WGS To Quantify MDR-TB Transmission

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Tuberculosis (TB)

- Phthisis (gr.)
- Consumption
- White plague

Mycobacterium tuberculosis
TB is a deadly disease...

Deaths during the last 200 years

Paulson *Nature* 2013 502: S1-S3

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>10.0 million</td>
<td>1.3 million</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>560,000</td>
<td>230,000</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>~ 50,000</td>
<td>~ 25,000</td>
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</tbody>
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＞50% Case-fatality: → Entering Post-Antibiotic Era!
The Problems

- Diagnostics
  ~120 years old

- Drugs
  ~50 years old

- Vaccine
  ~100 years old
# Tuberculosis Treatment

<table>
<thead>
<tr>
<th></th>
<th>2 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
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<tr>
<td>Rifampicin</td>
<td></td>
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<td>Pyrazinamide</td>
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<td>Ethambutol</td>
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<tr>
<td>Fluoroquinolones (e.g., ciprofloxacin, moxifloxacin, gatifloxacin), ethionamide, rifabutin, rifapentin and rifalazil), amikacin, kanamycin, capreomycin, viomycin, PAS, cycloserine...</td>
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</tbody>
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**2nd line drugs: 2 years**

**DOTS**

**MDR-TB**

**XDR-TB**
From Drug-sensitive to XDR-TB

- No resistance plasmids
- No horizontal gene transfer
Global Phylogeography of *M. tuberculosis*

Number of cases
- All forms of TB: 10.0 million
- MDR-TB: 560,000
- XDR-TB: ~ 50,000

Number of deaths
- All forms of TB: 1.3 million
- MDR-TB: 230,000
- XDR-TB: ~ 25,000

“Only” ~ 5% MDR / XDR
“Drug-Resistant Bacteria Are Less Fit”
Lab strains

Clinical strains

Gagneux et al. 2006 Science 312: 1944-6
Evolution of Drug Resistance

- DS
- DR
- Compensation

Borrell & Gagneux 2009 *IJTL* 13: 1456-66
Experimental Evolution

15 x (every 3 weeks)

RIF<sup>R</sup> mutants evolved

GENOME SEQUENCE
Compensatory Mutations in \textit{rpoA/C}

Comas et al. 2012 Nature Genetics 44: 106–110
In clinico Fitness of *rpoA/C* Mutations

![Graph showing fitness of *rpoA/C* mutations with *P* < 0.05 for high-burden regions compared to global regions.](https://example.com/graph.png)

- **Global:** 12% MDR strains with CM
- **High-burden:** 21% MDR strains with CM (High-confi. CMs), 31% All CMs

* * P < 0.05

Comas et al. 2012 *Nature Genetics* 44: 106–110
Population-based Study in Georgia
Georgian MDR(+) *Mtb* Dataset 2011-2013

- 659 MDR(+) strains
- 53% of all MDR(+)

Secondary *rpoA/B/C* mutation:
- Present (77%)
- Absent

DR-profile:
- MDR (39%)
- Pre-XDR (46%)
- XDR (15%)

Clustering:
- Clustered (43%)

Gygli *et al.* unpublished
Bias Towards **Lineage 2** (Univariate Analysis)

$p = 3.16 \times 10^{-9}, X^2 = 34.8$

$p = 0.7\text{n.s.}, X^2 = 0.12$

Gygli *et al.* unpublished
Factors Associated with Increased Drug Resistance

Compensatory mutations in \( rpoA/B/C \)

- OR\(_{adj}\) 1.5
- CI\(_{95}\) 1.0 – 2.3

MDR

- OR\(_{adj}\) 2.7
- CI\(_{95}\) 1.5 – 4.8

Lineage 2

Isolation year 2013

- OR\(_{adj}\) 1.7
- CI\(_{95}\) 1.1 – 2.7

- OR\(_{adj}\) 3.1
- CI\(_{95}\) 2.4 – 4.1

XDR

Resistance Increase

Number of additional DR mut

Gygli et al. unpublished
Factors Associated with Clustering of MDR/XDR-TB

Compensatory mutations
- OR_{adj} 2.53
- CI_{95} 1.54 – 4.24

Lineage 2
- OR_{adj} 5.26
- CI_{95} 2.65 – 11.23

No. DR mut
- OR_{adj} 0.72
- CI_{95} 0.56 – 0.97

Clustering
- OR_{adj} 6.18
- CI_{95} 3.74 – 10.49

Prisons
- OR_{adj} 6.18
- CI_{95} 3.74 – 10.49

Age
- OR_{adj} 0.98
- CI_{95} 0.97 – 1.0

Lineage 2
- OR_{adj} 5.26
- CI_{95} 2.65 – 11.23

No. DR mut
- OR_{adj} 0.72
- CI_{95} 0.56 – 0.97

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Gygli et al. unpublished
MDR/XDR-TB in Prisons & Clustering

Isolate origin

- Prisoner
- Civilian

Incarceration
Proportion of strains

- 411

Clustering & Prisons
Proportion of strains

- 147
- 133
- 101

Gygli et al. unpublished
Reconstructing Transmission Trees

Transmission network
Arrows indicate direction of transmission
Numbers indicate pairwise distance in SNPs

Red: Prisoner
Yellow: Civilian
Contribution of Prisons to the MDR-TB Epidemic in Georgia

167 transmission events i.e. 75.5% linked to prisons

*Transmission events
**Of the total 217 high confidence transmission events

Gygli et al. unpublished
Contribution of Prisons to the MDR-TB Epidemic in Georgia

Transmission events with >0.5 posterior probability

87 transmission events i.e. 40% linked to prisons

9* 4.1%**

23* 10.6%** 55* 25.3%**

*Transmission events
**Of the total 217 high confidence transmission events

Gygli et al. unpublished
Conclusions

• Compensatory mutations in RNAP of RIF$^R$ *Mtb*
• High frequency in MDR/XDR ‘hotspots’
• Associated with progression MDR to XDR
• Associated with ongoing transmission of MDR/XDR
• High spill-over from prisoners to civilians

→ Compensatory evolution contributes to the spread of MDR/XDR-TB
→ Prisons as breeding grounds for fit MDR-TB
Thanks to...

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