Supranational Reference Laboratory and Private laboratories in RNTCP

Facing the Reality of MDR-TB: Challenges and Potential Solutions in India

New Delhi, India, 18-19 April 2011

N. Selvakumar
Deputy Director (Senior Grade)
Tuberculosis Research Centre (ICMR) Chennai

SRLN
TB SUPRANATIONAL REFERENCE LABORATORY NETWORK
Outline

• History, objectives & contributions of SRLN
• TRC-SRL and NRL in India: Reality
  Private labs in India
  Limitations
  Challenges
  Solutions
SRLN - History

• Started in 1994
• Initially 16 labs
  no selection criteria
  functional labs with strong commitment to NTPs
• Labs concentrated in Europe- 11 labs
  2 labs in India
• Extremely scarcity of good labs
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

28 SNRLs  Mar 2010
SRLN – Terms of reference

• Permanent functional lab
• DRS in the country / region, trends
• Commitment to
  support at least 2 countries in PT
  ensure quality of DRS and DOTS plus projects
  participate in annual network meetings / studies
• Participate in annual EQA with coordinating lab
• Provide information to policy decisions
Objectives of SRLN

- To determine global DR
- Trend of DR in regions
- EQAP
- Provide information to policy decisions
- Assessment of TB programmes
- Enhance lab capacity by training
SRLN – Global project on anti-TB drug resistance survey

Principles

- accurate sampling representing the population under study
- differentiation between new and previously treated cases
- quality assured lab results
Global project

- No. countries surveyed increased (35, 58, 77; total: 114, continuous-34, periodic-74)
- Provide guidance for DRS
- Prevalence of TB, MDR / XDR-TB known
- Make global & regional estimates
- Identified hot spots
In 2008, an estimated 390 000–510 000 cases of MDR-TB emerged globally (best estimate, 440 000 cases). Among all incident TB cases globally, 3.6% (95% confidence interval (CI): 3.0–4.4) are estimated to have MDR-TB. These estimates, which lie in the same range as the previous ones, are based on more data and a revised methodology. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. In 2008, MDR-TB caused an estimated 150 000 deaths.
Available data on anti-TB drug resistance, 2010

- Nationwide surveillance data
- Subnational surveillance data
- Nationwide recent survey data (since 2000)
- Subnational and/or old survey data (before 2000)
- No data available
Proportions of MDR among new TB cases, 1994-2010

China first national DRS, MDR-TB NC-5.7%; Tajikistan sub-national survey MDR NC-16%,
China first national: PTC-26%, 0.1 M MDR-TB
Tajikistan first sub-national survey, PTC- 62%, highest
### % of MDR-TB among new cases: latest data 2001-2009

**Nationwide Data**

1. Moldova (19.4%)
2. Estonia (15.4%)
3. Kazakhstan (14.2%)
4. Latvia (12.1%)
5. Armenia (9.4%)
6. Lithuania (9.0%)
7. Georgia (6.8%)
8. China (5.7%)
9. Jordan (5.4%)
10. Peru (5.3%)

**Sub-national Data**

1. Murmansk Oblast, Russia (28.3%)
2. Pskov Oblast, Russia (27.3%)
3. Arkhangelsk Oblast, Russia (23.8%)
4. Baku City, Azerbaijan (22.3%)
5. Ivanovo Oblast, Russia (20.0%)
6. Kaliningrad Oblast, Russia (19.3%)
7. Belgorod Oblast, Russia (19.2%)
8. Dushanbe City & Rudaki District, Tajikistan (16.5%)
9. Mary El Republic, Russia (16.1%)
10. Donetsk Oblast, Ukraine (16.0%)
% of MDR-TB among new TB cases since 1994

- Quality controlled data from 114 countries since 1994
- Only 22 out of 46 countries in Africa have data
- MDR-TB in 3.6% of incident TB cases in 2008
XDR-TB Findings:
- 58 countries reported at least one case of XDR-TB as of March 2010
- Representative data from 46 countries
- 5.4% of MDR-TB cases have XDR-TB

There are thought to be 25,000 cases of XDR-TB emerging every year
Key findings:
• Highest % ever recorded with 1 in 4 new TB patients diagnosed with MDR-TB in parts of north-west Russia
• Highest absolute numbers of MDR-TB cases are in China and India: nearly 50% of the world's burden
• Cases & Deaths - WHO estimates 440,000 MDR-TB cases and 150,000 deaths in 2008
• XDR-TB - 58 countries have reported at least one case of XDR-TB as of March 2010
• Positive Trends - Russian oblasts of Orel and Tomsk have reversed rising levels of MDR-TB
  - Downward MDR-TB trends in Estonia and Latvia
  - Sustained decline in Hong Kong SAR (China) and USA, stable low levels in western Europe
• Detection & Diagnosis
  - 7% of all estimated MDR-TB patients diagnosed and notified
The SRL Network
SYSTEM OF EXTERNAL QUALITY ASSURANCE

Coordinating Centre
Antwerp, Belgium

Panel of 30 coded isolates

Feedback !!

Network of 25 Supranational Laboratories

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

Panel of 20 coded isolates

Feedback !!

National/Regional Reference Laboratories
SRLN – organization of EQAP

• Coordinating lab
  1-5 rounds- Ottawa, Canada
  6-17 rounds- Antwerp, Belgium

Succeeded in
  standardization of techniques
  validation of methods
  improving the precision of reporting
SRLN – Panel of cultures

- 20 cultures
  - 10 in duplicates: for reproducibility
  - at least 10 resistant cultures for each of SHRE MDR strain not included
  - different combination of resistance
  - pre tested
  - Clinically well documented
Proficiency of DST in SRLN

• 9 Rounds (6-14) for first-line drugs.

• **RESULTS:** Of 600 strains, 10% excluded from evaluation.

• sensitivity and specificity at >95% for INH, RMP and SM and at >80% for Emb.

• 16 of 27 SRLs performed consistently better.

• **CONCLUSION:** The rounds succeeded in comparing the proficiency of laboratories, and should be further promoted for DST quality assessment. However, to function with greater precision and to ultimately improve the clinical relevance of DST, the INH and RMP judicial result gold standard also needs to take into account genotypic and treatment outcome information.

SRLN – contribution to policy development

1st and 2nd report
- MDR-TB wide spread
- localised/severe epidemics in former Soviet Union, China
- start of DOTS plus / Green Light Committee

3rd report
- suggested to include previously treated cases in DRS
- HIV status to be included
- population based DRS to know trends
- Unreliability of SLD DST
STP-GLI as an active facilitator of communication and provider of global infrastructure services synchronized to be a coherent network service

Key STP-GLI activities

**Guidance**
- Laboratory policies
- Laboratory manuals
- Training materials
- Resource mobilization
- National roadmap advice

**Assurance activities**
- Coordination of EQA
- Equipment specifications
- Global accreditation system
- Monitoring/evaluation

**Knowledge Sharing**
- Coordinating TA, training
- Communication technologies
- Online knowledge resource network

**Interface Connection**
- Matchmaking projects between countries and implementing partners
- National “roadmaps”
- Advocacy
- Other disease networks

**Capacity building**
(expanding SRLN, building diverse and flexible national, regional, international consultants base, systematic and structured training)
Reality:

TRC as SRL for SEA region

TRC as NRL for RNTCP
• One of two SRLs in SEA region
• supports
  India
  Sri Lanka
  Maldives
  DPR Korea
  – Development of protocols for EQA microscopy
  – EQA: Re-testing (RT) and panel testing (PT)
  – DST for MDR-TB suspects
- TRC- SRL

- in addition

  - Facilitating international training programmes on Lab diagnosis of MDR-TB : Thailand, India
    EQA microsocopy: India, Bhutan
  
  - Participation in WHO : GLI meetings, JMM
  
  - Consultancy: to Myanmar, Nepal, Bhutan, Bangladesh, India, Maldives, DPR Korea, Sri Lanka
TRC-SRL

EQA with coordinating laboratory in Belgium

16 rounds completed

Efficiency is acceptable in all rounds for FLDs except for Rif in 2 rounds (>80%)

Last three rounds DST for SLD included

Efficiency is acceptable for O, K, Am, Cap (80%)
TRC-SRL: PT with Belgium Lab.  
11 rounds; 30 cultures / round

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>11</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>H</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>R</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>E</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
TRC-SRL: PT of DST - SLD with Belgium lab
3 rounds; 30 cultures / round

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficiency</th>
<th>Reproducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kan</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ami</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cap</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Off</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
TRC as NRL for RNTCP

• First state-wise DRS in Gujarat
  MDR-TB
  <3% in new smear positives
  12-17% in re-treated cases

• DRS for Tamil Nadu and Rajasthan in 2011-2013
TRC as NRL for RNTCP India

- Labs under supervision: 28
  - 3 NRLs - NTI, JALMA, LRS
  - 8 IRLs – Tamil Nadu, Kerala, Andra Pradesh, Gujarat, Goa, Chhattisgarh, Sikkim, Pudhucherry
  - 6 RMRCs (ICMR) - Jabalpur, Port Blair, Dibrugarh, Patna, Bhuvaneswar, Jodhpur,
  - 11 Private labs - DFIT, BPRC - Andra Pradesh, Hinduja, SRL-Maharashtra, SRL, Quest - Delhi, SRL - West Bengal, Global Hospitals, CMC, SNHR - Tamil Nadu, Microcare - Gujarat
TRC as NRL for RNTCP

- Participating in Lab committee meetings
- Facilitating national training courses
- Revising modules and manuals for labs
- Training NRLs on DST for SLDs,
- Performing DST for SLDs on MDR isolates
TRC as NRL for RNTCP

Support to IRLs

• Establishment of Culture and DST
• Pre-assessment visits to IRLs/Private labs
• Accreditation of labs
• TA support to establish SOPs
TRC as NRL for RNTCP

EQA:
• RT- only for accreditation

• PT
• First round: 7 Labs
• 2nd round: 8 Labs
TRC-NRL: 1\textsuperscript{st} round PT of IRLs, DST FLD
11 labs 30 cultures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>8</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>H</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>R</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>
TRC-NRL: 2\textsuperscript{nd} round PT of IRLs, DST FLD  
8 labs; 30 cultures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>H</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>R</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
TRC as NRL for RNTCP
information to policy decisions

Operational Research

- Cough duration 2 weeks
- Two sputum samples for diagnosis
- Single positive smear - a case
- Concentration of carbol fuchsin in ZN
- Sensitivity of ZN and FM for CPC transported samples
- Transportation of samples in surveys
- LQAS tested in the field
- Re-staining is essential before umpire reading
- Software to analyse RT and PT results
8 Private / 3 NGO labs

- 11 labs
- Solid / Liquid culture / Line Probe Assay / geneXpert
- Comply fast with the requirements
- Good support to DOTS plus sites
Limitations / issues

• Not all HBC have NRLs

• Many HBC lack resources and / or expertise to do DRS

• Results of re-testing not known / available; neither NRLs in SNRLs nor SNRLs in coordinating laboratory

• EQA for LPA is to be framed and studied

• Intermediate resistance in Rif

• Role in OR not defined
Limitations / issues

• Sri Lanka: Transport of clinical isolates

• Many players – PATH, FIND, WHO-SEARO, CTD, UNION, linkage with SNRL / NRL is not well defined

• Administrative issues delay accomplishment of work in time

• SRLs need certification for accreditation from coordinating lab
Challenges

• Inadequate or absence of regular staff and threat of contractual staff leaving

• Workload of SLR; IRLs

• Special requirements for introduction of newer rapid diagnostics – laboratory infrastructure and training

• Maintenance of BSL 3 facilities

• Mindset of employees to changes
Solutions

- ICMR/GOI- to recruit Microbiologists with career prospects
- WHO- Guidance for
  - NTPs to facilitate shipment of cultures
  - re-testing isolates from SRLs in coordinating lab
  - EQA for LPA
- RNTCP- guidance for
  - shipment of samples from districts to private labs
  - RT of isolates form DRS and DOTS plus at NRLs
  - training SNRL technical staff in international labs
Acknowledgements

PR Narayanan
A Thomas
Vanaja Kumar
Gomathi Sekar
Gopi
Ponnuraja
Sivagamasundari
Michel Premkumar
Rajaraman
Ravikumar
Devika
Shyam Sunder
Azger Thaskakeer
Prabu Seenivasan
Radhakrishnan
Devi Sangamithirai
Nagarjan
Anbarasu
Rathika
Jayasree
Staff –wash up room
Staff- media room

USAID, WHO,
Thank you