The Role of Genome Sequencing in Global Surveillance of Anti-tuberculosis Drug Resistance

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History of the Global DRS project

- Global Project launched
- SRLN launched
- 1st ed. DRS
- 1st global DRS report
- 1994
- 2nd ed. DRS guidelines
- 2nd global DRS report
- 1997
- 3rd ed. DRS guidelines
- 3rd global DRS report
- 2000
- 4th ed. DRS guidelines
- 4th global DRS report
- 2003 2004
- M/XDR-TB report
- 2008 2009 2010
- 5th ed. DRS guidelines
- 2008
- 2010
- 2016
- 2016 TB report
Global coverage on data on second-line resistance among MDR-TB patients, 2006-2016

88 countries
Survey operations

- ~ 15 national surveys ongoing each year
- ~ 15 national surveys in preparation each year
- Xpert MTB/RIF used in most surveys (often after smear microscopy)
- challenges with sample transport (in-country and also international)
- high workload for laboratories performing phenotypic testing

Solution: to replace conventional DST with NGS
Use of sequencing technologies in DR surveillance
project funded by BMGF and USAID: ~ 7,000 patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey site</th>
<th>Survey status</th>
<th>No. of patients (new &amp; retr)</th>
<th>Phenotypic DST method</th>
<th>Sequencing method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azerbaijan</td>
<td>nationwide</td>
<td>survey completed in 2013</td>
<td>748</td>
<td>LJ: RIF, INH MGIT: OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>nationwide</td>
<td>survey completed in 2011</td>
<td>955</td>
<td>LJ: RIF, INH MGIT: OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
<tr>
<td>Belarus</td>
<td>Minsk city</td>
<td>survey completed in 2011</td>
<td>201</td>
<td>MGIT: RIF, INH, OFX, MFX, PZA</td>
<td>Ion Torrent (WGS)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>nationwide</td>
<td>survey completed in 2013</td>
<td>1,503</td>
<td>LJ: RIF, INH MGIT: OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
<tr>
<td>Philippines</td>
<td>nationwide</td>
<td>survey completed in 2011</td>
<td>1,198</td>
<td>LJ: RIF, INH MGIT: OFX, MFX</td>
<td>Sanger</td>
</tr>
<tr>
<td>South Africa</td>
<td>Gauteng &amp; Kwazulu-Natal provinces</td>
<td>survey completed in 2014</td>
<td>1,651</td>
<td>MGIT: RIF, INH, OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>nationwide</td>
<td>survey completed in 2014</td>
<td>1,444</td>
<td>LJ: RIF, INH, OFX MGIT: MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
</tbody>
</table>
Ongoing and planned surveys in 2017

Ongoing:

- **DR Congo**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 1,500 sputum samples for 18 main gene targets
- **Djibouti**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 250 sputum samples for 18 main gene targets
- **Indonesia**: WGS (Illumina) on 1,400 isolates
- **Uganda**: WGS (Illumina) on 200 survey isolates

Planned to start in 2017:

- **Eritrea**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 550 sputum samples for 18 main gene targets
- **Ethiopia**: WGS (Illumina) on 1200 survey isolates
- **Swaziland**: WGS (Illumina) on 900 survey isolates
Use of sequencing data for surveillance

1. Assessment of test accuracy for RIF, INH, PZA, OFX, MXF, KAN, AMK in population-based surveys:
   - Very high specificity for all drugs (RIF, INH, PZA, OFX, MXF, KAN, AMK)
   - INH: suboptimal sensitivity vs. phenotypic test
   - FQL: suboptimal sensitivity vs. phenotypic test
   - AGL: suboptimal sensitivity vs. phenotypic test
   - New drugs (BQL, DLM): to be studied

2. Development of simple model for estimation of drug resistance proportions using genotypic data
Model for estimation of drug resistance using genotypic data

- NGS useful for measurement at the population level (DR surveillance)

- Apparent prevalence adjusted for test misclassification (bias-corrected prevalence)

- Propagate uncertainty using a simple Bayesian approach
Global DR surveillance: vision for the future (near future)

- Xpert MTB/RIF as entry test in surveys
- Targeted NGS from leftover of Xpert MTB/RIF cartridge (or from a new sputum sample)
- Estimation of resistance to multiple drugs based on NGS data
Acknowledgments

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