Transmission of Multidrug Resistance Tuberculosis in China

Qian Gao
School of Basic Medical Sciences, Fudan University
qiangao@fudan.edu.cn
2018.09.13, Suzhou
Outline

- Transmission of MDR Tuberculosis
  - MDR-TB in new cases
  - Resistance in treated cases
  - Recent transmission of MDR-TB
Globally in 2014, an estimated 480,000 cases & 190,000 people died of MDR-TB.

DR-TB: resistant to any first line anti-TB drug
MDR-TB: resistant to at least INH & RIF
XDR-TB: MDR+ FQs /any injectable drug

Global Tuberculosis report 2015, WHO

New cases

1.48 million/year

DR

37.79%

MDR

8.32%

XDR

0.68%

2007-2008 China National Survey
How DR Developed

- **Infectious Source**
- **Infection**
- **Disease**
- **Treatment**
  - **Drug Resistance**
  - **Non-Compliance**
  - **Poor Quality Drugs**
  - **Mono Therapy**

**Transmitted**
- **Poor TB Control**

**Acquired**

*Modified from Dr. Rob Warren*
**About 60% of MDR-TB were New Cases**

**MDR Rate** = MDR in New cases / Total of New cases

<table>
<thead>
<tr>
<th>Settings</th>
<th>No. of cases</th>
<th>DR No.</th>
<th>%</th>
<th>MDR No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>China</strong></td>
<td>7035</td>
<td>1016</td>
<td>14.4</td>
<td>199</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>India</strong></td>
<td>1380</td>
<td>385</td>
<td>27.9</td>
<td>134</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Indonesia</strong></td>
<td>1867</td>
<td>352</td>
<td>18.8</td>
<td>74</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>South Africa</strong></td>
<td>239</td>
<td>101</td>
<td>42.3</td>
<td>51</td>
<td>21.3</td>
</tr>
</tbody>
</table>

**Proportion** = MDR in New Cases / Total of MDR

- **More than 70% of DR were new cases**
- **About 60% MDR/XDR-TB were new cases, caused by transmission**

About 60% Treated DR-TB were Transmitted

Dogma: Treated patients were acquired DR

- Patients during treatment or re-treatment, **59%** of the increased resistance is due to transmitted

<table>
<thead>
<tr>
<th>Resistance increased: 81 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>different genotypes:</td>
</tr>
<tr>
<td>48 cases (59%)</td>
</tr>
<tr>
<td>identical genotypes:</td>
</tr>
<tr>
<td>33 cases (41%)</td>
</tr>
</tbody>
</table>

84% (27/32) is transmitted resistance


Among TB patients in Shanghai, the estimated rate of mixed infections was 5.6%.

Mixed infections were detected in 11.2% of TB cases in Heilongjiang.

Time of Transmission: Recent or Remote?

- **MDR-TB**
  - Treatment History
  - New cases (59%)
  - Treated cases (41%)

- Genotyping analysis
  - Reinfection
  - Multiple Infection
  - Truly acquired

- Transmission
  - Recent
  - Remote

- Transmitted Resistance
Time of Transmission: Recent or Remote?

- Infection...
- Latency
- Recent infection
- Reactivation Remote

5%, 1-2 year
How to Differentiate Recent Transmission?

- Molecular Epidemiology assumption
  - Identical genotype (Cluster strains) - recent transmission
  - Unique genotype – remote transmission & reactivation
  - Genotyping: IS6110-RFLP, VNTR, Whole Genome Sequence

![Diagram showing differentiation between recent and remote transmission based on genotyping results.](image)
Population-based Molecular Epidemiology

- From 2009 to 2012, still ongoing
- Selection of five field sites
- Covering ~5.8 million inhabitants
- Including all culture-positive TB

<table>
<thead>
<tr>
<th>Fields</th>
<th>Areas(km²)</th>
<th>Population</th>
<th>Prevalence of TB (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heilongjiang</td>
<td>3,756</td>
<td>520,000</td>
<td>512</td>
</tr>
<tr>
<td>Henan</td>
<td>1,307</td>
<td>868,000</td>
<td>497</td>
</tr>
<tr>
<td>Shanghai</td>
<td>604</td>
<td>1,634,000</td>
<td>96</td>
</tr>
<tr>
<td>Sichuan</td>
<td>966</td>
<td>838,000</td>
<td>544</td>
</tr>
<tr>
<td>Guangxi</td>
<td>2,473</td>
<td>456,500</td>
<td>477</td>
</tr>
</tbody>
</table>
• 2009 to 2012, all culture-positive TB were enrolled in five fields across China
• 41% MDR-TB were clustered and indicates recent transmission
• MDR-TB were more likely to be clustered than susceptible cases (41% vs 31%), suggesting a risk factor of recent transmission, aOR=1.86 (95% CI 1.25-2.63)

<table>
<thead>
<tr>
<th>Fields</th>
<th>No. of isolates</th>
<th>No. of clustered</th>
<th>cluster rate (%)</th>
<th>average cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wusheng, SC</td>
<td>414</td>
<td>90</td>
<td>21.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Pingguo, GX</td>
<td>324</td>
<td>117</td>
<td>36.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Weishi, HN</td>
<td>481</td>
<td>149</td>
<td>30.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Songjiang, SH</td>
<td>797</td>
<td>255</td>
<td>32.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Wuchang, HLJ</td>
<td>258</td>
<td>94</td>
<td>36.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>2274</td>
<td>705</td>
<td>31.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Genomic Cluster Analysis in Shanghai

- 2009-2012, 4.6% (367/7978) were MDR cases 60% were new cases
  - 38.6% (125/324) were VNTR-clustered
- Risk factor for recent transmission
  - diagnosis delay (≥ 2ms): aOR=2.3 (1.2-4.1)
  - elderly (≥ 65 ys): aOR=3.2 (1.4-7.4)
- MDR-TB in 91.9% (34/37) clusters were transmitted
- 86.8% (33/38) clustered cases accumulated additional resistance mutations, developed to pre-XDR & XDR cases

Most MDR-TB were Caused by Transmission

Treatment History

New cases (59%)

Treated cases (41%)

Genotyping analysis

Recent Transmission
Remote transmission
Reinfection
Multiple Infection
Truly acquired

Transmitted MDR-TB (>80%)

Acquired MDR-TB (<20%)
Tremendous Challenges

- **Case Detection: lacking human & financial resource**
  - less than 15% were diagnosed and treated
  - Backward technology, diagnosis delay (2~3 months)
  - >80% of the county TB lab did not perform culture

- **MDR Treatment: lacking drugs & financial support**
  - Insufficient treatment (not based on DST regimen)
  - Low success rate (<40%)

- **Transmission Control: NO any laws or regulations**
  - Almost no infection control
  - No restriction on MDR-TB patients
Take Home Messages

- **MDR-TB transmission is serious in China**
  - About 60% of MDR-TB were new cases
  - About 60% of DR in retreated cases caused by transmission
  - At least 1/3 of MDR-TB cases were due to recent transmission
  - Totally, more than 80% of MDR-TB cases were due to transmission
- **Timely DST is urgently needed for all bacteria positive patients!**
Acknowledgements

- Fudan University
- Research Fields CDC
- University of California, Davis

Funding:
- National Science and Technology Major Project of China
- National Science Foundation of China
Thanks!