Global Consultation of the
TB Supranational Reference Laboratory Network

14-15th April 2010
WHO Geneva
Objectives

• Disseminate recent developments in WHO policy guidance on new TB methods/tools
• Develop revised TORs for the SRLs
• Develop criteria for the selection of new SRLs and to evaluate existing SRLs
• Review the process for the creation of formal links between SRLs and national reference laboratories (NRL)s
• Discuss requirements and funding mechanisms for SRLs to develop and implement work plans for sustained coordinated technical assistance to countries beyond quality assurance for DST.
Stop TB Partnership Workgroups

• DOTS Expansion WG
• WG on New TB diagnostics
• TB/HIV WG
• MDRTB WG
• WG on New TB Drugs
• WG on New TB Vaccines
• Global Laboratory Initiative WG (Approved Nov 08)
Global Laboratory Initiative – Structure and Governance

<table>
<thead>
<tr>
<th>GLI Partners Committee</th>
<th>Core Group approves, governs, evaluates projects and advise GLI Secretariat</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLI Secretariat</td>
<td>GLI Core Group</td>
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<tr>
<td>GLI Partners Committee</td>
<td>(Organizations, STP Working Groups, Country NTP+Lab, SRLs, NGOs, etc)</td>
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<table>
<thead>
<tr>
<th>Technical Working Groups</th>
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<tbody>
<tr>
<td>Laboratory strengthening country roadmaps</td>
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<tr>
<td>HR development &amp; training strategy</td>
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<tr>
<td>Laboratory biosafety</td>
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<td>Laboratory accreditation</td>
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<tr>
<td>Other</td>
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</table>
THE STOP TB DEPARTMENT

Stop TB Strategy (TBS)
L. Blanc, Coordinator

Care Delivery Innovation

TB Operations & Coordination (TBC)
P. Nunn, Coordinator

Global Fund Collaboration

TB Laboratory Strengthening (TBL)
K. Weyer, Coordinator

Global Laboratory Initiative (GLI)

TB Monitoring & Evaluation (TME)
K. Floyd, Coordinator

Surveillance & Monitoring

Supranational Reference Laboratory Network (SRLN)

Epidemiology & Impact Assessment

Expanding-TB Project

Economics, Budgeting & Financing

Stop TB Partnership Secretariat (TBP)
M. Espinal, Executive Secretary

Advocacy & Strategic Planning

Social Mobilisation & Partnering

Branding, Marketing & Communication

Global Drug Facility (GDF) & Green Light Committee (procurement)

TB Research Movement

TB REACH

6 Regional Offices, all with TB teams

WHO Offices, including TB-specific staff in 45 countries

STB Director’s Office (STB/DO)
M. Raviglione, Director
D. Weil, Coordinator, Policy & Strategy

Policy, Planning, Research Coordination,
Resource Mobilization & Communications

Administration & Finance Operations Team (AFO)
A. Vijay, Department & Partnership Resource Administrator

M/XDR-TB Response

TB/HIV Response

TBTEAM

Regional Collaboration

Green Light Committee Mechanism (GLC)

Supranational Reference Laboratory Network (SRLN)

EXPAND-TB Project

6 Regional Offices, all with TB teams

WHO Offices, including TB-specific staff in 45 countries

4/29/2010

29 April 2010
Current WHO policy update and future

Christopher Gilpin

Global Consultation of the TB Supranational Reference Laboratory Network
14-15th April 2010
Content

- Current policy guidance
- Policy framework at country level
- Diagnostic algorithms
- Future directions
Current policy recommendations

• 2007
  – Liquid medium for culture and DST
  – Rapid speciation

• 2008
  – Line probe assays for rapid MDR-TB screening
• Automated liquid culture and DST (2007): Use of liquid culture systems in the context of a comprehensive country plan for strengthening TB laboratory capacity; in a phased manner starting at national/central reference laboratory.

• Rapid speciation (2007): Strip speciation for rapid *Mycobacterium tuberculosis* from non-tuberculous mycobacteria; established at regional or central level in combination with liquid culture.

• Line probe assays (2008): Use of line probe assays for rapid detection of *R* resistance within the context of country plans for MDR-TB management, including development of country-specific screening algorithms and timely access to quality-assured second-line anti-tuberculosis drugs; do not eliminate the need for conventional culture and DST capability; should be phased in, starting at national/central reference laboratory or those with proven molecular capability.

• Second-line drug susceptibility testing (2008): Reliable and reproducible for injectables and fluoroquinolones; to be conducted in national/central reference laboratories using standardised methodology and drug concentrations; routine DST not recommended for ethionamide, prothionamide, cycloserine, terizidone, PAS, thioacetazone, clofazimine, amoxicillin/clavulanat, clarithromycin, linezolid

• **LED microscopy (2010):** LED microscopy to replace conventional fluorescent microscopy and be phased in as replacement for ZN microscopy

• **MODS (2010):** Recommended for rapid detection of R resistance within the context of country plans for MDR-TB management, including development of country-specific screening algorithms and timely access to quality-assured second-line anti-tuberculosis drugs; do not eliminate the need for conventional culture and DST capability; should be phased in, starting at national/central reference laboratory, under strict laboratory protocols and quality assurance

• **NRA (2010):** Recommended as direct or indirect tests, for screening of patients suspected of having MDR-TB, and acknowledging that time to detection of MDR-TB in indirect application would not be faster than conventional DST methods using solid culture; to be used within the context of country plans for MDR-TB management, including development of country-specific screening algorithms and timely access to quality-assured second-line anti-tuberculosis drugs; do not eliminate the need for conventional culture and DST capability; should be phased in, starting at national/central reference laboratory, under strict laboratory protocols and quality assurance

• **CRI methods (2010):** Recommended as indirect tests, for screening of patients suspected of having MDR-TB, and acknowledging that time to detection of MDR-TB would not be faster than conventional DST methods using liquid culture; to be used within the context of country plans for MDR-TB management, including development of country-specific screening algorithms and timely access to quality-assured second-line anti-tuberculosis drugs; do not eliminate the need for conventional culture and DST capability; should be phased in, starting at national/central reference laboratory, under strict laboratory protocols and quality assurance

Implementing policy recommendations
Policy framework at country level

- Local epidemiology (TB, HIV, MDR-TB)
- Priorities for case detection
- Local laboratory capacity and networks
- Local laboratory human resources and skills base
- Local treatment policies for MDR-TB
- Financial resources
Analytical process

- Quantify or estimate TB, TB-HIV and MDR-TB burden
- Identify and target specific patient risk groups
- Quantify or estimate diagnostic tests to identify risk groups
  - Number of suspects to be screened
  - Number and type of laboratories at each service level
- Estimate budget for comprehensive laboratory services
  - All core components
  - Capacity for diagnostic and monitoring
  - Ancillary laboratory services (e.g. biochemistry, haematology)
Phased approach

• **Phase 1: Laboratory preparedness**
  – Assessment of TB laboratory networks and diagnostic policies
  – Upgrade of laboratory infrastructure and biosafety
  – Development and implementation of GLP, SOPS, QA, etc.
  – Training of core laboratory staff
  – Initiating NTP policy reform on diagnostics

• **Phase 2: Introduction of new diagnostics**
  – Integration of new diagnostics into NTP policies and procedures
  – Procurement and installation of instruments, reagents, and other essential supplies
  – Validation of new tools and laboratory performance

• **Phase 3: Impact assessment**
  – Continued mentoring, technical support and oversight
  – Assessment of impact of new diagnostics
Laboratory algorithm

Starts with
• Screening strategies for suspects
• Microscopy services as entry point
Positive MICROSCOPY (ZN or Fluorescence)
- Negative
- No result

Positive CULTURE (Solid or Liquid)
- Negative
- No result

Positive DRUG SUSCEPTIBILITY TESTING-1st LINE (Solid or Liquid)
- Not MDR, resistant other drugs
- Susceptible
- No result

Positive IDENTIFICATION (SPECIATION) (Conventional/Commercial)
- Susceptible
- Not MDR, resistant other drugs
- No result

XDR DRUG SUSCEPTIBILITY TESTING-2nd LINE (Solid or liquid)
- Not XDR, resistant other drugs
- Susceptible
- No result

District

NRL/regional

AFB

TB/NTM

Drug resistance

SRL/NRL
District

Positive

Negative

No result

Line Probe Assay

Positive

Negative or no result

No result

AFB

TB/NTM

Drug resistance

Drug Susceptibility Testing-1st Line (Solid or Liquid)

MDR

Not MDR, resistant other drugs

Susceptible

No result

Identification (Speciation) (Conventional/Commercial)

Susceptible

No result

Drug Susceptibility Testing-2nd Line (Solid or liquid)

XDR

Not XDR, resistant other drugs

Susceptible

No result

NRL/regional

SRL/NRL
Policy considerations

- Current technologies not mutually exclusive
  - Conventional culture capacity required for SM- specimens
  - Conventional DST capacity required to detect XDR-TB
- Liquid culture and line probe assay considered as gold standards, to be phased in without loss of existing solid culture and DST capacity
- LED microscopy as alternative for both fluorescence and conventional light microscopy
- Selected non-commercial culture and DST methods not alternatives for gold standards, but may provide interim solution
MDR-TB diagnosis using solid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Solid culture</th>
<th>1st line DST</th>
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</thead>
<tbody>
<tr>
<td>24h</td>
<td>6-8w</td>
<td>3-4w</td>
</tr>
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</table>

MDR-TB diagnosis after 9 to 12 weeks

MDR-TB diagnosis using liquid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Liquid culture</th>
<th>1st line DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>2-3w</td>
<td>1-3w</td>
</tr>
</tbody>
</table>

MDR-TB diagnosis after 3 to 5 weeks

MDR-TB diagnosis using line probe assay, liquid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Line probe assay</th>
<th>Liquid culture</th>
<th>1st line DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>24h</td>
<td>2-3w</td>
<td>1-3w</td>
</tr>
</tbody>
</table>

MDR-TB diagnosis after 1 to 2 days

MDR-TB diagnosis after 3 to 5 weeks
MDR-TB diagnosis using solid culture and DST

- Microscopy: 24h
- Solid culture: 6-8w
- 1st line DST: 3-4w

MDR-TB diagnosis after 9 to 12 weeks

MDR-TB diagnosis using NRA

- Microscopy +: 24h
- Solid culture: 6-8w
- NRA direct: 6-9d
  - MDR-TB diagnosis after 6 to 9 days

- Microscopy -: 24h
- Solid culture: 6-8w
- NRA direct: 7-21d
  - MDR-TB diagnosis after 7 to 11 weeks
MDR-TB diagnosis using liquid culture and DST

- Microscopy: 24h
- Liquid culture: 2-3w
- 1st line DST: 3-4w

MDR-TB diagnosis after 5 to 7 weeks

MDR-TB diagnosis using MODS

- Microscopy (positive): 24h
- MODS direct: 2-21d
- MODS indirect: 6-9d
- Liquid culture: 2-3w

MDR-TB diagnosis after 2 to 21 days

MDR-TB diagnosis after 3 to 4 weeks
### XDR-TB diagnosis using conventional solid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Solid culture</th>
<th>1st line DST*</th>
<th>2nd line DST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>6-8w</td>
<td>3-4w</td>
<td>3-4w</td>
</tr>
</tbody>
</table>

* Methods not validated or standardised

XDR-TB diagnosis after 12 to 16 weeks

### XDR-TB diagnosis using liquid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Liquid culture</th>
<th>1st line DST</th>
<th>2nd line DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>2-3w</td>
<td>1-3w</td>
<td>1-3w</td>
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</tbody>
</table>

XDR-TB diagnosis after 4 to 9 weeks

### XDR-TB diagnosis using line probe assay, liquid culture and DST

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>LPA</th>
<th>Liquid culture</th>
<th>1st line DST</th>
<th>2nd line DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>+</td>
<td>2-3w</td>
<td>1-3w</td>
<td>1-3w</td>
</tr>
<tr>
<td>LPA 24h</td>
<td>-</td>
<td>2-3w</td>
<td>1st line DST</td>
<td>2nd line DST</td>
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</tbody>
</table>

XDR-TB diagnosis after 4 to 9 weeks
Anticipating new diagnostics

Challenges of implementation

Feasibility, contract, development phases
- Evidence for regulatory approval

Evaluation phase
- Evidence for making policy

Demonstration phase
- Global Policy

Access phase
- Evidence for scaling up

Global Impact
- Evidence for measuring impact

Moving from demonstration to access and impact requires that new diagnostic tools are integrated into functional laboratory services

Essential instruments, reagents, supplies

Additional components to ensure quality diagnostic services

Logistics and supplies

Human Resources (Guidelines Technology transfer)

Infrastructure

Quality Assurance

Linked referral systems and reporting
The Future - Maintaining a tiered system approach

- **Reference Labs**
  - Surveillance
  - Reference methods
  - Network supervision

- **Regional Labs**
  - Resolution testing (screening-test negative drug resistance)

- **District Level**
  - Screening
  - Passive case finding
  - Detect and treat

- **SubDistrict Level**
  - Clinical Screening
  - Primary care

- **Microscopy Level**
  - Auto NAAT +40% /2h
  - LED FM +10%
  - Manual NAAT +25%
  - ZN 2-3d

- **Community Level**
  - Expected 2014
  - RDT

- **Surveillance**
  - Reference methods
  - Network supervision

- **Resolution testing**
  - (screening-test negative drug resistance)
Acknowledgements

- WHO-STB laboratory staff
- WHO Expert Groups
- WHO STAG-TB
- Global Laboratory Initiative (GLI) Core Group
- GLI Technical Working Groups
- GLI Partners involved in laboratory strengthening