Drug Resistant TB
A Global Threat

John K. Podgore, DO, MPH
Professor Pediatrics - UNTHSC
Clinician, Tarrant County Health Department
Tuberculosis Service
The Global Health Crises Due to Drug-resistant TB

Although the incidence of tuberculosis has been decreasing in most parts of the world, some regions are undergoing an increase in the emergence of multi-drug resistant TB (MDR-TB) which presents a worldwide threat for several reasons.
77 Countries reported at least 1 case of MDR-TB in 2011
Why is the emergence of TB drug resistance a global threat?

1. Drug resistant tuberculosis treatment has poorer outcomes.
2. Treatment of MDR-TB with effective therapy is very costly and the second-line drugs have increased toxicity.
3. Most MDR-TB currently occurs in resource poor settings with limited diagnostic and treatment capabilities.
5. Extremely drug resistant cases of tuberculosis have been being reported which are functionally untreatable with most currently available drugs.
Outbreak of Resistant and Highly Lethal TB in S. Africa

- In 2005 large numbers of patients with multi-drug resistant TB (MDR-TB) and extensively resistant TB (XDR-TB) were identified in a rural hospital in Tugela Ferry, Kwa Zulu-Natal S. Africa

- Of 524 patients with positive sputum for TB 221 (41%) had MDR-TB and 53 (10%) had extensively resistant TB (XDR-TB) which was resistant to all 6 drugs tested. (rifampicin, Ethambutal, streptomycin, ciprofloxacin and kanamycin)

- The mortality rate was 98% in patients with XDR-TB and the median survival was 16 days
Outbreak (continued)

- All tested were HIV positive and never been treated for TB and had limited or no access to ARV drugs.

- High rates of MDR-TB and XDR-TB were also recorded from patients at health care facilities in the region and many were HIV negative.

- Previous nosocomial outbreaks of MDR-TB have occurred in HIV infected populations in the mid-1990’s in New York and elsewhere of lesser magnitude and with less public attention.
A Short History of TB Drug Resistance

- TB was detected in the spine of an Egyptian mummy living over 4,000 years ago.
- In the pre-TB antibiotic era TB was fatal in approximately 50% of individuals within 5 years of onset of disease.
- Streptomycin discovered in 1943 by Selman Waksman (Waksman was awarded a Nobel Prize).
- 1948 report that most patients on streptomycin monotherapy developed resistant TB.
A Short History of TB Drug Resistance (Cont.)

- In the 1990’s there was a rise in multi-resistant TB and an outbreak of a virulent transmissible strain in New York City that received considerable attention which soon vanished.

- An outbreak of XDR-TB in a rural health center in South Africa was reported at the International AIDS Conference in Toronto in 2006.

- By 2011 77 Countries reported at least one case of MDR-TB and approximately 9% of 650,000 MDR-TB infected cases worldwide were classified XDR-TB.

- Countries tested by CDC revealed XDR-TB in 4% of US isolates, 15% in S. Korea, and 19% in Latvia.
Drug-Resistant TB Definitions

- **Mono-Resistant:**
  - Resistance to a single drug

- **Poly-resistant:**
  - Resistance to more than one drug, but not the combination of isoniazid and rifampicin

- **Multi drug-resistant (MDR):**
  - Resistance to at least isoniazid and rifampicin

- **Extensively drug-resistant (XDR):**
  - MDR plus resistance to any fluoroquinolone and at least 1 of 3 injectable drugs (amikacin, kanamycin, or capreomycin)
What is XXDR-TB

- This term has been used by some for extremely drug resistant TB and sometimes these organisms are referred to as “totally drug resistant”

- First reported in 2007 for a strain of TB resistant to all first-line drugs as well as all second-line drugs (it has been used in the media but the term is not recognized by the WHO due to the current lack of a reliable susceptibility test for some of the TB drugs used in treatment and new standard testing procedures are necessary for the newer drugs undergoing clinical trials
Clinical Manifestations of MDR-TB

- MDR-TB are or are not clinically distinguishable from drug-susceptible TB at the outset

- Signs, symptoms, and radiological findings are similar initially to drug-susceptible TB
Persons at Increased Risk for Drug Resistance

- History of prior treatment with TB drugs
- Contacts of persons with drug-resistant TB
- Smears or cultures that remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks
Consequences of MDR-TB

- Delay in diagnosis
- Treatment duration extended
  - 18-24 months
- Increased mortality
  - Effectiveness decreases
  - Toxicity increases
- Second line drugs required
- Expensive to treat
- Community transmission
Treatment for MDR-TB

- Usually the initial regimen for MDR-TB will consist of at least 3 TB drugs the patient has not used before (a single drug should never be added) and as many as 6 drugs may be used.
- There are detailed dosages and possible options available depending on many factors.
- Ideally therapy should be based on reliable TB drug sensitivity testing and managed by a TB expert.
Management of Drug Resistant TB

- Considerable attention must be paid to treatment supervision and support.
- A patient-centered approach to DOT is an important element of successful care.
- Adverse effects of second-line drugs are common and may be severe. Monitoring for these effects is essential.
Categories of Antituberculosis Drugs: WHO

- **Group 1- First-line drugs**: Isoniazid, rifampicin, ethambutol, pyrazinamide
- **Group 2- Injectable agents**: kanamycin, amikacin, capreomycin, streptomycin
- **Group 3- Fluoroquinolones**: levofloxacin, moxifloxacin, ofloxacin
- **Group 4- Oral bacteriostatic agents**: ethionamide, cycloserine, para-amino salicylic acid (PAS), prothionamide, terizadone
- **Group 5- Unclear role**: clofazimine, linezolid, amoxicillin/clavulanate, imipenem/cilastatin, thioacetazone, high-dose isoniazid, clarithromycin
TB Drug Susceptibility Testing

- In the 1990’s WHO introduced a laboratory quality assurance program with quality assurance supervision and assisted over 100 national laboratories in six continents to have standardized culture and drug susceptibility techniques.

- In 2000 – 2004 CDC and local studies of 17,690 TB isolates 20% were MDR-Tb positive and 2% were identified as XDR-TB

- Assessment showed 4%, 15% and 19% of XDR-TB isolated from specimens from the USA, S. Korea, and Latin America, respectfully.
Problem of identifying and treating MDR-TB Globally

- Most settings with high MDR levels lack laboratory capacity for testing second-line drugs.
- Therefore most patients with XDR-TB are rarely treated on the basis of reliable drug sensitivity testing.
- Standard drug susceptibility test results require adequate laboratory facilities and 6 to 8 weeks to isolate TB and perform susceptibility tests.
- Rapid diagnostic tests are just becoming available in some regions with the help of international funding.
New Rapid TB diagnosis and drug resistance assays

- Xpert MTB/RIF assay (detects presence of TB and Rifampin resistance by PCR assay)
- MTBDR Plus assay (also a rapid molecular assay using line-probe)
- MTBDR sl (requires a culture isolate and can rapidly assay multiple second-line TB drugs)
Third Line Drugs for XDR-TB

- Some of these drugs are classified by WHO as Group 5 drugs.
- Promising new drugs available for clinical use are bedaquiline and delaminid (not currently in US).
- Currently 11 main categories of drugs are regularly tested for susceptibility and the STOP TB Partnership is conducting ongoing prospective studies of MDR-TB.
- These studies suggest that TB with resistance to all drugs tested is rare.
Update on TB Drug Resistance

John K. Podgore

**Discovery**
- Lead optimisation

**Preclinical development**
- Good laboratory practice
- Toxicity studies

**Clinical development**
- Phase 1
- Phase 2
- Phase 3

**Cyclopeptides**
- CPZEN-45
- PBTZ169
- AZD-5847

**Diarylquinolines**
- BTZ043
- TBA-354
- Bedaquiline
- Delamanid (OPC-67683)

**DprE inhibitors**
- DC-159*
- Q203
- (TMC-207)
- Linezolid
- Novel regimens†
- PA-824
- Rifapentine

**Indazoles LeuRS inhibitors**
- SQ609
- SQ641

**Ureas, macrolides, Azaindole**
- TBI-166

**Mycobacterial gyrase inhibitors**
- Sutezolid
- Pyrazinamide analogues (PNU-100480)
- Ruthenium(II) complexes
- Tedizolid

**Spectinamides**
- SPR-10199

**Translocase-1 inhibitors**
- SQ-109

**Chemical classes:**
- Rifamycin; oxazolidinone; nitroimidazole; diarylquinoline; benzothiazinone; ethylenediamine
How we can prevent MDR TB

- Initial treatment with standardized regimens (HRZE)
- Directly observed therapy (DOT)
- Drug susceptibility testing for all retreatment cases and screening of new cases with rapid tests for resistance
- Infection control precautions and education in potential risk settings
- Monitor local drug resistance through surveys
- Effective contact management
Prevention (continued)

• Global funding to assist efforts for prevention and control in resource poor countries
• Increased efforts in rapid testing and new drugs
• Increased surveillance measures
• Research and improve public health measures
• Improve education and decrease poverty
TB Case Study

- 21 year old male from Asia in a normal state of health noted to have a +TST and RUL infiltrate on physical exam prior to leaving to study at a university in the USA

- No history of fever, cough, hemoptysis, night sweats, or fatigue but had a 15 pound weight loss in past 4 months

- Started on non-DOT RIPE therapy and reported weight gain and improved CXR at 6 weeks

- No evidence of sputum smears or cultures taken or results

- Told he could continue TB therapy in the USA
Case Study (continued)

- Reported to student health and told them he was on TB meds
- Sent to local health department where he had chest x-ray and sputum collected x 3 and put of DOT with RIPE
- Low level sputum smear positive reported and he was placed on airborne precautions
- In 4 weeks MDR-TB identified and RIPE stopped and he was referred for admission to a special state hospital facility for MDR-TB therapy
TB Referral Center in Texas
Case study (continued)

- At state hospital pt. denied fever, chills, cough, and had gained 10 pounds since start of RIPE in Asia
- Chest x-ray revealed RUL infiltrate with no cavities
- TB isolate resistant to INH, Rifampin, PZA, Ethambutal, Streptomycin, and Ethionamide
- Susceptible to Kanamycin, Amikacin, Capreomycin, PAS, Ciprofloxacin, Levofloxacin, Linezolid, Clofazimine, and Cycloserine
TB Case Study (continued)

- Pt. started on amikacin (intravenous for 12 months), and moxifloxacin, Cycloserine, PAS and Linezolid for 24 months
- Isolate susceptible and in therapeutic range for all 5 drugs
- Sputum smears and cultures negative after 4 weeks of therapy
- Discharged from state hospital after 2 months and completed 24 months of therapy at local health department
Stop TB Strategy to reach the 2015 MDGs

1. Pursue high-quality DOTS expansion and enhancement
   a. Political commitment with increased and sustained financing
   b. Case detection through quality-assured bacteriology
   c. Standardized treatment with supervision and patient support
   d. An effective drug supply and management system
   e. Monitoring and evaluation system, and impact measurement

2. Address TB/HIV, MDR-TB and other challenges
   - Implement collaborative TB/HIV activities
   - Prevent and control multidrug-resistant TB
   - Address prisoners, refugees and other high-risk groups and special situations

3. Contribute to health system strengthening
   - Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
   - Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
   - Adapt innovations from other fields

4. Engage all care providers
   - Public-Public, and Public-Private Mix (PPM) approaches
   - International Standards for TB Care (ISTC)

5. Empower people with TB, and communities
   - Advocacy, communication and social mobilization
   - Community participation in TB care
   - Patients’ Charter for Tuberculosis Care

6. Enable and promote research
   - Programme-based operational research
   - Research to develop new diagnostics, drugs and vaccines
OBJECTIVES

Update audience on the global threat of MDR-TB
Review the emergence and epidemiology of MDR-TB
Present the risk-factors for acquiring MDR-TB
Review the methods for detecting MDR-TB strains
Describe the current and potential new MDR-TB drugs
Discuss the strategies proposed to control MDR-TB