The WHO/IUATLD Supra-National Reference laboratory network for tuberculosis

L. Rigouts, F. Portaels (ITM, Antwerp)
A. Van Deun (ITM / Union)
A. Wright (WHO / TDR)
• History and overview of the project
• SRLN current status and Terms of Reference
• 10th round of proficiency testing
• Contribution to TB control
SRL History

Created in 1994

- support global drug resistance surveillance (DRS)
The Global Project on Anti-TB Drug Resistance Surveillance

Objectives
- Estimate the magnitude of drug resistance globally
- Determine trends
- Provide data to inform policy decisions
- Evaluate the progress of TB programmes
- Strengthen laboratory networks

Publications:
Guidelines for surveillance of drug resistance in tuberculosis.
revision (1997/2006)

Global Reports:
1st report: 1997 → 35 settings
2nd report: 2000 → 58 settings
3rd report: 2004 → 77 settings
Prevalence of MDR-TB among new cases 1994 - 2002

The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delineation of its frontiers or boundaries.

Data Source: WHO/IUATLD Global Project
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization
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The Global Project on Anti-TB Drug Resistance Surveillance

**Principles:**

- Accurate sampling represents population under study
- Differentiation between new and previously treated cases
- Quality assured laboratory results
SRL History (cont.)

• Originally 16 laboratories
  – no proper selection criteria
    • quality assurance + links with higher-prevalence countries
    • selection monopolised by WHO
      (exclusive source of finance)
  – heavy concentration in Europe
    • low-income: only 2 labs (India)
      extreme scarcity of good laboratories
    • new SRL being certified (middle income)

• Now 26 laboratories
The Supranational Laboratory Network (SRLN) 2005 (links with >150 countries)

Africa: 2
Americas: 5
Middle East: 1
Europe: 11
South Asia: 2
Western Pacific: 5
SRL Terms of reference

- Permanent functional laboratory
- Commitment to support at least two countries
  - PT
  - QA of surveys / DOTS-Plus
  - Training where necessary
- Commitment to participate in meetings/studies
  - 5 annual network meetings
  - 2 SLD studies ongoing
- Participate in annual EQA (PT), fulfil performance criteria
The SRL Network
SYSTEM OF EXTERNAL QUALITY ASSURANCE

Coordinating Centre
Antwerp, Belgium

Network of 25 Supranational Laboratories

Panel of 30 coded isolates
Feedback !!

Panel of 20 coded isolates
Feedback !!

Sample of isolates for rechecking (DRS/DOTS-Plus)

National/Regional Reference Laboratories
Organization of proficiency testing

• Coordinating laboratory:
  – rounds 1 to 5 by Ottawa, Canada: succeeded in
    • standardization of techniques
    • validation of methods
    • improved precision
  – rounds 6 to 11: Antwerp, Belgium: continuation
    • Expansion to 24 laboratories
Panel constitution

• 20 strains
  – 10 of those in duplicate: reproducibility analysis
  – attain significance after two successive rounds (LQAS)
    no error: 95% efficiency reached
    max. 2 errors: 90% efficiency reached

• Panel targets
  – 50% prevalence of resistance (any drug)
  – non-MDR subset
  – various combinations of resistance
  – clinically well documented
  – extensive pre-testing
<table>
<thead>
<tr>
<th></th>
<th>No. of labs with results in the range of</th>
<th>Average score</th>
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<tbody>
<tr>
<td></td>
<td>100%</td>
<td>95-99%</td>
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<tr>
<td>ISONIAZID (19 R, 9 S / 2?)</td>
<td></td>
<td></td>
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<tr>
<td>Sens.</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Spec.</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Effic.</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>RIFAMPICIN (15 R, 13 S / 2?)</td>
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<td></td>
</tr>
<tr>
<td>Sens.</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Spec.</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Effic.</td>
<td>13</td>
<td>1</td>
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<tr>
<td>STREPTOMYCIN (18 R, 10 S / 2?)</td>
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<td></td>
</tr>
<tr>
<td>Sens.</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Spec.</td>
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</tr>
<tr>
<td>Effic.</td>
<td>10</td>
<td>4</td>
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<tr>
<td>ETHAMBUTOL (6 R, 16 S / 8?)</td>
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<td></td>
</tr>
<tr>
<td>Sens.</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Spec.</td>
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<td>2</td>
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<tr>
<td>Effic.</td>
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## Summary results Round 5 to 10

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>Rifampicin</th>
<th>Streptomycin</th>
<th>Ethambutol</th>
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<tbody>
<tr>
<td>Results evaluated</td>
<td></td>
<td></td>
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<tr>
<td>total</td>
<td>2391</td>
<td>2106</td>
<td>2091</td>
<td>2099</td>
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<tr>
<td>range individual labs</td>
<td>73 - 117</td>
<td>65 - 103</td>
<td>66 - 102</td>
<td>65 - 103</td>
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<tr>
<td>Sensitivity</td>
<td></td>
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<tr>
<td>average</td>
<td>100%</td>
<td>100%</td>
<td>96%</td>
<td>94%</td>
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<tr>
<td>range individual labs</td>
<td>97 - 100%</td>
<td>93 - 100%</td>
<td>76 - 100%</td>
<td>34 - 100%</td>
</tr>
<tr>
<td>Specificity</td>
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<td></td>
<td></td>
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<td>99%</td>
<td>99%</td>
<td>98%</td>
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<tr>
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<td>90 - 100%</td>
<td>84 - 100%</td>
<td>90 - 100%</td>
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<tr>
<td>Efficiency</td>
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<tr>
<td>average</td>
<td>99%</td>
<td>99%</td>
<td>97%</td>
<td>96%</td>
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<tr>
<td>range individual labs</td>
<td>97 - 100%</td>
<td>93 - 100%</td>
<td>86 - 100%</td>
<td>79 - 100%</td>
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<tr>
<td># of SRL reaching 90-95% efficiency</td>
<td>ALL 21</td>
<td>20 / 21</td>
<td>17 / 21</td>
<td>19 / 21</td>
</tr>
<tr>
<td>LQAS assured</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>17</td>
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</table>
SRL proficiency looks good

• Over time persistent excess errors:
  isoniazid: none
  rifampicin: one laboratory
  streptomycin: one laboratory
  ethambutol: two laboratories

• Excess errors
  – not linked to specific methods
  – periodically seen in several labs
    • systematic: changed detail of technique?
    • random: manipulation errors
But may be over-estimated

- Judicial result criterion
  - evaluating precision, not necessarily accuracy?
  - forces to exclusion of problem strains

- Strains excluded (<80% agreement)
  round 6 to 10
  - isoniazid: 2
  - rifampicin: 9
  - streptomycin: 10
  - ethambutol: 11
Samples for rechecking DRS

• Limitations
  – international transport of TB strains
  – lack of funding
  – Africa: links with SRL not clearly defined + vague / scattered over different SRL
Network contribution to TB control

• Drug resistance surveillance
  – better standardization of testing
  – quality assurance of surveys
  – more reliable data available
Cumulative DRS population coverage by WHO region - expected 2007

- AFR
- AMR
- EMR
- EUR
- SEAR
- WPR
Africa high HIV incidence, 48,141
Latin America, 11,301
Eastern Mediterranean Region, 18,330
Africa low HIV incidence, 10,449
Central Europe, 1,462
Established Market Economies, 1,681
Western Pacific Region, 152,018
South-east Asia, 114,967
Eastern Europe, 65,853

Global burden: 424,203 cases
Network contribution to TB control

- Strengthening TB laboratory services: still limited
  - focusing of activities: TB high-burden countries
    - Eastern Europe, Central Asia, Far East = OK
    - But hardly Africa
  - broadening the scope
    - AFB-microscopy network support
    - strengthening (and expansion?) of culture for diagnosis
DRS and Policy development
Phase 1: 1994-2002

**DRS findings** (1\textsuperscript{st} and 2\textsuperscript{nd} report)

MDR-TB widespread, localized/severe epidemics, especially in FSU/China

**Policy recommendations**

Start of DOTS-Plus / GLC

Pilots expanding, evaluation of projects, increased access
DRS and Policy development
Phase 2: 2002 – present

DRS findings (3rd report)
Must evaluate Cat II in some settings as well as Cat I in areas of high INH resistance prevalence, look at DRS and HIV

Policy recommendations
Treatment guidelines updated
• Population based 1\textsuperscript{st} line drug surveys important for trend analysis (reliable DST for H and R)

• Clear need to supplement population based DRS, with small cohort studies relevant for DOTS-Plus
  • Small surveys combined with history of treatment / antibiotic use to inform DOTS-Plus regimens
  • Obstacles: 2\textsuperscript{nd} line DST much less reliable, lab capacity for 2\textsuperscript{nd} line not developed locally (studies ongoing)
Challenges remaining

• Drug resistance testing
  – DST reliability and clinical significance
    • intermediate results? Techniques?
  – low- and middle income countries?
    • relative priority of DRS versus AFB-microscopy

• Capacity building
  – in low-income: DST and/or microscopy?
Challenges remaining

• Role in general TB research?
  – Not original objective
  – limited to some SRL
    • e.g. IUATLD clinical trials programme
  – extension on individual basis?