
<td>Not mentioned</td>
<td>neg culture</td>
<td>comment</td>
<td></td>
</tr>
<tr>
<td>CDC</td>
<td>Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care facilities, 2005</td>
<td>all</td>
<td>Not mentioned</td>
<td>neg culture</td>
<td>comment</td>
<td></td>
</tr>
<tr>
<td>Department of Health</td>
<td>The Interdepartmental Working Group on Tuberculosis: The prevention and control of tuberculosis in the United Kingdom: Department of Health – Publications</td>
<td>all</td>
<td>Not mentioned</td>
<td>neg culture</td>
<td>case by case</td>
<td></td>
</tr>
<tr>
<td>Bureau of Tuberculosis Control</td>
<td>Tuberculosis (TB): Clinical Policies and Protocols</td>
<td>all</td>
<td>Not mentioned</td>
<td>neg smear + neg culture</td>
<td>if possible</td>
<td></td>
</tr>
<tr>
<td>Public Health Agency Canada</td>
<td>Canadian Tuberculosis Standards 6th Ed.</td>
<td>all</td>
<td>Not mentioned</td>
<td>3 neg cultures</td>
<td>guideline</td>
<td></td>
</tr>
</tbody>
</table>

### Infection Control

- **Hypothetical Infectiousness**
- **Start of therapy**
- **Disease Progression (t)**
  - t=0
  - t1
  - t2
  - t3
Extensively Drug Resistant (XDR) TB
Recent Outbreak in Kwazulu Natal, SA

1500 patients evaluated

544 (35%) with TB  
995 (65%) without TB

221 (41%) MDRTB  
323 (59%) Susceptible

53 (10%) XDRTB

• 52 died, All HIV+ died
• Time to death=16 d
Mortality Associated with MDR TB Outbreak in New York, 1990s

<table>
<thead>
<tr>
<th>Facility</th>
<th>% HIV-infected</th>
<th>% Mortality</th>
<th>Median interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosp. A</td>
<td>93</td>
<td>72</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Hosp. B</td>
<td>100</td>
<td>89</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Hosp. C</td>
<td>95</td>
<td>77</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hosp. D</td>
<td>91</td>
<td>83</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hosp. E</td>
<td>14</td>
<td>43</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hosp. F</td>
<td>82</td>
<td>82</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hosp. I</td>
<td>100</td>
<td>85</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

TREATMENT OUTCOMES

Culture Conversion

- California: (1993-2006)
  - XDR TB - 46.7%  MDR TB – 87.3%
  - XDR TB - 195 days  MDR TB – 98.5 days

- Germany: (2004-2006)
  - XDR TB – 80%  MDR TB 87.2%

- Latvia: (2000)
  - MDR TB 77%  - median time 60 days

- South Korea: (1995-2004)
  - XDR TB - 66%  MDR TB – 67%
Factors Associated with Good Treatment Outcomes for MDR TB

- Younger age
- Absence of cavities
- HIV negative
- Primary disease
- Hospitalization
- Culture conversion by 3 months
- ? Surgery
- Sensitivity to ofloxacin
- No prior therapy with ofloxacin
- Fewer # drugs MTB is resistant to
- More effective drugs in regimen
- Appropriate therapy
- Linezolid?

New Treatments for MDR TB

- TMC 207
- Otsuka
- PA 128
- Linezolid
  - NIH and TBTC studies in progress
  - Already in wide use globally
TMC 207 in Primary MDR TB

![Graph showing time to culture conversion](image)

**Figure 2.** The Proportion of Patients with Positive Sputum Cultures and Time to Conversion. Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Management of Contacts of MDR TB

- Treat for 6 months or observe without treatment
  - Use drugs source case is sensitive to
    - Choose 2: EMB, FQN, PZA
  - HIV positive and immunocompromised persons should be encouraged to accept treatment
    - Treat HIV-positive persons for 12 months
- **Follow for 2 years regardless of treatment**
  - CXR and clinical evaluation
THEY ALWAYS COME BACK

Unless You Do It Right The First Time!