Resistance to pyrazinamide and fluoroquinolones: results from a multi-country surveillance project

45th Union World Conference on Lung Health
28 October - 1 November 2014, Barcelona, Spain
DRUG-RESISTANT TB
SURVEILLANCE & RESPONSE

World Health Organization
Rationale

- Shorter regimens for the treatment of TB are urgently needed to accelerate control of this disease

- New regimen in Phase III trials:
  - PaMZ: results expected in 2018

- No population-level data on resistance to FQLs and PZA
Objectives of the FQLs and PZA surveillance project

- Primary objective:
  - to assess the prevalence of resistance to FQLs (OFX, MFX) and PZA in new and previously treated, RIF-susceptible and RIF-resistant TB cases.

- Secondary objectives:
  - to assess proportions of cross-resistance between OFX, MFX, GFX, and LFX;
  - to assess the correlation between phenotypic DST of OFX and MFX (gold standard) and sequencing of \textit{gyrA} and \textit{gyrB};
  - to assess the correlation between phenotypic DST of PZA and sequencing of \textit{pncA};
  - to evaluate the feasibility of using sequencing technologies for surveillance of drug resistance in TB.
### Project sites

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey site</th>
<th>Survey status</th>
<th>No. of patients (new - retreatment)</th>
<th>Responsible laboratory</th>
<th>Phenotypic DST</th>
<th>Sequencing method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azerbaijan</td>
<td>nationwide</td>
<td>survey completed in 2013</td>
<td>789 (549 - 240)</td>
<td>NRL</td>
<td>SRL Borstel</td>
<td>SRL Borstel (Sanger)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>nationwide</td>
<td>survey completed in 2011</td>
<td>1,344 (1,050 - 291)</td>
<td>NTRL</td>
<td>SRL Antwerp</td>
<td>SRL Milan (Illumina)</td>
</tr>
<tr>
<td>Belarus</td>
<td>Minsk city</td>
<td>survey completed in 2011</td>
<td>224 (156 - 68)</td>
<td>NRL</td>
<td>SRL Stockholm</td>
<td>SRL Stockholm (Sanger)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>nationwide</td>
<td>survey completed in 2013</td>
<td>1,593 (1,379 - 212)</td>
<td>NRL</td>
<td>SRL Karachi</td>
<td>SRL Karachi (Sanger)</td>
</tr>
<tr>
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<td></td>
<td>SRL Antwerp</td>
<td>SRL Milan (Illumina)</td>
</tr>
<tr>
<td>South Africa</td>
<td>Gauteng &amp; Kwazulu-Natal provinces</td>
<td>testing ongoing</td>
<td>2,000 * (1,500 - 500) *</td>
<td>NRL</td>
<td></td>
<td>NRL (Illumina - WG)</td>
</tr>
</tbody>
</table>

* Expected number as testing is still ongoing
Laboratory work

6 SRLs: Antwerp, Borstel, Johannesburg, Karachi, Milan, Stockholm

- **FQLs:**
  - all strains tested for resistance to OFX (2.0 µg/ml) and MFX (0.5 µg/ml) (MGIT);
  - all strains resistant to OFX &/or MFX tested for resistance to GFX (2.0 µg/ml), MFX (2.0 µg/ml), LFX (1.5 µg/ml) and OFX (2.0 µg/ml);
  - all strains resistant to OFX &/or MFX and 10% of susceptible undergo gyrA & gyrB sequencing (Azerbaijan, Belarus, Bangladesh, Pakistan); all strains undergo gyrA & gyrB sequencing (South Africa).

- **PZA:**
  - all strains undergo sequencing of pncA;
  - all strains with pncA mutation and 10% of wild type strains tested for resistance to PZA (MGIT) (Bangladesh, Pakistan); all strains tested for resistance to PZA (MGIT) (Azerbaijan, Belarus, South Africa);
  - strains with discordant phenotypic and sequencing results tested with modified Wayne method.
Preliminary findings on PZA resistance

- PZA resistance is low in the general population with exception of EEU
- PZA resistance is lower than RIF resistance in all sites
- PZA resistance significantly higher in RIF-resistant strains (30%-80%)
- PZA resistance higher previously treated TB cases

When comparing sequencing with phenotypic DST:
- Sensitivity: 80%-90%
- Specificity: 99%
Preliminary findings on fluoroquinolones resistance

- OFX 2.0µg/ml resistance is generally lower than RIF resistance
- MOX 2.0µg/ml resistance very low
- OFX/MXF 2.0µg/ml resistance higher in RIF-resistant strains and previously treated TB cases
- Limited cross resistance between OFX 2.0µg/ml and MXF2.0µg/ml / GFX2.0µg/ml
- Sens. and Spec. of sequencing in line with literature data for OFX 2.0µg/ml
- gyrB sequencing doesn't appear to significantly impact overall Sens. and Spec.
Next steps

- Two new countries joining the project: Philippines (1,300 strains), Ukraine (1,800 strains) (October)

- Dissemination of initial results (October-December)

- Extend sequencing to *rpoB*, *inhA*, *katG* (2015)

- WGS in 3 countries (Azerbaijan, Bangladesh, Ukraine) in addition to South Africa (2015)

- Collection of programmatic treatment outcomes (2015)
Acknowledgments

Implementing group:
- NRLs/NTRL and NTPs of Azerbaijan, Bangladesh, Belarus, Pakistan, South Africa
- SRLs of Antwerp, Borstel, Karachi, Milan, Stockholm
- WHO (CO, RO, HQ)

Donor Agencies:
- BMGF
- USAID
- TB Alliance

Technical partners:
- CDC
- NIH