Transmission of MDR/XDR Tuberculosis in Shanghai

Qian Gao
Shanghai Medical College
Fudan University
Drug Resistant TB in China
The Highest DR-TB Burden Country

- New TB cases/year: 1.3 million
- Cases with any DR: DR-18.6%
- MDR: MDR-7.6%
- XDR

2000 National survey
Objective

- Whether XDR-TB existed in Shanghai?
- The rate of XDR-TB among MDR-TB patients?
- Where did MDR/XDR-TB come from?
Study Design

- DST: Proportion method be used,

  - isoniazid (0.2μg/ml)
  - rifampin (40.0μg/ml)
  - streptomycin (4.0μg/ml)
  - ethambutol (2.0μg/ml)
  - ofloxacin (2.0μg/ml)
  - kanamycin (30.0μg/ml)
  - capreomycin (40.0μg/ml)
  - amikacin (40.0μg/ml)
  - 4-aminosalicylic acid (1.0μg/ml)
Definition

- **MDR TB.** Resistant to at least INH and RFP
- **XDR TB.** Resistance to at least INH, RFP, a FQ and one of three injectable second-line drugs
- **Pre-XDR TB.** Resistant to INH and RFP and either a FQ or a second-line injectable drug, but not both.
- **Simple MDR TB.** Resistant to just INH and RFP but not pre-XDR TB and XDR-TB.
Patients Selection

TB new cases 2004-2007
19,722

TB cases with a sputum culture 12,530

TB Cases with a positive culture 6,200 (49.5%)

TB cases of MTB with DST result 4,379

MDR TB cases 247 (5.64%)

TB cases no culture result

TB cases a negative culture


Not MDR 4,132
XDR in Shanghai

Recovered MDR-TB
175 (100%)

Simple MDR
109 (62.3%)

XDR-TB
11 (6.3%)

Pre XDR
55 (31.4%)
## Case Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 175 (%)</th>
<th>Simple MDR n = 109 (%)</th>
<th>Pre-XDR n = 55 (%)</th>
<th>XDR n = 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>35 (20.0)</td>
<td>24 (22.0)</td>
<td>11 (20.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>30-44</td>
<td>53 (30.3)</td>
<td>37 (33.9)</td>
<td>13 (23.6)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>45-59</td>
<td>57 (32.6)</td>
<td>26 (23.9)</td>
<td>23 (41.8)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>60-74</td>
<td>20 (11.4)</td>
<td>14 (12.8)</td>
<td>6 (10.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>10 (5.7)</td>
<td>8 (7.4)</td>
<td>2 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>105 (60.0)</td>
<td>69 (63.3)</td>
<td>30 (54.5)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Treated</td>
<td>70 (40.0)</td>
<td>40 (36.7)</td>
<td>25 (45.5)</td>
<td>5 (45.5)</td>
</tr>
</tbody>
</table>
MDR/ XDR in China

- Beijing Chest Hospital, 2002.01-2005.12,
  - INH, RFP, SM, EMB, AmK, OFX, PZA, ETH, PAS (9 drugs)
  - 10.75% (207/1926) MDR, 6.28% (13/207) XDR


- Beijing Tuberculosis & Thoracic Tumor Research Institute, 1998.06-2006.03
  - INH, RFP, SM, EMB, KM, CPM, AK, 1321Th, PAS, OFX, LFX, RIFT (12 drugs)
  - 34.8% (673/1934) MDR
  - 67 MDR, 22 XDR, 15 TDR (more than 24 months in the Institute treated patients)

MDR/XDR Epidemic

- Where did the MDR/XDR come from?
  - Treated cases: acquired drug resistance
    - Poor Patient Management
      NEED BETTER PATIENT CARE
  - New cases: primary drug resistance (>50%)
    - Transmission of drug resistant TB
      NEED BETTER TB CONTROL
Is the Required DR Really Required?

Mechanism Vs. Surveillance

Primary = No Prior Therapy

Acquired ≠ Currently or Previously Treated

(Gene mutation on one strain)

Some previously treated patients can be reinfected
Study Objective

To investigate the cause of drug resistance among treated patients, using genotyping techniques
Research Hypothesis

- Sensitive strain
- Resistant strain
- Acquired resistance
- Primary resistance
- Multiple infection
- Resistant strain
Specimen Collection

n Case definition of treated patients
  n Patients with recurrent tuberculosis
  n Patients still under treatment

n Criteria for specimens
  n Isolates from 1999-2004, stored at Shanghai CDC
  n Two or more isolates with different drug susceptibility test results were collected from individual treated patients
Sampling Frame

TB patients, 1999 to 2004: 6,622

TB patients with discordant drug susceptibility test results: 100

Both isolates have genotype results: 38

Second isolate was drug susceptible or resistant to fewer drugs: 6

Second isolate resistant to more drugs: 32
Genotyping Methods

- MIRU typing for all isolates
- IS6110-RFLP typing for isolates with identical MIRU patterns
- Classification of drug resistance
  - Acquired drug resistance: identical MIRU and RFLP patterns
  - Primary drug resistance: different MIRU or RFLP patterns
Results

- Among total 32 patients, 27 (84%) patients had a pair of isolates with discordant MIRU or RFLP patterns.
- 5 patients (16%) had a pair of isolates with identical MIRU and RFLP patterns.
- Among treated patients, 84% DR were due to primary drug resistance.

Li X et al. JID 2007, 195: 864-869
Conclusion

- 5.6% of the TB cases were MDR, and 6.3% of the MDR TB were actually XDR in Shanghai.
- >50% MDR / XDR TB patients were new cases.
- Among treated patients, 84% DR were due to primary drug resistance.
- **Ongoing transmission of MDR/XDR is a serious problem in Shanghai, probably in China too. New strategies to block the transmission of MDR/XDR-TB are urgently needed**
Acknowledgment

- Fudan University
  - Ming Zhao
  - Peng Xu
  - Xia Li
  - Ying Zhang

- University of California, Davis
  - Kathryn DeRiemer

- Shanghai CDC
  - Jian Mei
  - Xiaohong Gui
  - Lili Wang
  - Jie Wu

- Institute for Systems Biology
  - Peter M. Small
Thank you!