Drug resistance surveys: an overview of progress and latest developments

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Global project on anti-TB drug resistance surveillance since 1994

Objectives:
• To estimate the magnitude of drug resistance
• To determine trends over time
• To enable a prompt and effective public health response

Main technical partners:
• Project hosted by WHO
• NTPs, Supranational TB Reference Laboratories (SRLs), US CDC, KNCV, The Union

Main donor agencies:
• The Global Fund, USAID, PEPFAR, BMGF
Overview of progress
Meeting of the Tuberculosis Surveillance and Research Unit (TSRU) March 19-21, 2014 – Hanoi, Viet Nam

Data sources, 1994-2017

90 countries with continuous surveillance (representing only 4% of the TB burden)
70 countries with surveys

Data available for
- 97% of global TB burden
- 37 of 40 high MDR-TB and/or TB burden countries
Criteria for representative surveillance data

• WHO Global TB Report
  - ≥80% new cases have rifampicin testing result

• WHO Standards and Benchmarks
  - ≥75% new cases have rifampicin testing result
Meeting of the Tuberculosis Surveillance and Research Unit (TSRU) March 19 - 21, 2014, Hanoi, Viet Nam

Global coverage of data since 2007

Approximately 10 surveys underway and 10 in planning phase each year
Proportion of new TB cases with MDR/RR-TB, 2016

Global: 4.1%
European Region: 19%
Proportion of previously treated TB cases with MDR/RR-TB, 2016

Global: 19%
European Region: 55%
Estimated incidence of MDR/RR-TB, 2016

47% from India, China, Russian Federation
Proportion of isoniazid resistance among new cases

New cases: 7.2% isoniazid-resistant and rifampicin-susceptible
Previously treated cases: 10.1% isoniazid-resistant and rifampicin-susceptible
WHO treatment guidelines for isoniazid-resistant tuberculosis

Supplement to the WHO treatment guidelines for drug-resistant tuberculosis
Second-line drug resistance

- Globally, 6.2% of MDR-TB cases have XDR-TB

- Short-course MDR/RR-TB and INH-monoresistance regimens rely on fluoroquinolones

- Globally, 20% of MDR/RR-TB cases have resistance to one or more fluoroquinolone
  - moxifloxacin resistance varied from 8-27% across five settings studied

Developments: Xpert MTB/RIF and sequencing
WHO’s End TB Strategy - universal drug susceptibility testing

- Countries should focus on continuous surveillance among:
  - previously treated cases
  - high risk groups (contacts of RR-TB patients)
  - certain patient groups (PLWHA, children)

- Subsequent expansion of testing to new cases

- Ultimately, broadening scope from rifampicin to other drugs

Molecular tools will facilitate this transition
Xpert MTB/RIF in surveys

• Logistically easier
  - surveys can be repeated more frequently

• Strengthens sample transport and testing network
  - facilitates transition to continuous surveillance

• *But* information beyond rifampicin resistance may be limited (depending on diagnostic algorithm)
Sequencing approaches

• Analysis of genetic make-up of *M. tuberculosis*

• **Whole genome sequencing on culture**
  - up to 200 strains per run (3-4 days per run)

• **Targeted gene sequencing on preserved sputum**
  (Deeplex-MycTB assay from GenoScreen)
  - bypasses need for culture
  - less information than whole genome
Sequencing as a tool for surveillance

• Estimate prevalence of resistance to a range of drugs at population level

• Inform development of molecular diagnostics
  - now and in the future

• Predict resistance to new drugs

WHO guidance to be released in late 2018
Sequencing in surveys (2013-2018)

• WHO coordinating a multi-country project funded by BMGF, TB Alliance, USAID

• **First global initiative** using sequencing at the population level among all TB cases *(background documents 3d, 3e)*
  - Prevalence of resistance to a range of drugs
  - Agreement between sequencing and phenotypic tests

• Over 7,000 isolates sequenced and phenotypically tested from surveys in 8 countries
Sequencing in surveys (2013-2018)

Completed: Azerbaijan, Bangladesh, Belarus, Djibouti, Pakistan, Philippines, South Africa, Ukraine

Underway: DR Congo, Eritrea, Ethiopia, Indonesia, Swaziland
Estimating prevalence of drug resistance by sequencing

Analysis
• Classify mutations using established framework
  - associated or not associated with resistance
• Account for sensitivity and specificity using Bayesian approach

Interpretation
• Overall, sequencing produces consistent results and has comparative advantages to phenotypic testing
Prevalence of isoniazid (INH) resistance by different methods

INH phenotypic testing versus katG/inhA sequencing

Zignol et al. Lancet Infect Dis. 2018
Requirements for scaling-up sequencing

- Reduced costs  
  - sequencing already cheaper than full panel of first- and second-line phenotypic testing in an SRL ($150 versus $230 per sample)

- Enhanced staff capacity

- Standardized methodology, e.g. DNA extraction and sample preparation

- Standardized nomenclature to record, report and analyse data (current initiatives – ReSeq platform, CRyPTIC consortium)

- Quality assurance system
Conclusions

- TB has the largest and oldest antimicrobial resistance surveillance project globally

- Still require more country-specific data for
  - a wider range of drugs
  - more time points

- Promote molecular technologies as a means to achieving universal coverage of drug susceptibility testing