Treatment and Management of Multidrug-Resistant TB Patients and their Contacts

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Centers for Disease Control and Prevention
July 15, 2015
Objectives

- Definitions
- Discuss the epidemiology and pathogenesis of MDR TB
- Discuss MDR TB treatment principles and new drugs
- Review special situations
Definition of Drug Resistant TB

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

- **ODR TB**
  - Resistant to INH, sensitive to RIF, with or without resistance to other first or second-line drugs
  - Resistant to RIF, sensitive to INH, with or without resistance to other drugs
  - Resistance to any (1 or more) first-line drugs (EMB, PZA, SMN) other than INH or RIF
2005: Extensively drug-resistant (XDR) TB
Definition of XDR TB

- 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
2012: Totally drug-resistant TB?

Panic and chill in the air as TDR-TB claims 3 of 12 lives

India only the third country where the deadliest form of tuberculosis has struck

People the 12 patients came in contact with to be identified and tested for TB

Less than a week after top chest physician Dr Zane J Udawadia broke the news of presence of totally drug-resistant tuberculosis (TDR-TB) cases in the city, it was revealed on Friday that three of the 12 patients he studied have died in the past two weeks.

Nobody would have known of these deaths if the Directorate of Health Services and BMC’s health officers, completely taken aback by Dr Udawadia’s research, had not launched a drive to visit the 12 patients to collect sputum samples of their family members.

While the identities and addresses of the 12 patients are not available, Mumbai Mirror traced one of the dead patient’s family to its Patilwadi, Ranade Road, Dadar (west) home.

Supriya Davare, 20, died on January 5 after three years of being treated for TB across four hospitals. She was first diagnosed with TB when she was in class 12.

Ashok Davare, her distraught father, said she was last taken to the TB Hospital in Sewri on December 28. “They told her she was in the last stage. My daughter shrank from 42 kg to 18 kg in the three years she was being treated.”
Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Ali Akbar Velayati, MD; Mohammad Reza Masjedi, MD; Parissa Farnia, PhD; Payam Tabarsi, MD; Jalladein Ghanavi, MD; Abol Hassan ZiaZarifi, PhD; and Sven Eric Hoffner, MD

Background: The study documented the emergence of new forms of resistant bacilli (totally drug-resistant [TDR] or super extensively drug-resistant [XDR] tuberculosis [TB] strains) among patients with multidrug-resistant TB (MDR-TB).

Methods: Susceptibility testing against first- and second-line drugs was performed on isolated Mycobacterium tuberculosis strains. Subsequently, the strains identified as XDR or TDR M. tuberculosis were subjected to spoligotyping and variable numbers of tandem repeats (VNTR).

Results: Of 146 MDR-TB strains, 8 XDR isolates (5.4%) and 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) or had other resistant patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months' duration with five drugs (isoniazid [INH], rifampicin [RF], streptomycin, ethambutol, and pyrazinamide). The median of in vitro drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrants (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. In such cases, the smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), EAI (21.7%), and CAS (17.3%) superfamilies of M. tuberculosis. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases.

Conclusions: The isolation of TDR strains from MDR-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries. Now the next question is how one should control and treat such cases.
Emergence of Totally Drug Resistant (TDR) TB

- XDR TB plus cycloserine, PAS, all injectables
- 15 TDR isolates; 56% Iranian, 30% Afghani
- Cases + smear/culture after 18 months Rx
- 95% XDR/TDR had history of prior TB treatment
- 10% had resistance to all second line drugs (Iranian)
  - Believed due to exposure to aminoglycosides and FQ for treatment of other respiratory diseases
- Recent transmission was not the reason for emergence of TDR

Chest 2009; 136:420-425
Timebomb
The Global Epidemic of Multi-Drug-Resistant Tuberculosis

Lee B. Reichman, M.D., M.P.H.
with Janice Hopkins Tanne

“A chilling account.” —The New York Times
Impact of MDRTB

- 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
- Recommendations for contacts have been soft
Treatment Costs

- Direct costs, mostly covered by the public sector
- $134,000 per MDR TB patient (average)
- $430,000 per XDR TB patient (average)
- $17,000 per non-MDR TB patient

Epidemiology
TB ANYWHERE IS EVERYWHERE

The image
The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.

The image also represents the vulnerability of the disease, located anywhere, everywhere.

Preventable and curable.

GLOBAL PLAN TO STOP TB.

WORLD TB DAY
Percentage of New Cases with MDR-TB
Latest available data, 1994-2014

Percentage of new TB cases with MDR-TB

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. © WHO 2014. All rights reserved.
Percentage of Previously Treated TB Cases with MDR-TB

Latest available data, 1994-2014

Percentage of previously treated TB cases with MDR-TB

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The global TB situation (1)

<table>
<thead>
<tr>
<th>All forms of TB</th>
<th>Estimated incidence, 2013</th>
<th>Estimated number of deaths, 2013</th>
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<tr>
<td></td>
<td>9.0 million</td>
<td>1.1 million*</td>
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<tr>
<td></td>
<td>(8.6–9.4 million)</td>
<td>(1.0–1.3 million)</td>
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<tr>
<td>HIV-associated TB</td>
<td>1.1 million</td>
<td>360,000</td>
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<td>(1.0–1.2 million)</td>
<td>(310,000–410,000)</td>
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<tr>
<td>Multidrug-resistant TB</td>
<td>480,000</td>
<td>210,000</td>
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<tr>
<td></td>
<td>(350,000–610,000)</td>
<td>(130,000–290,000)</td>
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</tbody>
</table>

Source: WHO Global Tuberculosis Report 2014

* Excluding deaths attributed to HIV/TB
27 High MDR TB Burden Countries

- 27 high MDR TB burden countries account for >85% of estimated MDR TB cases worldwide
- Highest levels in eastern Europe and central Asia
- Less than 25% of the people estimated to have MDR TB were detected in 2012

XDR TB

- XDR TB had been reported by 92 countries by the end of 2012
  - 13 countries had >10 XDR TB cases
  - On average, 9.6% of MDR TB cases have XDR TB

- Highest in:
  - Azerbaijan (Baku city: 12.8%)
  - Belarus (11.9%)
  - Lithuania (24.8%)
  - Tajikistan (Dushanbe city and Rudaki district: 21%)

Primary Anti-TB Drug Resistance, United States, 1993 – 2013*

*Updated as of June 11, 2014.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
Primary MDR TB, United States, 1993 – 2013*

*Updated as of June 11, 2014.
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2013*

*Updated as of June 11, 2014.
Note: Based on initial isolates from persons with no prior history of TB.
Primary MDR TB in U.S.-born vs. Foreign-born Persons
United States, 1993 – 2013*

% Resistant

0 1 2 3


*Updated as of June 11, 2014.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Note: Extensively drug-resistant TB (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.
Which Patients are at Risk of Drug Resistant TB?

- Birth/residence in country with high incidence of drug resistant TB
- U.S. residents who travel to high risk areas
- 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
Why Do We Have Drug Resistance?

- Inadequate treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence

Treatment failure / relapse with drug resistant TB

Transmission of drug resistant TB
Transmission of Drug-Resistant TB

- Transmitted same way as drug-susceptible TB

- Drug resistance is divided into two types
  - Primary resistance develops in persons initially infected with resistant organisms
    - Healthcare-associated transmission
    - Community transmission
  - Secondary resistance (acquired resistance) develops during TB therapy
    - Nonadherence to therapy
    - Inappropriate therapy
## Emergence of Resistance

(Inappropriate Therapy)

<table>
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<tr>
<th>Treatment</th>
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<td>Ethambutol</td>
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### Susceptibility

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<td>Rifampin</td>
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<td>Ethambutol</td>
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# Emergence of Resistance

(Nonadherence and Inappropriate Therapy)

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<th>Treatment</th>
<th>6/08</th>
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<td>Rifampin</td>
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DOT - daily directly observed therapy
Drug Resistant Mutants Selected by:

- Non-adherence
- Malabsorption
- Inadequate drug regimen
Rates of Natural 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 = $10^9$-$10^{11}$
## Treatment Strategies

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Description</th>
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<tbody>
<tr>
<td>Standardized treatment</td>
<td>Regimen is designed based on Drug Resistance Surveillance (DRS) data from a representative patient population</td>
</tr>
<tr>
<td>Empirical treatment</td>
<td>Regimen is individually designed based on patient’s previous history of TB treatment and DRS data as above</td>
</tr>
<tr>
<td>Individualized treatment</td>
<td>Regimen is designed based on the patient’s previous history of TB treatment and individual DST results</td>
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</tbody>
</table>
# Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*/Moxifloxacin*

*Not approved by the U.S. Food and Drug Administration for use in the treatment of TB*
Drug Activity Against TB
Bactericidal vs. Bacteriostatic

**Bactericidal**
- INH
- Rifampin
- Streptomycin
- Capreomycin
- Kanamycin/Amikacin
- Moxifloxacin

**Bacteriostatic**
- PZA
- Ethambutol
- Levofloxacin (*may be bactericidal*)
- Ethionamide
- PAS
- Cycloserine
Third-Line Drugs Used in MDR TB Treatment

- **Linezolid**
  - Used since 2000 in selected cases
    - More recently a 2\textsuperscript{nd} or 3\textsuperscript{rd} line drug
  - Adverse effects of pancytopenia and peripheral/optic neuritis
    - May or may not be reversible
    - May or may not be ameliorated by vitamin \( B_6 \)
    - Consider using 600 mg daily (300mg/day being studied)
  - Use with caution with selective serotonin reuptake inhibitors (SSRIs)
  - Lactic acidosis
  - Expensive
Third-Line Drugs Used in MDR TB Treatment -2

- **Clofazimine**
  - More commonly used in patients with leprosy
  - Used in selected cases
  - Needs Investigational New Device (IND) from FDA

- **Bedaquiline**
  - 1\textsuperscript{st} new class of TB medication approved since RIF
  - New class of antibiotics, diarylquinolones
  - Given as part of MDR combination therapy
  - New mechanism of action: inhibits ATP synthase
Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

First-line drugs

Pyrazinamide
Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin

Injectable agents

Amikacin
Capreomycin
Streptomycin
Kanamycin

PLUS One of these

PLUS One of these

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center
**Step 1**

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

**Step 2**

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

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center
### Step 1

**Use any available**

**First-line drugs**
- Pyrazinamide
- Ethambutol

**PLUS**

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**PLUS**

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

**Consider use of these if there are not 4-6 drugs available**

**3rd-line drugs**
- Linezolid
- Clofazimine
- Bedaquiline
- High-dose isonizid
- Imipenem
- Amoxicillin/Clavulanate

### Step 2

**Pick one or more of these**

**Oral second-line drugs**
- Cycloserine
- Ethionamide
- PAS

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

### Step 3

**Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center**
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).
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
- Capreomycin is the initial injectable agent of choice
- Surgery should be considered if a patient’s cultures fail to convert to negative after 4 months of appropriate treatment
Rifampin Resistance

- Resistance to RIF is generally associated with cross-resistance to rifabutin and rifapentine
  - When RIF resistance is present but *in vitro* sensitivity to rifabutin is reported, treatment should still be the same as if RIF-resistant

- For all with RIF-resistance (mono-RIF or MDR TB), consider extended therapy (up to 24 months) if:
  - There is cavitary or extensive disease
  - The patient is HIV-positive or has risk factors for HIV infection
  - The patient is immunosuppressed
  - Time to culture conversion is prolonged
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.
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 2\textsuperscript{nd}-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
New Treatments for MDR TB

- Bedaquiline (Janssen)
- OPC-67683: Delamanid (Otsuka)
- PA 824 (nitroimidazol-oxazine)
- Linezolid
  - NIH and TBTC studies in progress
  - Already in wide use globally
Linezolid for TB

- Used as second and third line treatment for MDRTB
- Has adverse effects:
  - affects the bone marrow
  - peripheral neuropathy
  - optic neuropathy
  - hepatic dysfunction
  - muscle injury

Pts had improved survival with the lower dose of 300mg/day instead of 600mg/day
Bedaquiline (SIRTURO™) TMC207

- First new TB drug since RIF (1970)
- New class of potent anti-TB drugs: diarylquinolones
  - Accumulates in the body by binding to phospholipids
- Used as part of combination therapy for pulmonary MDR TB in adults (>18 yrs)
- Administered under DOT
- New mechanism of action: inhibits mycobacterial adenosine triphosphate (ATP)-synthase
  - BDQ binds to ATP-synthase, the main energy source for *M. tb* growth
  - Prevents it from supplying energy for the cell, therefore killing the bacterium
FDA Approval of BDQ

- MDR TB is orphan disease in USA: 98 pts in 2011
- Approved as an orphan drug 12/31/12
- Endpoint: sputum culture conversion
  - Mean culture conversion was 83 days compared to 125 days (79% of patients at 24 weeks)
- Found the drug efficacious
- 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)
QT Prolongation

- Drugs used to treat TB or NTMs
  - Fluoroquinolones
  - Clofazimine
  - Delaminid
  - 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, bradyarrhythmias, uncompensated heart failure
- This effect can be additive
Delamanid (OPC-67683)

- 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
- Had prolongation of the QT intervals
- Nov. 2013: European Medicines Agency (EMA) recommended conditional approval
  - Likely effective in treating drug resistant TB over 6 months as it had in the 2 month study
  - Additional studies required for data on long-term benefits and safety
    - Phase III trials currently underway with data expected within next 3 years
Standard MDR-TB regimens currently recommended by WHO

- Intensive phase of 8 months treatment using at least 4 second line drugs with proven effectiveness plus PZA
  - Total treatment of 20 months
  - Recommendation on duration of treatment is subject to adaptation based on patient response to treatment


Shorter Regimens for MDR TB

Shorter regimens for MDR TB:

- Typically last 9-12 months (differs from standard WHO recommended 20 month MDR TB regimen)
- Less costly and likely to be better tolerated by patients
- Evidence on their use reported in Bangladesh with success rates comparable to those for treatment of drug-susceptible TB
- Being introduced by National TB Programs in African countries (Benin, Cameroon, Central African Republic, Cote d’Ivoire, DR Congo, Niger, Swaziland)
Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

Completion 5.3%
Cure 82.5%
Death 5.35
Default 5.8%
Failure 0.5%
Relapse 0.5%

Km=kanamycin; Cfz=clofazimine; Gfx=gatifloxacin; E=ethambutol; H=high-dose isoniazid; Z=pyrazinamide; Pto=prothionamide

STREAM: standardized treatment regimen of Anti-TB drugs for patients with MDR TB

- Trial is currently taking place in Ethiopia, South Africa and Vietnam, India
- Plan to recruit at least 400 patients with MDR-TB
- High dose Fluoroquinolones and clofazimine with a 7 drug regimen for 9 months:
  - Moxi, colfazimine, ethambutol and PZA for 9 months, with supplemental prothionamide, kanamycin and INH during the 4 month intensive phase
- The trial is expected to run for 2 years, with results available in 2016
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 MDR LTBI in Contacts of Two Multidrug-Resistant TB Outbreaks

1. Epidemiology and background on the MDR TB outbreaks in Chuuk Island
2. Review of outbreak response and treatment of contacts with MDR LTBI
3. Findings from our observational cohort study
4. Informal MDR LTBI Poll
2007 Chuuk, FSM
2 MDR TB Cases

5 DR strain:
INH, RIF, PZA
EMB, Strep

3 DR strain
INH, RIF, ETH
MDR TB in Chuuk State, 2007

• 2 cases initially reported to CDC/WHO
• MDR TB cases sent home with no treatment
  • Four of first five cases died in 8 mo. period
  • 2-year-old child and mother with MDR TB
• One-year delay to acquire MDR TB second-line drugs
• Overwhelmed, understaffed TB program with no MDR TB treatment experience
• Fragile infrastructure, power, water, roads
HOSPITAL INTENSIVE CARE UNIT
SURGICAL, MEDICAL, OB-GYN
PEDIATRIC-SURGERY AND
PEDIATRICS
DIRECTOR

WELCOME TO SURGICAL WARD
EVERYBODY DESERVES TO LIVE

No Chewing Betelnut
Inside Our Hospital
2007 – 2014 MDR TB Outbreak Chuuk, FSM

5 DR strain: INH, RIF, PZA
3 DR strain: INH, RIF, ETH
24 Cases
17 cases
MDR TB Epicurve and Outcomes in Chuuk, FSM

- **Died Prior to Treatment**
- **Died During Treatment**
- **Completed Treatment**

![Chart showing the number of new cases of MDR TB from January 2007 to July 2014, categorized by outcome.](chart-image)

- **January 2007 (Jan-07)**: 1 death
- **July 2007 (Jul-07)**: 2 deaths
- **January 2008 (Jan-08)**: 0 deaths
- **July 2008 (Jul-08)**: 0 deaths
- **January 2009 (Jan-09)**: 0 deaths
- **July 2009 (Jul-09)**: 0 deaths
- **January 2010 (Jan-10)**: 0 deaths
- **July 2010 (Jul-10)**: 0 deaths
- **January 2011 (Jan-11)**: 0 deaths
- **July 2011 (Jul-11)**: 0 deaths
- **January 2012 (Jan-12)**: 0 deaths
- **July 2012 (Jul-12)**: 0 deaths
- **January 2013 (Jan-13)**: 0 deaths
- **July 2013 (Jul-13)**: 0 deaths
- **January 2014 (Jan-14)**: 0 deaths
- **July 2014 (Jul-14)**: 0 deaths

There were no new cases of MDR TB from January 2014 to July 2014.
## MDR TB Case Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>3-Drug Resistant</th>
<th>5-Drug Resistant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>17</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Average age (yrs)</td>
<td>29.1</td>
<td>16.2</td>
<td>21.6</td>
</tr>
<tr>
<td>Females (%)</td>
<td>14 (82%)</td>
<td>14 (58%)</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Pediatric cases &lt; 15 y.o. (%)</td>
<td>5 (29%)</td>
<td>12 (50%)</td>
<td>17 (41%)</td>
</tr>
<tr>
<td>Extra-pulmonary cases (%)</td>
<td>4 (24%)</td>
<td>2 (8%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Culture positive cases*</td>
<td>3 (17%)</td>
<td>11 (44%)</td>
<td>14 (34%)</td>
</tr>
</tbody>
</table>

* 53% Culture positivity among adult pulmonary MDR TB cases
# MDR TB Treatment Regimen

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peds</td>
<td>Adults</td>
<td>Peds</td>
</tr>
<tr>
<td>amikacin/capriomycin</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>ethambutol</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>levofloxacin</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>ethionamide/prothionamide</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>para-amino-salicylic acid</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>cycloserine</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

* All cases were placed on B6
<table>
<thead>
<tr>
<th>Category</th>
<th>3-Drug Resistant</th>
<th>5-Drug Resistant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Eligible to complete*</td>
<td>16</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td># Completed treatment</td>
<td>16</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td># Relapsed (Feb, 2015)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% Tx Success</td>
<td>100%</td>
<td>95%</td>
<td>97%</td>
</tr>
</tbody>
</table>

* Excludes cases that were untreated and died prior to arrival of second-line drugs and excludes cases that are still on MDR TB treatment.
MDR TB Treatment Success Rates

- 2009 WHO Baseline
- 2015 WHO Goal
- 2014 Chuuk FSM

*The Global Plan to Stop TB 2011 – 2015, Transforming the Fight, WHO 2011
Summary Results of Chuuk Contact Investigation, July 2008

- Two distinct, simultaneous MDR TB outbreaks on Weno Island
- 232 identified and evaluated contacts
Should Infected Contacts of MDR TB Cases be Treated?

- Few evidence-based recommendations for the treatment of MDR TB contacts
- Balancing risk of treating vs. not treating
- Feasibility of providing treatment to completion
- Toxicity concerns — “above all, do no harm”
- Length of treatment
Reasons to Treat Infected Contacts of MDR TB Cases

- Treat MDR TB while bacterial burden low
- Decrease likelihood of progression to TB disease
- Severe consequences of clinically active MDR TB for patient and community
Use of Fluoroquinolones in Children for Treatment of MDR TB: Literature

- South African series
  - Of 64 children who did not receive any treatment, 13 (20%) developed TB
  - Of 41 children who received 2–3 drug treatment, 2 (5%) developed TB

Challenges of Treating MDR LTBI — Tolerability

- Following 1992 MDR TB outbreak in hospital, decision to treat MDR LTBI in 16 employees
  - 6-month PZA + ofloxacin regimen
  - 14 of the 16 experience adverse events and discontinue treatment

- CDC/ATS guidelines in 2000: 6–12 month course of PZA + FQ or EMB

- PZA + levofloxacin poorly tolerated in subsequent case series
  - All 17 contacts discontinued treatment due to intolerability (median therapy 32 days)

LTBI Treatment of MDR TB Contacts in Chuuk — Objectives

- Determine feasibility of implementing MDR LTBI treatment and follow-up in a resource-limited setting
- Study tolerability of MDR LTBI regimens
- Potentially, study efficacy of MDR LTBI regimens
Chuuk MDR LTBI Management Plan

- MDR LTBI treatment by DOT for 1 year
- FQ-based regimens
  - Children received FQ + ethambutol or ethionamide
- Monthly questionnaires by field workers
  - Symptom screen and missed doses
- Quarterly visit by healthcare provider
- Biannual chest radiograph and clinical evaluation
- Contacts followed for 2 years after completion
MDR TB Contact Evaluation

- Among the 232 identified contacts, 6% attack rate during July 2008–Jan 2009
  - 5 patients diagnosed with MDR TB
  - 9 additional patients developed MDR TB while awaiting LTBI treatment
  - 1 out of every 7 (14%) pediatric household contacts awaiting MDR LTBI developed MDR disease during the 6-month start-up waiting period.

- Two contacts who had not been identified during contact investigations also found to have MDR TB

- 119 other TST (+) with no evidence of active TB
Principles of LTBI Treatment for Contacts of MDR TB Cases

- Always exclude TB disease before beginning LTBI treatment
- Estimate likelihood of infection with and risk of progression to MDR TB
- Choose LTBI regimen of ≥2 drugs to which source case susceptible
- Efficacy largely dependent on adherence and completion of therapy
Treatment of MDR TB Contacts in FSM

STUDY RESULTS
MDR LTBI Treatment

- MDR LTBI n=119
  - Initiated Treatment n=105
  - Refused Treatment n=14
Chuuk Experience — Follow-up Visits

- TB program conducted monthly visits with the 105 patients to record
  - Occurrence of TB symptoms and side effects
  - Number of missed doses

- 1,038 (82%) monthly visits completed

- Post-treatment follow-up
  - 90% at 18 months
  - 50% at 24 months
  - 85% at 36 months
## Chuuk Experience — Adherence

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion, all (N=105)</td>
<td>93</td>
<td>89%</td>
</tr>
<tr>
<td>Healthcare personnel (n=21)</td>
<td>14</td>
<td>67%</td>
</tr>
<tr>
<td>Child &lt;12 yrs (n=26)</td>
<td>25</td>
<td>96%</td>
</tr>
</tbody>
</table>
Chuuk Experience — Discontinuation of Treatment

- 12 patients discontinued treatment
  - 3 contacts after becoming pregnant
    - 1 additional patient restarted and completed post-delivery
  - 5 contacts after being lost to follow-up
    - 4 healthcare workers
    - 1 adult household contact
  - 4 contacts due to side effects
    - 3 healthcare workers
    - 1 child with elevated liver enzymes
Procuring Second-Line Medications
Chuuk Experience — Timing of Side Effect Onset during MDR LTBI Treatment

- % Reporting Side Effect Each Month

- Cumulative % Discontinued Due to Side Effect
Chuuk Experience — Conclusions

- **Treatment effectiveness**
  - No randomized trials to show efficacy
  - Efficacy difficult to demonstrate with low numbers

- **Important outcomes**
  - High completion rate
  - Regimens were safe and tolerable
  - LTBI treatment by DOT is doable
  - No patients treated for MDR LTBI developed TB disease
Pharmacokinetics of Levofloxacin in Children Treated for, or Exposed to, Multidrug-Resistant Tuberculosis — United States Affiliated Pacific Islands, 2010–2011

Sundari Mase, MD, MPH
John Jereb, MD
Charles Peloquin, PharmD
Terence Chorba, MD, DSc
Sapna Bamrah, MD
Richard Brostrom, MD, MSPH
** Patients / Parents consented to public use of picture

*Photo by Richard Brostrom, MD, MS-PH*
Keys to Success: Systems

- US Department of the Interior funds $2M +
- Chuuk State Public Health disaster declared and extended
- Focus on re-establishing DOT, DOPT
- Costs for MDR LTBI not calculated
  - Homes and villages were places where DOT for TB cases already in place
  - Additional workload was incremental
Deliver MDR prevention by DOPT
Keys to Success: Operational

• Design MDR LTBI program as an opportunity for “best practices” model, rather than an opportunity for a randomized control trial.

• Forms created for
  – Daily community worker checklists
  – Monthly LTBI report summary for each case
  – Quarterly physician visit for each case
Clinic Follow-Up of MDR-TB Contacts on Prophylaxis

Patient Name: ________________________________  Medical Record Number: ______

Month: [ ] 1  [ ] 2  [ ] 4  [ ] 5  [ ] 7  [ ] 8  [ ] 10  [ ] 11  [ ] Other

Purpose: The purpose of your visit is to:
1. Rule out the onset of infectious TB
2. Review possible adverse effects of treatment
3. Evaluate for adverse effects of treatment
4. Encourage adherence for completion of therapy
5. Rule out pregnancy in all women on moxi or levo
   Remember: moxi or levo not recommended while pregnant or breast feeding.
6. Required reporting for Public Health/TB Control

1. TB Symptoms:
   [ ] None  Or if yes:  [ ] Cough  [ ] Fever  [ ] Night sweats  [ ] Weight loss  [ ] Anorexia
   Describe Symptoms: ____________________________________________________________

2. Possible medication side effects:
   [ ] None  [ ] Nausea  [ ] Abd pain  [ ] No Appetite  [ ] Jaundice  [ ] Rash
   [ ] Tendon Pain  [ ] Dizzy/HA  [ ] Eye Problems  [ ] Other: ____________________
   Are complaints consistent with drug side effects: [ ] Yes  [ ] No

3. Compliance: Number of missed doses this month: ______

4. Dr. Fred Notified?  [ ] Not needed  [ ] Yes  DOT Worker Sign: ____________________

Keys to Success: Training

- Hands on training for local staff
  - Drs. Brostrom and Bamrah spent more than 30 weeks in Chuuk
- Training provided to clinical staff, others
- Regular (monthly to quarterly) case reviews by phone
Keys to Success: Individual

- Local Champions:
  - talented, determined, dedicated
  - Dr. Dorina Fred
  - Dr. Lyma Setik
Regional Spinoff: Capacity Development

• Improved MDR capacity across the Pacific

• Creation of novel Pacific SLD stockpile
  – Palau MDR case
  – Not for prevention....yet!

• Multi-agency MDR TB support network
  – WPRO Manila, WPRO Suva, SA Adelaide, SPC, CDC, DOI

• Acquisition of GeneXpert systems in Pacific (10)
Putting out the fire in Chuuk

January 2008

– 5 dead from MDR
– 15 MDR cases on tx, with 21 more not yet dx’d
– More than 100 infected close contacts identified

January 2015

– Completed treatment of last known MDR case
– No new cases diagnosed in the past two years
– Completed treatment of more than 100 known contacts
Acknowledgments

- Dr. Dorina Fred, Chuuk State TB Controller
- Dr. Lyma Setik, Chuuk State TB Program
- Dr. Mayleen Ekiek, FSM TB Controller
- Dr. Sundari Mase, CDC DTBE
- Andy Heetderks, CDC
- Dr. Mitesh Desai, CDC EpiAid Team Lead
- Australian Respiratory Council
- CNMI Public Health Department
- Chuukese Women’s Council
- US Department of the Interior, Roylinne Wada
- Drs. Masae Kawamura, Ann Loeffler, Gisela Schecter
Resources

- **CureTB**: Binational TB Referral Program for TB patients and their contacts who travel between the United States and Mexico  
  http://www.curetb.org/

- **TBNet**: A multi-national TB patient tracking and referral project designed to work with mobile, underserved populations  
  http://www.migrantclinician.org/network/tbnet

- **National Jewish Medical Center**  
TB RTMCCs, 2013-2017
Areas of Coverage

- Curry International Tuberculosis Center
- Mayo Clinic Center for Tuberculosis
- New Jersey Medical School Global Tuberculosis Institute
- Heartland National Tuberculosis Center
- Southeastern National Tuberculosis Center

* Center Location