Surveillance of resistance to anti-TB drugs: What is it and how does WHO recommend it should be done?

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TB surveillance and surveys: a training workshop for consultants

Geneva - 24-27 May 2011
Main reference

- Three main principles of drug resistance surveillance
- Most recent WHO recommendations
- Main components of a survey and potential roles of consultants
- Continuous surveillance
Three main principles of anti-tuberculosis drug resistance surveillance

1. Collected data should accurately represent the TB patient population in the country/ geographical setting under study
   - Continuous surveillance based on routine drug susceptibility testing (DST) of the entire patient population
   - Survey = a study to ascertain the drug resistance profiles of a sample of patients, representative of the entire patient population

Two main survey designs:
1. 100% diagnostic centre sampling, and 2. cluster sampling
Survey designs:

100% diagnostic centre sampling vs cluster sampling

Geographic area with 5 diagnostic centres
Survey designs:
100% diagnostic centre sampling vs cluster sampling

100% sampling of diagnostic centres

All centres enroll for the same duration
Survey designs:
100% diagnostic centre sampling vs cluster sampling

Surveillance of resistance to anti-TB drugs
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Survey designs:
100% diagnostic centre sampling vs cluster sampling

Cluster sampling, probability-proportional to size

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Three main principles of anti-tuberculosis drug resistance surveillance

1. Collected data should accurately represent the TB patient population in the country / geographical setting under study
   - Continuous surveillance based on routine DST of the entire patient population
   - Survey = a study of a sample of patients representative of the entire patient population

2. Quality-assured laboratory results
   - DST methods must be chosen from those that are WHO-recommended:
     - Solid or liquid culture
     - Line probe assays or Xpert MTB/RIF for detecting rifampicin resistance
     - Selected non-commercial methods
   - Supranational Reference Laboratory Network:
     - 29 laboratories providing quality assurance via:
       - Proficiency testing and rechecking

Most up-to-date information: http://www.who.int/tb/laboratory
Three main principles of anti-tuberculosis drug resistance surveillance

1. Collected data should accurately represent the TB patient population in the country / geographical setting under study
   - Continuous surveillance based on routine DST of the entire patient population
   - Survey = a study of a sample of patients representative of the entire patient population

2. Quality-assured laboratory results
   - DST methods must be chosen from those that are WHO-recommended; solid or liquid culture
   - Supranational Reference Laboratory Network

3. Differentiation between new (previously untreated) and previously treated cases
   - <1 vs ≥ 1 month of previous treatment
   - Specimens must be taken before starting a treatment regimen
Continuous surveillance of previously treated cases is a priority in all settings. Previously treated patients should be disaggregated by subcategory:

- Relapse (returned after previous treatment success)
- Failed a new patient regimen using first-line drugs only
- Failed a retreatment regimen using first-line drugs only
- Failed a regimen including second-line drugs
- Return after default
- Other
- Unknown
Continuous surveillance of previously treated cases is a priority in all settings. Previously treated patients should be disaggregated by subcategory:

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**MDR-TB among patients in Bangladesh**

![Bar chart showing percentage of MDR-TB cases](Damien Foundation areas, 2008)
Surveys should be conducted periodically among new cases, when capacity for continuous surveillance is not yet in place.

All previously treated cases at the selected diagnostic centres should be enrolled during the time of the survey, but targeting a special sample size for them is not recommended.

Focus of surveys on sputum smear positive cases, in order to reduce burden on laboratories performing culture.

Note: HIV-positive TB patients are more likely to be smear-negative. If HIV is correlated with drug resistant TB, this could introduce bias.

Phenotypic (solid, liquid culture) or newer genotypic (line probe assays, Xpert MTB/RIF) DST methods can be used.

Drugs to be reported on: rifampicin, isoniazid ➔ if MDR-TB: fluoroquinolones, 2\textsuperscript{nd}–line injectables and ethambutol.
2009 DRS Guidelines: Main recommendations

- Focus on public sector patients treated by the National TB control programme (NTP), but include into the sampling frame any PPM (public private mix) projects that report cases to the NTP
- Statistical advice should be part of the survey plan from the beginning
- Surveillance should be linked to patient care:
  - Treatment should be made available for patients diagnosed with drug-resistant forms of TB
- Capture of information on patients’ HIV status is highly encouraged
- In order to determine other possible associations with drug resistance, surveys should capture other patient information:
  - Age
  - Sex
  - Social factors: history of imprisonment, substance abuse, etc.
Main components of a survey

1. Selection of a representative sample
2. Patient interview to get accurate clinical data (previously treated?)
3. Collection and transport of sputum
4. High-quality drug susceptibility testing
5. Retesting a subset at SRL
6. Flow of clinical and lab data
7. Data entry, management and analysis
Main components of a survey: potential duties of a survey consultant

1. Selection of a representative sample
   - Determine appropriate design of a survey (sampling design and geographic area)
   - Calculate sample size
   - Select clusters/diagnostic centres

2. Patient interview to get accurate clinical data
   - Development of a patient clinical information form, including formation of questions
   - Ensuring interviewers / patient enrollers are trained properly

3. Collection and transport of sputum (together with partner SRL)
   - Logistics: how will specimens get from all diagnostic centers to DST labs in a short amount of time?
   - Consider rolling cluster enrollment
   - Consider involving intermediate culture laboratories
Main components of a survey: potential duties of a survey consultant

4. High-quality DST (together with partner SRL)
   - Selection of DST lab(s), considering quality of work and burden
5. Retesting a subset at the SRL (together with SRL)
   - Determine numbers of specimens to send
   - Facilitate logistics
6. Flow of clinical and lab data
   - Centrally monitor enrollment of patients by diagnostic centre; monitor progress of DST
7. Data entry, management and analysis
   - Assist with creation of database and data management plan
   - Assist with data analysis

Overall:
- Development of a protocol
- Troubleshooting
Continuous drug resistance surveillance

- 2010 M/XDR-TB report: Introduction of global quality indicators for measuring the representativeness and accuracy of 2008 continuous surveillance data
- Continuous surveillance data can be classified as Class A and B (or neither)
## Continuous drug resistance surveillance

### Class A and B quality indicators

<table>
<thead>
<tr>
<th></th>
<th>Class A</th>
<th>Class B</th>
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<tbody>
<tr>
<td>1. Case detection rate:</td>
<td>≥ 50%</td>
<td></td>
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<tr>
<td>2. Positive culture among notified pulmonary cases:</td>
<td>≥ 50%</td>
<td>≥ 35%</td>
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<td>3. DST results for INH and RIF among culture positive cases:</td>
<td>≥ 75%</td>
<td>≥ 50%</td>
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<tr>
<td>4. NRL DST proficiency testing results for INH and RIF in cooperation with SRL:</td>
<td>≥ 90% accuracy</td>
<td></td>
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Drug resistance surveillance: what data is routinely collected from all countries (as of 2011)

http://www.stoptb.org/tme/

The WHO global TB data collection system

This system allows National TB Programme representatives and WHO regional offices to complete the annual TB data collection forms online. The system is managed by WHO’s Tuberculosis Monitoring and Evaluation team in Geneva.

National TB Programme representatives are strongly encouraged to use this system as this will ensure that the most accurate data are used in forthcoming WHO Global TB Control Reports.

Features

- Secure and easy method to record and validate data.
- Screens available in English, French and Spanish.
- No need to submit a paper form or Excel spreadsheet.
- Data are saved securely as soon as you start work on your report.
- Share the job of completing the report among your colleagues.
- No need to complete your report at once; you and your colleagues can log on and edit parts of the report as often as necessary.

Access

Please contact us if you need a password for yourself or a colleague or if you need help accessing and using the system.
Drug resistance surveillance: what data is routinely collected from all countries*

1. Numbers of MDR-TB cases
2. Numbers of TB cases with isoniazid resistance but not rifampicin resistance
3. Numbers of TB cases with rifampicin resistance but not isoniazid resistance
4. Among MDR-TB cases, numbers with:
   • Resistance to any fluoroquinolone
   • Resistance to any second line injectable drug
   • XDR-TB
5. To determine Class A/B status:
   • Numbers of notified cases that are culture positive
   • Numbers of culture positive cases that have DST results for isoniazid and rifampicin
6. Association between MDR-TB and 1.) HIV and 2.) sex

* with new molecular diagnostics, this is going to be revised!
Thanks

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http://www.who.int/tb/challenges/mdr