Drug resistance surveillance: progress to date and emerging innovations

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1. Global project on anti-TB drug resistance surveillance

2. Coverage of surveillance

3. Emerging innovations

4. Conclusions and vision for the future
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Global project on anti-TB drug resistance surveillance launched in 1994

Objectives:
- To estimate the magnitude of drug resistance
- To determine trends in drug resistance

Main technical partners:
- Project hosted by WHO
- Supranational TB Reference Laboratories, The Union, US CDC, KNCV

Main donor agencies:
- USAID, The Global Fund, PEPFAR, BMGF
Principles of anti-TB drug resistance surveillance

1. Sample accurately represents population under study:
   - Examples: continuous surveillance, surveys of 100% sampling or probability-proportional-to-size cluster

2. Quality assured laboratory results:
   - Supranational TB Reference Laboratory Network (SRLN)
   - First-line DST on new and previously treated TB cases: rif & inh
   - Second-line DST on MDR-TB cases only: usually ofx & kan

3. Differentiation between new and previously treated cases:
   - patient interview
   - clinical records
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Data from surveillance and surveys:
153 countries with >95% of world’s population and TB cases

- Continuous surveillance based on routine drug susceptibility testing of TB patients:
  - 80 countries
  - RIF result for ≥ 60% of new pulmonary TB cases
  - RIF result for ≥ 75% of previously treated TB cases

*Note*: WHO Standards and Benchmarks for TB surveillance (Standard B2.1): RIF result for ≥ 75% of new pulmonary TB cases

- Ad hoc epidemiological surveys of nationally representative sample of TB patients:
  - 73 countries
  - ~ 10-15 surveys each year are ongoing
Global coverage of RIF and INH data
1994-2015
Repeat surveys or continuous surveillance

- 100 countries with at least 2 years of data
  - 35 countries with 2 years of data
  - 65 countries with ≥ 3 years of data (843 country-year data points)
  - 12 countries with linear trend (increasing or decreasing)

- Challenging to assess trends at global, regional and also country level:
  - different types of trends
  - repeat surveys not powered to detect differences in proportions

- Trends analysis published in 2014 global TB report:
  - MDR-TB in new cases was 3.5%, no changes with previous years
Global coverage on data on second-line resistance among MDR-TB patients

78 countries
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Xpert MTB/RIF for surveillance

- Reduces logistic challenges for sample transport
- Reduces demand on labs (expertise and time)
- **Universal testing coverage for rifampicin** could be achieved through gradual roll-out

- Depending on algorithm, cannot investigate other resistance patterns not associated with RIF resistance, but
  - RIF resistance necessitates a change in treatment regimen
  - RIF resistance usually associated with other drug resistance patterns
Molecular assays used in 18 surveys

- Surveys can now be conducted in countries with limited culture capacity
  - Xpert MTB/RIF:
    - already used in: DR Congo, Djibouti, Pakistan, Papua New Guinea, Senegal, Zimbabwe
    - planned to be used in 2016 in: Burkina Faso, Cote d'Ivoire, Eritrea, Indonesia, Lao PDR, Malawi, Swaziland
  - Line Probe Assays:
    - already used in: Lesotho, Nigeria, Rwanda, Sudan, Tanzania
Surveys based on molecular assays

18 countries
Xpert MTB/RIF in surveys

Conventional
1200-1500 cultures

Xpert MTB/RIF
100 cultures
### Use of sequencing technologies in DR surveillance

new project funded by BMGF and USAID: ~ 7,500 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>
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<tr>
<td>Bangladesh</td>
<td>nationwide</td>
<td>survey completed in 2011</td>
<td>948</td>
<td>LJ: RIF, INH, MGIT: OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
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<tr>
<td>Belarus</td>
<td>Minsk city</td>
<td>survey completed in 2011</td>
<td>203</td>
<td>MGIT: RIF, INH, OFX, MFX, PZA</td>
<td>Ion Torrent (WGS)</td>
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<tr>
<td>Pakistan</td>
<td>nationwide</td>
<td>survey completed in 2013</td>
<td>1503</td>
<td>LJ: RIF, INH, MGIT: OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
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<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>
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<td>South Africa</td>
<td>Gauteng &amp; Kwazulu-Natal</td>
<td>survey completed in 2014</td>
<td>1,568</td>
<td>MGIT: RIF, INH, OFX, MFX, PZA</td>
<td>Illumina (WGS)</td>
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<tr>
<td>Ukraine</td>
<td>nationwide</td>
<td>survey completed in 2014</td>
<td>1,350</td>
<td>LJ: RIF, INH, MGIT: MFX, PZA</td>
<td>Illumina (WGS)</td>
</tr>
</tbody>
</table>
Characteristics of sequencing

- Sequencing is the most accurate molecular test available
- High throughput: up to ~ 200 strains per run/3-4 days
- Cheaper than standard phenotypic testing
- Still based on isolates but possible on sputum in near future

Test accuracy:
- RIF: possibly equivalent to phenotypic test
- PZA: possibly equivalent to phenotypic test
- INH: low sensitivity compared to phenotypic test
- FQL: low sensitivity compared to phenotypic test
- AGL: low sensitivity compared to phenotypic test
- New drugs (BQL, DLM): to be studied
Use of sequencing results in surveillance

- Suboptimal accuracy (low sensitivity) for some drugs but results can be reliably used in surveillance

- Topic discussed at WHO Expert Meeting on Policy Guidance for DST (Mar 2016)

- Adjustment for test misclassification needed (bias-corrected prevalence)
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Conclusions and vision for the future

- All countries to establish continuous surveillance systems:
  - at least for RIF resistance, e.g. based on Xpert MTB/RIF

- Countries to conduct ad hoc surveys:
  - every 5 years
  - to investigate drug resistance patterns beyond RIF (INH, PZA, FQL, AMG, ...)
  - to monitor emergence of resistance to new drugs (BQL, DEL)
  - based exclusively on genome sequencing on sputum samples?
Question for discussion

Does the Task Force agree with the following vision for drug resistance surveillance based on the two components below? If not, what modifications are proposed?

a) The establishment of national continuous surveillance systems for at least rifampicin resistance;

b) The implementation of ad hoc surveys every 5 years for investigating patterns of resistance to a broader range of drugs.