The Transmission Dynamics of MDR TB

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China (from WHO)

<table>
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<tr>
<th>MDR-TB estimates of burden</th>
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<td>% of new TB cases with MDR-TB</td>
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<td>% of retreatment TB cases with MDR-TB</td>
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<td>MDR-TB cases among incident total TB cases in 2008</td>
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Acquisition of resistance

Incorrect therapy
Poor adherence
Malabsorption
Poor Drug Quality

Exposure in health care facility or community
Delayed diagnosis and treatment
Slow culture conversion
Transmissibility of specific MDR strain

Routes to drug resistant TB

DOTS

Uninfected

MDR

MDR
Gaps
Diagnosis

Smear Microscopy
Fast and Cheap
Misses 20-70% of cases
No DST

MTB Culture and DST
3-8 Week Delay
Better Sensitivity
Some DSTs Expensive and Difficult

Rapid Diagnostics
Fast but Expensive
Good Sensitivity
Incomplete DST
Treatment for MDR

**Access**
Funding and HR Gap
Increased access

**MDR Treatment Outcomes**
Highly variable based on:
- Extent of DR (XDR)
- Political Will
- Treatment approach

**Need for New drugs**
- Development
- Clinical Trials
Notified cases of MDR-TB (2004-2006) and projected patients to be treated (2007-2008) compared to estimated burden of MDR-TB

Estimated 650,000 new MDR-TB cases each year

Proportion of the MDR case load being diagnosed and treated.
MDR Case Finding and Active Surveillance

Who?
High risk groups
• TB Contacts
• HIV-infected
• Other risk factors

Where?
• Use of Molecular Epidemiology to identify transmission hot-spots
• Real time spatial mapping of MDR cases
1. MDR strains more likely to be transmitted. OR = 5.6
2. Beijing genotype more likely to be transmitted. OR = 12.1
3. Hospitalization associated with transmitted MDR strains compared to transmitted DS strains. OR = 18.3

Among TB cases who failed therapy, 84% were infected with a new DR strain, suggesting ongoing transmission of MDR TB.
Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance

IY Gelmanova, a S Keshavjee, b,c,d VT Golubchikova, e VL Berezina, e AK Strelis, f,g GV Yanova, g S Atwood d & M Murray a,h

Fig. 3. Kaplan-Meier survival curves for hospitalization as a factor associated with time to acquisition of multidrug resistance

Survival estimate to acquisition of MDR-TB

Time since treatment began (months)
4000 index cases
16000 households
Lima, Peru: Study, Health District and Case Locations

Health Districts
- Carabaylo
- Lima 1
- Lima 2
- Lima 3
- Lima 4
- Los Olivos
- Rimac
- SMP

Kilometers

Map showing the distribution of health districts and case locations in Lima, Peru.
Spatial Distribution of TB Clusters of Size 10 or More
Figure 4. Putative Transmission Networks Constructed from Genotyping Data versus Whole-Genome Data for 32 Patients.

Whole-Genome Sequencing and Social-Network Analysis of a Tuberculosis Outbreak

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Drug Sensitive

Mono-resistant

MDR

XDR

Epidemiologic studies

Epidemic modeling

Sequencing

2000 Global Strains *M. tuberculosis*

Public database of TB resistance mutations and their frequency in clinical samples

Development for active surveillance and high throughput diagnostics

Targeted Sequencing of 28 drug resistance genes

Link drug sensitivity profiles and clinical phenotypes to mutations

Retest those with discrepancies
DR TB Priorities

• Early and accurate diagnosis of DR TB to improve clinical care.
  – Cheap molecular tools useable at local level
• Development of new drugs and protocols for testing of drugs in the pipeline.
  – Development and testing of new drugs in multiple populations
• Molecular and spatial surveillance to identify routes of transmission
  – Integration of new molecular tools with routine surveillance.