Expanding and Accelerating access to Tuberculosis Diagnostics and Laboratory Services

2nd Meeting of the Global Laboratory Initiative (GLI)

jointly organised by
World Health Organization & Fondation Mérieux

MEETING REPORT
CONFIDENTIAL

The meeting was held at Les Pensieres Conference Center in Veyrier du Lac – France
October 15 & 16, 2009

The following report summarizes the information provided during this meeting based on abstracts and speaker’s lectures, procedure specifics for research investigation are not detailed in this report.

Report Issued Dec 7, 2009
Meeting Reporter: Valentina Picot
Disclaimer

Information on this report was obtained from the lectures and abstracts given by the speakers as per scientific agenda on the Combining Immunotherapy a Fondation Mérieux meeting held in June 2009 at “Les Pensieres” conference center in Veyrier du lac, France. All graphs, flow charts and images were obtained from the speaker’s presentations to facilitate the comprehension on the subject.

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Background

Drug-resistant TB, notably multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, present formidable challenges to TB control due to its more complex diagnosis and treatment. Recent scenarios developed by the World Health Organization (WHO) show that gains made in TB control stand to be reversed if drug-resistant TB is not addressed as a matter of priority in high-burden settings. The 62nd World Health Assembly (WHA) Resolution on TB in May 2009 inter alia calls for universal access to diagnosis and highlights the need for significant strengthening of laboratory services to meet the diagnostic challenges of drug-resistant and HIV-associated TB.

In recognition of the critical constraints of TB diagnostics and laboratory services, an unprecedented effort in improving and expanding TB laboratory capacity is currently underway, spearheaded by the Global Laboratory Initiative (GLI) and its network of international partners. At the same time, the TB diagnostics pipeline is growing, new technologies are regularly assessed by WHO with a view towards rapid policy development and deployment, and innovative partnerships are being formed, mobilizing and optimizing resources while ensuring that laboratory quality standards, appropriate infrastructure, and adequate technical capacity are put in place.

Epitomized by the Call for Action from the Beijing MDR-TB Ministerial Summit, 1-3 April 2009, and underscored and supported by private industry (diagnostics and drugs) during the Seattle Pacific Health Summit, 16-18 June 2009, the global effort to scale up diagnosis, treatment and care of drug-resistant and HIV-associated TB, involving both the public and private sector, is rapidly gaining momentum. TB laboratory constraints, however, centre on cross-cutting health systems issues such as infrastructure and human resource development, and thus require a coordinated, integrated approach to laboratory capacity strengthening within the context of national laboratory strategies and plans. This in turn requires a concerted effort by all stakeholders, facilitated by a global platform for discussion, debate and knowledge sharing. The Fondation Mérieux established an Annual Forum in 2008 to provide such a platform, with the ultimate aim to improve diagnosis of infectious diseases in resource-constrained settings. These annual meetings aim to:

- Increase global awareness on the importance of diagnostics for infectious diseases
- Highlight the specific needs of developing countries
- Exchange lessons learned from ongoing initiatives
- Agree on priorities to move forward and on the respective roles of partners

The GLI and Fondation Mérieux together hosted the first Annual Forum on Moving Forward in Diagnosis of Infectious Diseases in Developing Countries in May 2008, focused on TB diagnostics and laboratory capacity strengthening. In October 2009, GLI and Fondation Mérieux are once again proud to host the Second Annual GLI Meeting, focused on expansion and acceleration of TB laboratory strengthening, using contemporary technologies in best-practice models, and guided by the most recent WHO policies.
Aim and Objectives

The meeting aims to bring together leading global agencies, international technical and funding partners, policy makers from high-burden countries, representatives from research organizations, nongovernmental agencies, patient communities and other key stakeholders working in partnership to address the challenges of diagnostics and laboratory services in TB control.

Specific objectives are to:

• Provide an update on the TB diagnostics pipeline, performance characteristics of new diagnostics and the potential for their implementation in TB control under different epidemiological and resource settings;
• Share experiences and lessons learnt on implementation of integrated laboratory strengthening activities at global, regional and country level, highlighting the benefit of innovative partnerships;
• Prioritize activities to create conditions for rapid laboratory scale-up, human resource development and improved quality management in response to the WHA call for universal access to diagnosis;
• Launch a global roadmap for accelerated laboratory strengthening through partner collaboration, resource mapping and novel mechanisms for increased country technical assistance.
PLENARY SESSION

Welcome and Opening

Christophe Longuet, Medical Director of the Merieux Foundation opened the meeting by welcoming participants to the second annual meeting of the GLI, expressing the honor to have for the second time partner with the GLI to jointly organize this years meeting wishing for a great conference and outcomes. He also explained briefly the activities of the Foundation, established 42 years ago to fight infectious diseases in developing countries by developing and making available new and affordable approaches in the field of prevention, diagnostics and therapeutics. The Foundation’s activities fall under four main categories: 1) strengthening medical and research infectious disease laboratories in developing countries; 2) training and information sharing, including “North-South dialogue”; 3) patient support programs in developing countries; and 4) applied research. This meeting was part of the Foundation’s training and information sharing activities.

Karin Weyer, WHO Secretariat of the Global Laboratory Initiative gave a short speech wishing for a successful meeting and welcome all participants and thank all the people involve in making it happen.

Hiro Nakatani, from the World Health Organization, welcome too all participants to this opportunity to get together for this initiative. Mentioning few aspects in the context of laboratory strengthening the work of WHO and the international community. In recent years shift of attention was observed from a vertical disease control efforts to a more horizontal approach of issues such as the health system and social determinants of health. But whether vertical or more horizontal approaches we are finally measured by the contribution of health improvements; thus is a natural conclusion that we most work together that we need both approaches. In terms of laboratory, this is one of the best ways to understand what is a health system that contributes in both approaches to disease control efforts. In recent years, results from diagnostic test guides the majority of the health decisions or critical to health; however, we all recognized that there are several barrier for the implementation of diagnostics of diseases of importance in low and middle income countries, such as lack of recognition of laboratories as an integral part of disease control leading to poor and unsafe laboratory infrastructure, insufficient and unfunded country level strategic plans for laboratories, inadequate number of skill lab staff, slow development of diagnostic tools and delay and slow technology transfer, insufficient and uncoordinated technical assistance at country level and this is a continuous. All of these are health system issues that are very much a concern and all initiatives planned to tackle these problems are essential as the integrated platforms for laboratory diagnostic services for various infections diseases as HIV, TB, Malaria. This is an exiting time to let all these plans as flowers bloom, for this we need to be prepared to provide universal access to diagnostics as well as for treatment of tuberculosis and integrated new tools and laboratory services.

We are glad to work with Fondation Mérieux to host this meeting to provide a place for knowledge sharing to consolidate efforts in the quest of GLI.
<table>
<thead>
<tr>
<th><strong>GLI Strategic Priorities</strong></th>
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<tbody>
<tr>
<td>• Establish GLI partnership projects</td>
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<tr>
<td>• Develop templates for country-specific roadmaps for laboratory strengthening</td>
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<tr>
<td>• Develop human resource strategies</td>
</tr>
<tr>
<td>• Develop appropriate laboratory biosafety standards</td>
</tr>
<tr>
<td>• Develop a TB lab accreditation system</td>
</tr>
<tr>
<td>• Move new diagnostics into countries</td>
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</table>
Towards Universal Access: Urgent Actions Needed to Respond to TB and MDR-TB
Mario Raviglione, WHO Stop TB Department

Latest global TB estimates - 2007

<table>
<thead>
<tr>
<th>All forms of TB</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.27 million (139 per 100,000)</td>
<td>1.77 million (27 per 100,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB (MDR-TB)</td>
<td>511,000</td>
<td>~150,000</td>
</tr>
<tr>
<td>Extensively drug-resistant TB (XDR-TB)</td>
<td>~50,000</td>
<td>~30,000</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.4 million (15%)</td>
<td>456,000</td>
</tr>
</tbody>
</table>

About half a million of cases on MDR and 150 000 deaths and about half a million deaths on TB-HIV associated.

HIV prevalence among TB cases, 2007, Global estimate: about 1.4 million TB/HIV cases and 456,000 TB/HIV deaths a year.

MDR-TB % among new cases, 1994-2007

Important to highlight that those countries in red as China, Russia etc have more than 10% of their TB cases as MDR-TB.
It is important to consider than when we speak about 10% in a Russian and / or China population this means a significant number of patients.

**Top 19 settings with MDR among new cases > 6% (1994-2007)**

<table>
<thead>
<tr>
<th>Country</th>
<th>MDR Rate</th>
</tr>
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<tbody>
<tr>
<td>Baku City, Azerbaijan</td>
<td></td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td></td>
</tr>
<tr>
<td>Donetsk Oblast, Ukraine</td>
<td></td>
</tr>
<tr>
<td>Tomsk Oblast, RF</td>
<td></td>
</tr>
<tr>
<td>Tashkent, Uzbekistan</td>
<td></td>
</tr>
<tr>
<td>Kasakhstan*</td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td></td>
</tr>
<tr>
<td>Mary El Oblast, RF*</td>
<td></td>
</tr>
<tr>
<td>Ivanovo Oblast, RF*</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td></td>
</tr>
<tr>
<td>Liaoning Province, China</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td></td>
</tr>
<tr>
<td>Armenia</td>
<td></td>
</tr>
<tr>
<td>Orel Oblast, RF</td>
<td></td>
</tr>
<tr>
<td>Henan Province, China</td>
<td></td>
</tr>
<tr>
<td>Inner Mongolia Autonomous Region</td>
<td></td>
</tr>
<tr>
<td>Heilongjiang Province, China</td>
<td></td>
</tr>
<tr>
<td>Georgia</td>
<td></td>
</tr>
<tr>
<td>Dominican Republic*</td>
<td></td>
</tr>
</tbody>
</table>

MDR – TB can follow different trends according to the country however what is known is that good care management, infrastructures and other matter are in placed to tackle MDR-TB, the disease can be contained, controlled and treated.

**Countries with at least one confirmed XDR-TB case, as of June 2009**
Treatment success on target (>85%), case detection stalling after years of expansion. The aim is to reach universal coverage of 100%, this requires improvement in the point of care, diagnostics, treatment tools and better laboratory infrastructures.

Africa: 47%; Europe 51%; East. Med: 60%
Europe: 70%, Africa: 75%, Americas: 75%

TB prevalence and mortality

The trends show to be towards achievement of the targets, although, for mortality is unlikely to achieve due particularly to the situation in Africa and Eastern Europe. On track for both in AMR, EMR and SEAR, on track for prevalence in WPR and will not be reached in AFR and EUR.
Incidence is the ultimate indicator of the TB epidemics
TB incidence rates stable or falling slowly after epidemic peaks in Africa and Europe

What are the challenges in 2009?
- DOTS not of high quality everywhere; only 63% of all estimated cases officially notified; delayed diagnosis.
- TB/HIV, especially in Africa; MDR-TB, especially in former USSR and China; XDR-TB everywhere and in Africa.
- Weak health systems and services compromising TB care; lack of bold policies on laboratory services, free access to care, drug quality, human resources, infection control, etc.
- Not all practitioners, non-state and even governmental, working at high standard; weak links public-private
- Communities often un-aware, un-involved, not mobilised
- Research not yet delivering innovative tools, and operational research often outside of the interest of TB "controllers"
The direction today is stated in the bottom mentioned documents, highlighting the following numbers:

2006-2015:
$ 60 billion necessary to control TB in endemic countries
$ 11 billion necessary to develop new tools.

New challenges require the Stop TB Strategy
The Global Plan 2006-2015 defines direction and costs
According to this graph in 2007 were 3600 MDR-TB cases out of 30,000 notified that were put on treatment under GLC standards = 1% of the estimated SS+. And this percentage has increased to about 3% of all MDR-TB being put under GLC standards. In 2009, 14,000 projected.

Though importantly about 90% of MDR-TB cases not being detected at all and this is an important failure that needs to be tackle in the diagnostics and laboratory part in the majority of the countries.

Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050

This graph portraits that the current strategy will not allow to reach the TB elimination target and there is a crucial need on new tools and set up strategies to reach these targets.
Bottlenecks to scale-up M/XDR-TB prevention and management drawn from the meeting of Global Tuberculosis Control and Patients care held in China on April 2009.

- Major gaps in TB control
- Extremely weak M/XDR-TB management and care
- Health workforce crisis
- Inadequate laboratories
- Quality of anti-TB drugs not assured
- No restriction of anti-TB drug use
- Absent infection control
- Insufficient research
- Major financial gaps

From: The Beijing "Call for Action" on TB Control and Patients Care, April 2009

62nd World Health Assembly, 2009, Prevention & control of M/XDR-TB
WHA62.15 Member States are urged to:

Achieve universal access to diagnosis and treatment of M/XDR-TB
1. Develop a comprehensive framework for management and care of M/XDR-TB, including DOT, community-based and patient-centred care.
2. Strengthen health information and surveillance systems.
3. Aim to ensure removal of financial barriers for equitable access, and protect patient's rights.
4. Make available sufficiently trained and motivated staff.
5. Strengthen laboratory systems and accelerate access to faster and quality-assured diagnostic tests.
6. Engage all public and private care providers in managing TB and strengthen primary care.
7. Ensure infection control policies developed and implemented in every care facility.
8. Ensure un-interrupted supply of first- and second-line medicines which meet WHO. PQ or strict national regulatory authority standards, and that FDC of proven bioavailability are prioritized.
9. Strengthen mechanisms to ensure that TB medicines are sold on prescription only by accredited providers.
10. Undertake effective advocacy, communication and social mobilization.
11. Establish national targets to accelerate access to treatment.

Enhance quality and coverage of DOTS in achieving targets to prevent MDR-TB
Use all possible financial mechanisms to fulfil commitments and fill funding gaps
Increase investments in operational research and R&D for new tools

Control of M/XDR-TB requires more than just TB programmes’ efforts
Policy changes are fundamental
- Remove financial barriers (UHC)
- Establish a network of labs ensuring rapid molecular tests are available
- Ensure availability of quality drugs
- Regulate the use of all anti-TB drugs
- Introduce infection control
- Promote R&D
- Mobilize resources domestically and internationally

Diagnosing and treating MDR-TB in the un-reachable is the challenge.
This slide basically just shows the importance of diagnostics within the whole activities for STOP TB.

Need for new Diagnostics at each Level of the system

When test strips became available is when we will be able to diagnose TB rapidly.
Potential impact of new diagnostics in SE Asia

LED microscopy will improve the diagnosis of TB but the impact on incidence will be limited, much better is obtained with molecular testing (in green) and major impact if we have a Dipstick at the point of care.

WHO's functions in re-tooling - Two phases
1. Norms, standards and policies - *From research and evidence into policy*
   - Expert committees, review of evidence inform STAG-TB discussion
   - STAG-TB recommends to WHO and policy is made, with guidelines
   - Dissemination to Member States, GF, UNITAID, World Bank...
   - Operational Research for adaptation and revision of policies

2. Strategies, guidance towards implementation - *From policy to practice*
   - Guidelines for countries
   - Technical assistance, training for implementation
   - Support for resource mobilization

WHO's recently endorsed technology in diagnostics
• 2007: Liquid culture media
• 2007: Rapid speciation technology
• 2008: Line-probe assays
• Future processes:
  • 2009: LED microscopy
  • 2010: Other NAAT...

The example of the Line Probe Assays from Research to Policy and Practice
1. Winter 2007-08: Evidence from literature and new study in SA
2. March 2008: WHO Expert Committee's review & recommendations
3. June 2008: STAG-TB recommends to WHO to promote LPAs
4. 1st July 2008: WHO announces a new policy recommending use of LPAs for all countries for rapid MDR-TB diagnosis
5. 1st July 2008: UNITAID announces US$ 26 million support
The way forward in laboratory strengthening – what will WHO do?
- Support the Global Laboratory Initiative secretariat
- Promote with ministries the need to strengthen labs
- Support countries in their search for financing externally (UNITAID, WB, GF, bilaterals etc) or domestically
- Coordinate with all partners to make GLI a success
- Pursue endorsement of new technology, related policy making, and transfer of technology
- Never stop promoting research into new diagnostics and the need for a point-of-care tool
- Favour integrated technology and broad laboratory network development.

Scaling Up Management and Control of Multidrug-Resistant TB – What will it take?
Paul Nunn, WHO Stop TB Department

Today there is a global epidemic of TB affecting some 9.7 million people a year, at the moment this is 95% drug acceptable with minor forms of resistance and about 5% is Multi or extensive forms of drug resistant TB.

What we are concerned about is preventing that most susceptible epidemic of TB from becoming mostly an epidemic of drug resistant TB, and what will it take to scaling up.

This is the plan, scaling up means to treat 80% of smear and/or culture-positive MDR-TB cases by 2015.

Target: Total patients to be treated over 7 years = 1.4 million

![Graph showing the cumulative response plan and what has been approved by the Green Light Committee (GLC).]

The plan for to 2009 as shown above is to treat 63000.

Global MDR and XDR –TB Response Plan

Where are we now in respect the plan? In 2009, 3% of incident cases will be treated according to WHO standards. About a similar number will be treated within the countries but not according to WHO standards, to make for about 6 or 7%.

As shown in the following graph, we can observe the cumulative of the response plan and what has been approved by the Green Light Committee (GLC).
According to the plan we are way behind but in an optimistic approach we can anticipate seeing the pattern the potential catching up over the years.

To achieve that scaling up what will it take?
- Money
- Greatly strengthened laboratories with new tools
- Infection control
- Coordination

Global Plan projections of funding required for MDR-TB, 2009–2015
MDR-TB budgets and funding, 2009

Observing the above left graph with budgets and right graph where real funding money is to be spent, there is a significant difference as there is less money spent than the anticipated budgets. (This even taking into account that data from S. Africa that was not received). Cost per patient treated
The above graph shows what the funding includes. One can observe that the cost of drugs is of major importance; also shows that the way patients are managed changes the cost incurred as observed for hospitalizations.

Costs estimated from detailed costing studies in Tomsk (Russia), Estonia, the Philippines and Peru, adjusted for pattern of drug resistance, country income level, anticipated use of hospitalization.

Funding required 2009 - 2015

The total expenditure that is believed to be necessary over 7 years is of US$16.9 billion, average US$2.4 billion per year. Much higher than existing budgets and funding.
Also the Treatment costs include not only the drugs but as shown in the below graph, the programme management, hospitalizations and second line drugs.

Reducing cost of second-line drugs and use of hospitalization would substantially lower funding requirements.

Main cost components, 2009–2015

As shown in main cost components each items include related costs as administrative controls for infection control or recurrent and capital expenditures in laboratory diagnosis that need to be considered in the global cost requirements.

Funding required by region

Most of the funding required is in Europe (total US$8.9 billion), followed by Asia (US$7.1 billion, mostly in China and India).
Over the years MDR-TB will increase funding requirements and will cover a higher percentage over the total TB expenditures.

Following a more detail analysis of the Infection control costs, 2009-2015 addressing 22 High Burden Countries plus 14 MDR High Burden Countries.

<table>
<thead>
<tr>
<th>DR or non DR</th>
<th>Predominant locus of care</th>
<th>Scenario 1 MDR Facilities only</th>
<th>Scenario 2 All TB Facilities and Community Health Centres</th>
<th>Scenario 3 All Facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR only</td>
<td>Community</td>
<td>758</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>DR only</td>
<td>Hospitalised</td>
<td>1,045</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>DR Non DR</td>
<td>Community, Community</td>
<td>n/a</td>
<td>1,088</td>
<td>3,898</td>
</tr>
<tr>
<td>DR Non DR</td>
<td>Hospitalised, Community</td>
<td>n/a</td>
<td>1,425</td>
<td>4,240</td>
</tr>
<tr>
<td>DR Non DR</td>
<td>Hospitalised, Hospitalised</td>
<td>n/a</td>
<td>1,728</td>
<td>4,546</td>
</tr>
</tbody>
</table>

Work in progress as of October 2009

The above table shows that depending on the scenario used to address TB and MDR control costs can double and triple. (number above are in millions).

The question then is: How can the required funding be mobilized?

Can patients pay?

Catastrophic health expenditure is defined as 40% of household "capacity to pay". "Capacity to pay" based on income after basic subsistence needs are met. As observed above very few countries under the horizontal bar can potentially pay, in most countries this is not possible, patients just can’t pay.
The Global Fund and UNITAID – the good news

As shown in the above graph in round 9 there is a significant increased in the amount of plain funding by the TB set of proposals.

The Global Fund and UNITAID – the sad news

NB. assumption Global Fund and UNITAID financing sustained at 2009 levels

Both institutions are unlikely to finance more than a relatively small share of the costs of MDR-TB diagnosis and treatment, unless either
a) both agencies mobilize substantially more funding and/or
b) the cost of MDR-TB diagnosis and treatment can be reduced

Can High Burden Country (HBC) governments pay?
Commission on Macroeconomics and Health (2001) suggested middle-income countries could finance 96–100% of health care needs.

High Level Taskforce (HLTF) on Innovative International Financing for Health Systems is focusing on low-income countries.

<table>
<thead>
<tr>
<th>Income Level</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Income (GNI &lt;US$ 936 per capita)</td>
<td>Bangladesh, DR Congo, Ethiopia, Kyrgyzstan, Myanmar, Nigeria, Pakistan, Tajikistan, Uzbekistan, Viet Nam</td>
</tr>
<tr>
<td>Lower-middle income (GNI US$ 936–3705 per capita)</td>
<td>Armenia, Azerbaijan, China, India, Indonesia, Philippines, Moldova, Ukraine</td>
</tr>
<tr>
<td>Upper-middle income (GNI US$ 3706–11455)</td>
<td>Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Latvia, Lithuania, Russian Federation, South Africa</td>
</tr>
</tbody>
</table>

Some aspects of Coordination

The Green Light Committee
- Started up as a Committee – to give a green light to MDR management proposals – AND prevent development of further resistance
- GLC has approved 108 projects in 68* countries with 59,142 patients approved for treatment. About 20,000 have started treatment
- Also provides technical support for proposal development, follow-up, monitoring and evaluation and policy advice to WHO, and now to GFATM
- All GF MDR proposals require the "Green Light"
- GLC ensures quality of drugs, using its own procurement agent buying from stringent drug regulatory agency approved suppliers, or WHO pre-qualified suppliers (Stream A)
- GLC will soon approve "Stream B" that allows countries to procure drugs themselves from similarly QA'ed suppliers

Some other things needing coordination
- Better information
- Involvement of the private sector
- Human resources
  - Training, planning, recruitment
- Technical support
  - Short-, middle-, long-term
  - Centres of excellence
- Matching diagnoses with treatment
- Coordinating with other disease control programmes

Conclusions
- Substantial increases in funding are required for TB control going forward
- Fund-raising strategies need much more focus on national domestic expenditure needs
- More attention needed on reducing costs of commodities and models of care
- Countries may effectively postpone targets.
Laboratory Strengthening in Response to TB Diagnostic Challenges: Achievements of the Global Laboratory Initiative
John Ridderhof, CDC & Chair GLI

The Stop TB is a partnership with participation of several workgroups as DOTS Expantion, TB diagnostics, TB/HIV, MDRTB, TB Drugs, TB Vaccines and the GLI. Everyone recognizes that this the work of partnership collectively to stop TB.

Global Laboratory Initiative – Structure and Governance

In this structure we want make sure we dont exclude anyone that is working actively on TB and that is essential on the decision making process.

The Supra National Reference Laboratory Network SRLN created is a brand for quality as assures the accuracy and the quality of the world wide resistance surveillance.

GLI core group
• Chair Dr John Ridderhof
• WHO Secretariat – Dr Karin Weyer
• IUATLD – Dr Armand Van Deun
• FIND – Dr Rick O'Brien
• CDC – Dr Tom Shinnick
• NTP/NRL – Dr Moses Joloba (Uganda)
• NTP/NRL/SRL – Dr Kai Man Kam (China)
• Observers
• Liaisons with other WGs
• *Civil society – Vijay K. Gupta
• *PEPFAR – Dr. John Nkengasong
• *USAID – Dr. Gavin Macgregor-Skinner
• *Open solicitation
• *New members
GLI core group members rotating off
• IOM – Dr Chris Gilpin
• SRL and Euro TB lab task force – Dr Francis Drobniewski (UK)
• SRL – Dr Lucia Barrera (Argentina)
• Civil society – Case Gordon

GLI Partners
– American Society for Microbiology (ASM)
– Association of Public Health Laboratories (APHL)
– Bill & Melinda Gates Foundation
– Centers for Disease Control and Prevention (CDC)
– CDC Global AIDS Programme (GAP)
– Fondation Merieux
– Foundation for Innovative New Diagnostics (FIND)
– International Union Against TB and Lung Disease
– PEPFAR
– USAID
– KNCV
– Merieux Alliance
– Management Sciences for Health (MSH)
– Médecins Sans Frontières
– National TB Programmes
– WHO
– UNITAID
– and growing …

This group of partners can be seen as a coop, as we all contribute but also get a lot by doing it; while able for instance to determine protocols and guidelines that can be harmonized to all and then dedicate more time to the actual activities.

GLI strategic priorities, developed with all the partners.
• Accelerating evidence-based policy development on diagnostics and laboratory practices
• Promoting a structured framework/roadmap for TB laboratory strengthening within the context of national laboratory plans at country level
• Developing a comprehensive set of tools, norms and standards based on international standards and best-practice
• Advancing laboratory strengthening through global, regional and local partnerships
• Developing multi-level laboratory human resource strategies to address the capacity crisis
• Accelerating new diagnostics into countries.

GLI Projects are run on behalf of GLI, and adhere to a collaborative spirit
• aligned with strategic agenda and priorities
• complementarity with other projects
• Liaison to GLI-S is established
• project review process established
• adequate partner representation requirements satisfied
• information networks utilized
GLI Guidance, Tools, Programs, this are some of the examples of tools and guidelines etc, that have been put together by different organizations.

For Instance, the TBCAP is one of the most active partners in supporting and identifying what are priority projects.

TBCAP = KNOV, RIT/JATA, IUATLD, WHO, CDC …..

An example of the tools developed from TBCAP as follows:

TBCAP Tools Completed
• Standard Operating Procedures (SOPs)
• Management Information System (MIS)
• Logistics/supply management tool
• Culture and DST training (“workshop in a box”)
• EQA training (“workshop in a box”)

TB CAP Toolbox
This TB CAP Laboratory Toolbox contains five products recently developed to support countries in strengthening their laboratory services:
1. Standard Operating Procedures (SOPs)
   Generic instructions on laboratory procedures, including: test methods, operation of equipment, laboratory organization, quality control, safety practices, and record keeping
2. Logistics/Supply Management Tool.
   Practical information on equipment specifications, recommendations on BSC installation, guidelines on laboratory commodity management, inventory control and algorithms, and spreadsheets for calculating quantities and costs of consumables.
3. External Quality Assurance package (EQA)
   Covering main areas of AFB-microscopy EQA: rechecking, panels and supervision; fluorescence; review of different AFB-microscopy techniques; AFB-microscopy training package.
4. Management Information System (MIS)
   Tools for reporting and monitoring of AFB-smears and supplies. Promotes also correct analysis, rechecking EQA important parameters, and culture internal quality control.
5. Culture & DST Package
12 modules on topics such as: bio-safety, C/DST, use and maintenance of equipment, R&R, and QM.
For more information please visit our website www.tbcta.org

TBCAP Tools
In Process
• Guidelines to purchase Lab Products (equipment specifications)
• Develop a country roadmap for laboratory strengthening
• Develop training and a manual on biosafety for laboratories

Roadmaps for TB Laboratory Strengthening
The concept of the roadmap to have national laboratory plans and all the programs working on one plan. And as new diagnostics are being developed

Assuring effective policies and plans for TB diagnostics strengthening are included in system-wide plans

Roadmaps for TB Laboratory Strengthening

Strategic Laboratory Plan

It is important to develop the consultation of experts so that we can take all the evidence from all the studies performed by the different partners involved, so that a group of experts can have that information and build common policies, recommendations and guidelines.

Recent WHO laboratory policies
• 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 level.
• Rapid speciation (2007): Strip speciation for rapid *Mycobacterium tuberculosis* from non-tuberculous mycobacteria; established at regional or central reference laboratory 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 supranational or national/central reference laboratories using standardised methodology and drug concentrations.

Available at: http://www.who.int/tb/dots/laboratory/policy/en/print.html
• In process:
  – LED microscopy as alternative for both fluorescence and conventional light microscopy (pending STAG endorsement).
  – Selected non-commercial culture and DST methods not alternatives for gold standards, but may provide interim solution (pending STAG endorsement).
Regarding EXPAND-TB
Accelerated uptake of new MDR-TB diagnostics in 27 countries, 2009 – 2013

- State-of-the-art commodities (instruments, tests, reagents) funded by UNITAID
- Leverage other local partners to address non-commodity components (infrastructure, training, etc.)
- Long-term mentoring and TA: in-country hands-on support to optimise technology and knowledge transfer, closely linked to capacity building;
- Full ownership of MOH, NTP, Laboratory
- Integrated laboratory approach (notably TB and HIV)
- Adjustment based on growing evidence (‘learning by doing’).

Recipient countries

Background: some of the milestones that has taken the dynamic of EXPAND-TB
- Initial project
  - UNITAID Board approval: April 2008,
  - Project Agreement signed: December 2008
  - 16 countries; ~74,000 patients
  - Time frame: 2009 – 2011
- Expansion project
  - UNITAID Board approval: May 2009
  - Project Agreement expected: December 2009
  - 11 additional countries; ~56,000 additional patients
  - Time frame: 2009 – 2013
- Revised Project Plan to cover 27 countries, ~129,000 patients, time frame 2009 - 2013
Biosafety Initiatives
– CDC/WHO Technical consultation, Atlanta, Sept 08
– Guidance on process, design principles and ventilation for laboratory construction and renovation (funding proposal).
– Recommendations and guidance for simple “Ventilated Workstations” for smear microscopy.
– Guidance and training on TB laboratory biosafety (TBCAP)

Global Laboratory Capacity Gap
To reach MDG targets, a global capacity need of 120 million smears, 60 million cultures and 6 million DST investigations must be met by 2015, requiring at least 6.1 billion USD by 2015;

Paris 2008 Meeting - GLI Challenges
• Majority of donor resources focused at country level
• There is no forum or structure to promote collaborations GLI, OGAC Lab WG, WHO HIV Collaborative, Polio, IDSR, etc.
• Address and promote TB technical needs and contribute to integrated systems
• Shortage of full time laboratory scientists in partner organizations to contribute to GLI---dependent on part-time volunteers.
• WHO GLI office is 3 technical staff
Harmonization of Global Support for Laboratory Strengthening  
October 28-30, 2009 Atlanta, Georgia USA  
Purposes of Meeting:  
1. To consider strategies and a framework for harmonizing approaches by international partners in their efforts to strengthen laboratory capacities and to produce sustainable laboratory systems, especially in resource-limited settings.  
2. To discuss formation of a partnership provisionally referred to as the “Global Alliance for Laboratory Strengthening.”  
3. To outline next steps for the meeting “The Public Health Lab of the Future” scheduled for July 2010: to identify a theme for the meeting, to explore topic areas where there is a need for harmonization and collaboration across programs, and to develop an agenda for what will be the first-ever meeting to look at global harmonization for laboratory strengthening.

STP-GLI as an active facilitator of communication and provider of global infrastructure services synchronized to be a coherent network service.
Session 1: Technology and Innovation to meet Public Health Needs
Chair: Rick O’Brien – FIND

Contemporary Diagnostics: Moving Towards Integrated Technology Platforms
Mark Perkins, Find

The talks explained approaches that FIND is putting together to integrate and simplify laboratory approaches across diseases. The context of this work is based on the Maputo declaration on strengthening of laboratory systems bringing some standardize approaches for laboratory service provision in the systems and technology level.

The nightmare scenario for laboratory testing is the amount of different equipment involved and the required service, maintenance and training involved. Thus moving from that towards integrated laboratory platforms that can be shared across multiple diseases reducing maintenance requirements and make them more effective.

At this time at FIND work is being done about 4 technology platforms:

- Optical or microscopy
- Growth based detection
- Nucleic acid application technologies
- Immunochromatography

For instance, regarding microscopy an integrated new generation of microscopes powered on LED technology that can be used for fluorescence microscopy as well as for other type of diagnosis as for parasites, urine samples, at an affordable price for developing countries.

Evolution of TB diagnostics in the public sector


Similar for culture, growth based detection, more integrated methods are being tested to seek more efficacy and less constraints. As shown below:


Complexity of conventional sputum decontamination in reference labs

Simplicity of MDR-XDRTB COLOUR TEST for regional labs

Combined optimizations: single-step decontamination (Vasanthakuri et al 1987), microscopic observation of growth, direct susceptibility testing for MDRTB testing & XDRTB screening, selective culture media (Mitchison et al), colour indication of culture positivity

MDR-XDRTB Colour Test for Regional Labs

1  Direct application of 2 drops to selective thin layer agar for incubation in room air for MDRTB testing & XDRTB screening

2  Colour growth detection & microscopy confirmation of morphology

3  Biosafety similar to sputum microscopy because sputum is smeared directly onto the plate which is then permanently double-sealed until autoclaving

Biosafety similar to sputum microscopy because sputum is smeared directly onto the plate which is then permanently double-sealed until autoclaving

Microscopy and culture are the two technologies most commonly used; however, other technologies are available and on the way to be more accessible in terms of use and costs.
The urgent need for a POC test

- Simple &
- Accurate &
- Robust &
- Rapid Test
- For qualitative TB case detection
- At the lowest level of health system: the health posts

What do we mean, when we talk about POC for TB:
We talk about a simple, accurate and robust rapid test, that can be performed by community health workers to diagnose TB at or near the site of patient care. At the lowest level of the health system, the health posts, where currently, patients are eventually referred to the next higher level, purely based on clinical symptoms.

Why do we need such a test:
According to the latest figures from WHO, almost half of the annual TB cases remain undiagnosed. Most of these patients are seen by their local clinic at one point. Diagnostic delays of 3-6 months fuel disease transmission and severity. According to mathematical models, a widely deployed rapid test could save 500000 lives per year.

Serodiagnosis of TB

![Figure 4. ROC curve of commercial rapid tests for the diagnosis of pulmonary tuberculosis (all patients, n=355)](image-url)
Sensitivity of selected antigens at >95% specificity level compared to healthy controls

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Europe, HIV– (n=71)</th>
<th>Africa, HIV– (n=79)</th>
<th>Africa, HIV+ (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB9.7</td>
<td>35%</td>
<td>79 %</td>
<td>91%</td>
</tr>
<tr>
<td>CFP10:ESAT6*</td>
<td>25%</td>
<td>64%</td>
<td>49%</td>
</tr>
<tr>
<td>TB10.2</td>
<td>21%</td>
<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>TB15.3</td>
<td>41%</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>TB16.3</td>
<td>55%</td>
<td>81%</td>
<td>88 %</td>
</tr>
<tr>
<td>TB51</td>
<td>31%</td>
<td>76%</td>
<td>48%</td>
</tr>
<tr>
<td>TB51.7</td>
<td>57%</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>aCry:MPT83</td>
<td>26%</td>
<td>83%</td>
<td>58%</td>
</tr>
<tr>
<td>38 kDa</td>
<td>19%</td>
<td>29%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Whole proteome screening of *M. tuberculosis* for diagnostic antigens

Integrated NAAT for TB/Rif: An update
Automated sample preparation
Amplification and detection
< 2 h

Workflow
- fully automated, with 1-step external sample prep.
- time-to-result < 2 h (walk away test)
- throughput: up to 1-48 tests / run
- no bio-safety cabinet
closed system (no contamination risk)

A technology platform for
- TB & Rif resistance
- TB Quinolone resistance
- Potential for HIV viral load

Xpert MTB/Rif: FIND Evaluation studies
Rigorous performance evaluation at 5 sites (>1500 TB suspects)
Included 2 sites with high HIV prevalence (80%) & 2 with high MDR prevalence (>30%)
By mid of last year, FIND started formal evaluation trials in collaboration with 5 partner sites aiming at a rigorous performance evaluation of this assay. The sites were reference sites with high quality standards, located in South Africa, Peru, India, Azerbaijan and Germany. TB and MDR Tb suspected patients were recruited from geographically diverse populations: The HIV prevalence was >70% at the South African sites, but low at the other sites. The culture positivity rate was particularly high at the tertiary care hospital Hinduja, in Mumbai India, and the DOTS treatment centers in Lima Peru. The MDR rates were highest at Hinduja and the State TB treatment institution for Detainees in Azerbaijan. Whereas all other settings processed sputum samples locally, the site in Azerbaijan shipped sputum samples to the German National Reference Lab for TB in Borstel for processing.

Xpert MTB/Rif: FIND evaluation studies

<table>
<thead>
<tr>
<th></th>
<th>AFB-</th>
<th>AFB+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture Positive</td>
<td>Culture Negative</td>
</tr>
<tr>
<td>MTB Detected</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>MTB Not Detected</td>
<td>7</td>
<td>171</td>
</tr>
</tbody>
</table>

Sensitivity 98.0%, Specificity 98.3%

Sensitivity for in S+/C+ = 100%, in S-/C+ = 91%

High accuracy for Rif detection
Sequencing data for discrepant results suggest Xpert correct
Role and Challenges faced by the Diagnostics Industry
Jean-François de Lavison, EDMA

PSC- Private Sector Constituency role in the partnership, structure:
It is constitute by companies involved and not involved in the field of health care but that interested in contributing to health care issues regarding TB.
• First independent evaluation in 2003-2004, recommended including NGOs and private sector on Coordinating Board.
• Constituency of >110 companies registered (health and non-health).
• PSC on Coordinating Board since October 2004 and member of the Execo since 2008.
• Active across Partnership board committees, working groups, committees, task forces.
• Participating in major Partnership activities and events.

Objectives:
• Leverage core business skills and capabilities, facilitate corporate sector participation, stimulate participation of the private sector in TB control.
• Bring business perspectives, input, expertise, and multi-faceted resources to the Partnership.

Concerning the EDMA (European Diagnostics Manufacturers Association)

EDMA Members:
-38 Corporate Associated Members (CAMs)
2006-2008
Amorfix, Arkray, Biosystems, BMD, Cellestis, Cepheid, Chiron, FIND Diagnostics, Focus, iagnostics, Genzyme, Innogenetics, Luminex, Mallinkrodt, MLT, Orion, Phadia, Philips, Randox, Sebia, Siemens, STAGO, TECAN, ThermoFisher, Tosoh.

-23 National Association Members (NAMs)
Through its affiliated National Associations, EDMA represents in total more than 500 companies (or over 700 legal entities) across Europe. Working to develop new IVD associations.
Mission is Advocating the value of Diagnostics – In Vitro Diagnostics (IVDs)
IVDs: Expense or Investment? in Health expenditures

Macro-economic data and Total Healthcare Expenditures show that:
The amount spent on IVDs out of the Total Healthcare Expenditure is less than 2% (i.e. around €20 per capita and per annum in EU15 and €6.2 in new members states) but that IVDs can influences about 64% of the medical decisions (JD. Kruse-Jarrest, Lab. Med. 18:213/1994).
In Europe, less than 10% of GDP is spent on healthcare in most countries (more than 15% for USA).

EDMA is campaigning to present laboratory testing as a valuable asset that is a cost-effective component of health maintenance and disease management. The overall aim is to ensure that healthcare resources are properly allocated and appropriately used. Laboratory testing has an important role to play in achieving this aim.

Defining & Voicing the IVD industry’s consensus position
This by the development of Key Messages & Fact Sheets highlighting the importance of diagnostics in the appropriate application of health care patient’s management and avoid expenditures on treatment and health care misused.
9 TOPICS: HIV, Cardiovascular Diseases, Diabetes, Nosocomial Infections, Tuberculosis, Cervical Cancer / HPV, Colorectal cancer, Prostate cancer, Theranostics

Also the EDMA is developing together with the American Association of Clinical Chemistry a program online where the patients himself can go to search for information regarding specific diagnostics and treatment of a given disease.

Lab Tests Online: HON-code certificate Awarded in Germany
Development of Key Messages & Fact Sheets
Global access to all sites www.labtestsonline.info

The program was presented to the European Commission at it was requested to have access of this site information accessed directly through their own website and in different languages. Today the information is available in great range of languages.

Regular participation in ongoing political and legislative processes:

Representing the industry viewpoint
IVDs Industry: Need to shape our future
TB IVD Initiative:
- Diagnostic Industry Leadership Forum (DILF) members agreed on the necessity of showing a global commitment of diagnostic industry on TB
- The EDMA ad hoc group’s main task will be identifying one or two concrete projects (Education – Advocacy) involving the IVD industry in general (and not promoting individual technology) in order to:
  1. Demonstrate that IVD testing contributes significantly to the diagnosis and treatment of TB by providing benefits to healthcare practitioners and patients
  2. Demonstrate that extensive IVD testing will be cost-effective and will improve healthcare outcomes
  3. Explain that IVDs offer an invaluable contribution to the prevention and treatment of TB
  4. Strengthen the role of Public Private Partnership (PPP)

Swiss representation: Geneva
- We need to represent all the IVDs associations and be a strong interface between diagnostic industry and inter governmental organizations (WHO, Global Fund, UNICEF,..). We need to secure an international policy environment and maximize access of IVDs to the global health initiatives in the world.
- We need to play a more constructive role in the Geneva based discussion around global health challenges. Today we are not present, it’s a lack (World Health Assembly..)

Proposals:
- Create a global non profit NGO (like IFPMA) representing the IVDs and develop a world health partnership
Only 4 years ago, estimated incidence of MDR TB (2003), this data from 2003 shows clearly that diagnosis of TB had an estimated 45% of detection and only a very small 5% of cases were diagnose with MDR-TB.
The target is to diagnose 80% of the MDR positive TB cases however the above table shows the reality. If case detection is not increased we are not going to increase our targets.

This is a great platform to understand how diagnostic technologies interact at each level, the question is how to integrate these diagnostic platforms and the opportunity to absorb new technology over the coming years.

To know that lab equipment is not the only innovations, other innovations are:
- Electronic information systems linking case-detection, cohort-analysis and procurement in all sites
- Active case-finding / contact tracing
- Infection control policies / technologies
- New drugs (and new regimens)
- Need for trials

All partners involved in a new global TB control strategy, but the same workforce

**Reality check 1: do we embrace progress made?**

Absolutely, most of us recognize opportunities
- Increased TB case detection
- Less delay to identify drug-resistance
- Diagnosis of smear negative TB
- Increased survival of HIV co-infected TB patients
- Decentralization of diagnosis of (resistant) TB
- Less false positive TB diagnosis (HIV related)
- Easier drug resistance surveillance, though we still don’t know the problem of MDR TB resistance worldwide.
- Diagnostic platforms (funding, human resources, integration)
Reality check 2: Is laboratory network design informed by programmatic vision (and realities) and epidemiological evidence?

The reality and needs in the field

- Coordination at country level often sub-optimal
- NTP and lab under different departments; parastatal and private labs
- Often many international partners doing their own project with little or not integration and coordination (no lab maintenance, no training, several different equipments provided by different institutions, etc).
- Often little integration between disease programmes
- Joint lab network planning crucial to cover and monitor
  - Estimated MDR-TB case-load
  - Actual notification: smear negative and positive TB
  - DRS data (FL and SLD-resistance in patient categories)
  - Diagnostic algorithm and programme design
  - Applications to Global Fund and other donors (diagnose and manage cases)
  - Private public mix models
  - Advocacy for Progress with developments of new technologies
  - Consensus on technical requirements: BSL 2+, 3, 2.7 ... it is fundamental to have a clear consensus of what are the requirements upon the type of lab to be build.

Reality check 3: Are programmes and partners ready to respond to the actions needed?

Actions needed:

- Overcome (natural) resistance to change with both countries and technical partners: priority-setting, NTP capacity. The resistance to change is understood as countries have made a lot of efforts to set up what is now available and have a hard time to incorporate new technologies. To support countries in this transition is necessary to think about algorithms today and now later when the new technology is already at the lab, thus to take care to:
  - Develop new diagnostic algorithms and programme design
  - Address HRD implications (human resources, training)
  - Link up with ‘strangers’ (Flu, HIV, PPM, academic setting), integrate laboratories.
- Address global second-line drug supply crisis
- Address imbalance between capacity to diagnose and capacity to treat. This is fundamental if patients are diagnose they must be treated.
- Assist national manufacturers to meet QA requirements, as is the example of China where they are manufacturers of their own diagnostic test.

Urgent need to set up country DR-TB coordinating and technical assistance mechanisms.
As observed in this graph the high majority of cases on those projects (data from 2004) were also resistant to second line drugs. Thus increasing the capacity to treat is not only difficult but costly.

The weakest link determines pace of scale-up to the 2015 Global Plan targets

It is a team work, if one of the partners cannot keep up pace we all cannot continue the pace. In order to be effective we need to coordinate our efforts, funding and the work force.

Governments
- Funding & Workforce
- Framework elements
  - lab, DRS: measure!
  - quality assured drugs
  - public private mix
  - HIV/TB cross-referral
  - information systems

STB Partnership
- Coordination and M&E !
- Donor mobilization
- Technical support models
- New tools
- Access to QA drugs

Conclusions
Excellent progress, but threat of imbalance!
- the capacity to diagnose differs from the capacity to treat, from available drugs and funding
- there is a need for a coordinating mechanism both at the global and country level that includes:
  - An overall coordinating body under the STP Board to which all the partners are to respond, with involvement of the Core Group of the MDR-TB WG and the GLI
  - Coordination within WHO (secretariats of WGs and subgroups) mirrored by coordinating bodies at national level, not only NTPs and Lab people but all partners involved.
New models required
  – aggressive technical assistance (learning by doing: need to evaluate)
  – involving private providers, public hospitals, private labs…
  – funding (global and country levels)
  – GLC procurement and GLC approval for countries that want to procure outside GDF (streams of engagement)

Show donors and countries that we (can) move
Session 2: Fast-Tracking Policy Development: Findings from Recent WHO Systematic Reviews  
Chair: Francis Drobniewski

Novel Approaches and New Methods to Increase Case Detection by Microscopy  
Karen Steingart, UCSF

The present talk has two objectives: present “hot off the press” findings from 3 systematic reviews concerning sputum microscopy and summarize the findings of the reviews using the GRADE approach.

Some relevant definitions taken from the Glossary of Terms, (The Cochrane Collaboration, Version 4.2.5, Updated May 2005)

- Systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.
- Meta-analysis is the use of statistical techniques in a systematic review to integrate the results of included studies.

Thus is possible to do a systematic review without a meta-analysis, however, a meta-analysis cannot be done without a systematic review.

Three systematic reviews were performed concerning sputum collection strategies, LED microscopy and sputum processing methods, the following questions were assessed.

- Are front-loaded and standard microscopy strategies comparable for diagnosing pulmonary TB when 2 specimens are examined?
- What is the diagnostic accuracy of LED fluorescence microscopy for pulmonary TB and how does it compare to Ziehl-Neelsen and fluorescence microscopy?
  - What do users think of LED fluorescence?
- Does bleach centrifugation increase the diagnostic accuracy of sputum smear microscopy for pulmonary TB?. The sputum processing look at several different sputum processing methods, however, the one concentrated here for the purpose of this study is bleach centrifugation;

Why carry out these reviews?

- Direct smear microscopy is the most widely available test for TB diagnosis but it suffers from moderate to poor sensitivity and high drop-out rate of patients.
- The Methods to optimize smear microscopy
  - Sputum processing
  - Fluorescence microscopy
  - Diagnostic test strategies
- High quality evidence is important for policy to be build, to further validate these methods.
Previous microscopy reviews

<table>
<thead>
<tr>
<th>Review (Date publication)</th>
<th>No. of studies</th>
<th>Median sample size</th>
<th>Principal findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum processing (2006)</td>
<td>83</td>
<td>256</td>
<td>Increase sensitivity (13%) with bleach centrifugation</td>
</tr>
<tr>
<td>Fluorescence microscopy (2006)</td>
<td>45</td>
<td>493</td>
<td>Increase sensitivity (10%) with fluorescence microscopy</td>
</tr>
<tr>
<td>Serial sputum examination (2007)</td>
<td>37</td>
<td>153</td>
<td>Only 2 - 5% increase in sensitivity with a 3rd sputum specimen</td>
</tr>
</tbody>
</table>

Since those studies there have been quite new findings in many aspects, What’s new?

- New studies
- New technique
  - light emitting diode
- New diagnostic strategy
  - “front-loaded” microscopy
- New methods of data analysis and presentation

Today is available a Standardized protocol for how to conduct systematic reviews of diagnostic accuracy published in 2008*, following the steps:

- Define review questions
- Identify and select studies
- **Assess study quality (QUADAS)**
- Extract, analyze, and present data
  - Graph results of individual studies
  - **Pooled estimates of sensitivity/specificity by hierarchical summary ROC and bivariate random effects methods**
  - Visualize and statistically assess heterogeneity
  - Explore reasons for heterogeneity
  - Forest plots, hierarchical summary ROC curves
- Interpret data


From this, it is important to highlight, first the assessing of study quality of QUADAS and second the ability statistically to look not only at sensitivity and sensibility separately but the ability to model them jointly. This give more sound estimates to provide evidence.
Quality assessment of diagnostic accuracy studies (QUADAS)

- Asks reviewers to assess 14 items
- Scores each item as ‘yes’, ‘no’, or ‘unclear’

In bold are items that are very essential as research shows that if we don’t have for instance blinding, the estimates on the QUADAS are often inflated. Hence those three items are very important to obtain in high quality.

Systematic review questions

The first question, as mentioned before:

- Are front-loaded and standard microscopy strategies comparable for diagnosing pulmonary TB when 2 specimens are examined?

Following the Sputum collection procedure

Smear preparation: Direct
Stain: Ziehl-Neelsen
Type of microscopy: Light
Reference standard: Culture

Front loaded strategy aims at collecting two specimen of sputum same day 1, unlike standard strategy where the second specimen is collected on day 2.

This can have a great impact in the patient in terms of convenience, transport and so forth, however, is this as accurate as the standard strategy?
For the above question regarding sputum collection all in Day 1, a Quality Assessment was done for (QUADAS).

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (high quality)</th>
<th>Unclear</th>
<th>No (low quality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Incorporation avoided?</td>
<td>☑</td>
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<td>☑</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>☑</td>
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<tr>
<td>Withdrawals explained?</td>
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<tr>
<td>External quality assurance?</td>
<td>☑</td>
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<tr>
<td>Selection criteria clearly described?</td>
<td>☑</td>
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<tr>
<td>Execution of index test described in sufficient detail?</td>
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</tr>
<tr>
<td>Execution of reference standard described in sufficient detail?</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

And so the black bar means that the QUADAS question is satisfied. Meaning that the studies performed on that review were very high standards.

HSROC curves

Seeing this graph one can deduct that diagnostic accuracy of both approaches seem very compatible, showing evidence that the two strategies work.
Systematic review questions
The second question, as mentioned before:

- **What is the diagnostic accuracy of LED fluorescence microscopy for pulmonary TB and how does it compare to Ziehl-Neelsen and fluorescence microscopy?**

- **What do users think?**

Following some generalities about Light Emitting Diode (LED) microscopy
Fluorescence microscopy has been shown to be more sensitive than ZN and more time efficient.

LED fluorescence microscopy uses ultra bright LED bulbs
- Less expensive
- Require less power (run on batteries)
- Very long half-life
- Lower maintenance
- No toxic components
- No UV production
- **Perform equally well without a darkroom (a very important point).**

This review find in LED fluorescence diagnostic accuracy
- Sensitivity 84% (76, 89); specificity 98% (97,99)
- Head-to head LED versus ZN
  - 6% (0.1, 13) greater sensitivity, comparable specificity (8 studies)
  - 46% less time to examine smears (14 comparisons)
- Head-to head LED versus conventional fluorescence
  - 5% (95% CI 0, 11) greater sensitivity, comparable specificity (7 studies)
  - same time to examine smears (7 comparisons)
- 94-100% of users would recommend implementing an LED system over ZN (FIND)

Systematic review questions
The third question, as mentioned before:

- **Does bleach centrifugation increase the diagnostic accuracy of sputum smear microscopy for pulmonary TB?**

Quality Assessment (QUADAS)
This result are not as good as those found in the Front Loaded studies of the first review question. Most take into account that for this review not all studies where blinded.

Forest plots, bleach centrifugation, culture reference
These are the results of the individuals studies.

Basically on the above table are the results of microscopy direct and those of microscopy after specimen has been processed with bleach centrifugation. Observing both approaches we can see that with Bleach centrifugation sensitivity goes up but for specificity is variable, further look into this is necessary. For this the speed of centrifugation was followed to observe if this affected the results outcome, results showed variability.

HSROC curves
The above curve of both techniques did not show one to be superior.

**Strengths and limitations**

- **Strengths**
  - Standardized systematic review protocol
  - Comprehensive search strategy
  - Rigorous data analysis methods

- **Limitations**
  - Variability in diagnostic accuracy estimates for sputum processing
  - Limited data in HIV-infected patients

**Concerns, in the outcome of these reviews:**

- **Front-loaded**
  - risk of TB transmission in health care settings
  - loss of morning specimen for culture
- **LED versus conventional fluorescence**
  - increased cost of EQA because of fading of slides
- **Sputum processing**
  - primary analysis presented included only studies with culture reference

**In the last part of this lecture, it was introduced:**

The Grading of Recommendations Assessment, Development and Evaluation - GRADE

*The GRADE approach provides a system for rating quality of evidence and strength of recommendations that is explicit, comprehensive, transparent, and pragmatic and is increasingly being adopted by organisations worldwide.* www.gradeworkinggroup.org

It is important to highlight that GRADE is concerned about what matter to patients, up to know we have spoke about diagnostic methodologies, technologies, in GRADE is about making sure the patient got their results, did they patient was started in treatment, etc.
GRADE and Patient-Important Outcomes

<table>
<thead>
<tr>
<th>Test positive</th>
<th>With TB</th>
<th>Without TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positive TP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Negative FN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test negative</td>
<td>False Positive FP</td>
<td>True Negative TN</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

TP - benefit from earlier diagnosis and treatment
TN - spare patients unnecessary treatment
FP - likely anxiety, possible morbidity from additional testing and treatment; may halt further diagnostic evaluation
FN - increased risk of severe disease from delayed diagnosis; continued TB transmission in the community

GRADE Summary of Findings - Microscopy

<table>
<thead>
<tr>
<th>Review Question (studies, participants)</th>
<th>Absolute Difference per 1000 persons (Prevalence 20%)</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard versus two-specimen front-loaded (7, 7308)</td>
<td>2, 0, 0, -2</td>
<td>Moderate</td>
</tr>
<tr>
<td>LED versus ZN light (6, 20155)</td>
<td>16, 0, 0, -16</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bleach centrifugation versus direct (9, 3923)</td>
<td>18, -16, 16, -18</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

Rapid Culture and Drug Susceptibility Testing using Non-Commercial Methods
Jessica Minion, McGill University

The present talk will give the outcomes of systematic reviews based on non commercial methods. Based on the two important drawbacks as it is that TB case detection is very low and that TB drug resistance is indeed a problem.

WHO Current Policy Recommendations
- 2007 Liquid medium for culture and DST (Drug Susceptibility Testing).
- 2008 Line probe assays for rapid MDR-TB screening

Along with those policy recommendations there have been initiatives to expand access to these diagnostics both trying to lower the cost and trying to build infrastructure. Meaning that
we are still in the phase of capacity building to provide the diagnostic devices, methods and labs infrastructure to accomodate for the changes.

Is there an intermediated method that can be implemented to accomodate for this transicion phase.

Are there non-commercial options for detection and DST that could serve as temporary solutions during capacity building?

In 2009, some of these options were evaluated as follows:

- Microscopically Observed Drug Susceptibility (MODS)
- Thin Layer Agar (TLA)
- Nitrate Reductase Assay (NRA)
- Colorimetric Redox Indicators (CRI)
- Phage-based Assays (including FAST Plaque™)

Review Question

“To perform systematic reviews of the literature and meta-analysis (where appropriate) of data examining the diagnostic accuracy and performance characteristics [of the assay] for the detection of drug resistance in MTB”.

Microscopically Observed Drug Susceptibility (MODS)

- Direct or indirect inoculation of patient specimens for detection & DST
- Liquid media – increased sensitivity and faster growth
- Microcolony detection – faster turnaround time
Results of Systematic Review (MODS)
(n = stands for number of studies)
• 9 studies were performed
  ? 6 direct inoculation
  ? 3 indirect inoculation

• Overall (Rifampin, n=8)
  ? Sensitivity = 98.0% (94.5, 99.3)
  ? Specificity = 99.4% (95.7, 99.9)

• If more stringent exclusion criteria (n=5)
  ? Sensitivity = 98.7% (89.4, 100)
  ? Specificity = 100% (95.8, 100)

• Out of the 6 studies that use direct inoculation - Direct only (n=6)
  ? Sensitivity = 96.8% (92.4, 98.7)
  ? Specificity = 99.0% (94.3, 99.8)

• Contamination Rates (n=7)
  ? MODS: 6.3%
  ? vs. solid media comparisons: 10.4%
  ? vs. liquid media comparisons: 4.1%

• Turnaround Time (n=6)
  ? Direct Inoculation: 11.6 days (range 6 – 21)
  ? Indirect Inoculation: 6.5 days (range 6 – 7)

Turnaround time is one of the aspects that seems to be more beneficial from these methods.

Thin Layer Agar (TLA)
• Direct or indirect inoculation of patient specimens for detection & DST
• Solid media instead of liquid – easier to manipulate
• Microcolony detection – faster turnaround time

Results of Systematic Review (TLA)
• 3 studies identified
  ? 2 direct inoculation
  ? 1 indirect inoculation

• All reporting 100% accuracy
• Contamination Rates (n=9)
  ? TLA: 11.8%
  ? vs. solid media comparisons: 5.5%
  ? vs. liquid media comparisons: 9.7%

• Turnaround Time (n=2)
  ? 11.1 days (range 11 – 11.2)

Nitrate Reductase Assay (NRA)

• Based on MTB’s ability to reduce nitrate to nitrite
• Simple, direct or indirect inoculation of patient specimens for detection & DST
• Sensitive detection of small amounts of metabolic biproduct improves turnaround time

KNO₃-containing media _______Add reagent to drug-free slant at day 7 (repeat day 10, 14)_____
Color development = growth

Results of Systematic Review (NRA)
• Overall (n=20)
  ? Sensitivity = 97.0% (95.0, 98.0)
  ? Specificity = 100% (99.0, 100)
• Direct only (n=5)
  ? Sensitivity = 96.0% (92.0, 98.0)
  ? Specificity = 99.6% (98.7, 100)
• Contamination Rate
  ? 4.8%
• Turnaround Time
  ? 7 – 14 days

Colorimetric Redox Indicators (CRI)

• Based on reduction of indicator by metabolically active MTB
• MIC determination using microdilution
• Sensitive detection metabolic activity improves turnaround time
Incubate microdilution plate 7 days

Add indicator to all wells, incubate overnight

Color change = growth

Results of Systematic Review (CRI)

- Overall (n=31)
  - Sensitivity = 98.0% (96.0, 99.0)
  - Specificity = 99.0% (99.0, 100)
- Direct only (n=2)
  - Sensitivity = 90.0% (68.3, 98.8)
  - Specificity = 100% (98.7, 100)
- Contamination Rate
  - 5%
- Turnaround Time
  - 7 days

Mycobacteriophage Assays: FAST Plaque™, in-house amplification, in-house luciferase reporter phage (LRP)

- Uses bacteriophage viruses to infect and detect viable MTB
- Amplification approach or luciferase light production
- 2 day turnaround time, direct or indirect detection & DST
Results of Systematic Review (Phage)

Overall (FAST Plaque™, n=15)
- Sensitivity = 95.0% (91.5, 97.1)
- Specificity = 95.3% (91.1, 97.6)

Overall (in-house amplification, n=11)
- Sensitivity = 98.7% (96.3, 99.6)
- Specificity = 98.2% (94.9, 99.4)

Overall (LRP, n=8)
- Sensitivity = 99.6% (35.6, 100)
- Specificity = 99.4% (93.4, 99.9)

Direct only (n=5, FAST Plaque™ only)
- Sensitivity = 93.0% (88.0, 96.7)
- Specificity = 96.3% (91.6, 98.4)

- Large range of contaminated or indeterminate results: 0 – 36% (mean = 5.8%)
- Primarily a problem for studies using direct specimens: 3 – 36% (mean = 20.4%)
  - 18 out of 28 arms using indirect specimens did not report any contaminated/indeterminate results
- 3 studies with arms using antibiotic supplement (NOA) showed decreased contamination by 36 – 94%
  - No statistically significant difference in accuracy
## Summary Findings

<table>
<thead>
<tr>
<th>Diagnostic (Reference)</th>
<th># Studies (Participants)</th>
<th>Pooled Accuracy Estimates from Meta-Analyses</th>
<th>Turnaround Time (direct)</th>
<th>Contamination Rates (direct)</th>
<th>Quality of Evidence</th>
<th>Costs (as per NDWG)</th>
<th>Resources (as per NDWG)</th>
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<tbody>
<tr>
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<td>Sens</td>
<td>Spec</td>
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<tr>
<td>MODS</td>
<td>9 studies (n=1474)</td>
<td>0.980</td>
<td>0.994</td>
<td>11.6 days</td>
<td>6.3%</td>
<td>Moderate</td>
<td>Equipment: ++ Consumables: ++</td>
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<td></td>
<td></td>
<td></td>
<td>Training: extensive Infrastructure: ++/+++</td>
</tr>
<tr>
<td>TLA</td>
<td>3 studies (n=439)</td>
<td>1.00</td>
<td>1.00</td>
<td>11.1 days</td>
<td>11.8%</td>
<td>Low</td>
<td>Equipment: ++ Consumables: ++</td>
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<td></td>
<td>Training: extensive Infrastructure: ++/+++</td>
</tr>
<tr>
<td>Phage – FASTPlaque</td>
<td>12 studies (n=2945)</td>
<td>0.950</td>
<td>0.953</td>
<td>1 – 2 days</td>
<td>20.4%</td>
<td>Very Low</td>
<td>Equipment: ++ Consumables: +++</td>
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<td></td>
<td>Training: moderate Infrastructure: ++/+++</td>
</tr>
<tr>
<td>CRI</td>
<td>31 studies (n=2498)</td>
<td>0.980</td>
<td>0.990</td>
<td>7 days</td>
<td>5%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
</tr>
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<td></td>
<td>Training: moderate Infrastructure: +++</td>
</tr>
<tr>
<td>NRA</td>
<td>19 studies (n=2304)</td>
<td>0.970</td>
<td>1.00</td>
<td>7 – 14 days</td>
<td>4.8%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Training: moderate Infrastructure: ++/+++</td>
</tr>
<tr>
<td>WHO-endorsed rapid test for DST (for comparison)</td>
<td></td>
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<tr>
<td>LPA</td>
<td>12 studies (n=4937)</td>
<td>0.981</td>
<td>0.987</td>
<td>1 – 2 days</td>
<td>Moderate</td>
<td></td>
<td>Equipment: +++ Consumables: +++</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Training: moderate Infrastructure: ++/+++</td>
</tr>
</tbody>
</table>

### Concerns and Issues

- Lack of data on outcomes other than accuracy (specificity and sensitivity)
- Quality of primary studies
  - ? Case control vs. Cross-sectional designs
  - ? Convenience sampling vs. Consecutive/Random
  - ? Retrospective vs. Prospective data collection
  - ? Reporting of blinding
- Non-commercial methods generally suffer from lack of standardization
- Large scale demonstration studies have not been performed, and are not likely to be performed
- Limited data using direct patient specimens, even though this would be the most important application
- Setting of implementation? Peripheral vs. central laboratories
- Biosafety concerns
- Specificity of species identification is not available with these tests.
Ensuring Adequate Laboratory Biosafety
Tom Shinnick, CDC

As we know, one of GLI's strategic priorities is to develop appropriate laboratory biosafety standards.

Biosafety is the application of a combination of administrative controls, containment principles, laboratory practices and procedures, safety equipment, and laboratory facilities to enable laboratorians to work safely with potentially infectious microorganisms.

Why is Biosafety Needed in the Tuberculosis Laboratory?
Risk of infection with *Mtb* is higher for TB lab workers than for other lab workers:
- 1.4-fold higher for TB microscopists
- 21.5-fold higher for DST technicians
Infection often results from unrecognized production of infectious aerosols and can also occur from needle sticks, through broken skin, etc.

Administrative Controls
- Supervision by an experienced scientist
- All personnel are well trained, proficient, aware of hazards, follow rules
- Routine medical surveillance
- Biosafety and operations manuals
- Emergency plans for spills, accidents, etc.
- Appropriate facilities and safety equipment

Good Laboratory Practices include
- Restrict or limit access when working
- Biohazard warning signs
- Prohibit eating, drinking and smoking
- Prohibit mouth pipetting
- Minimize splashes and aerosols
- Decontaminate work surfaces daily
- Decontaminate wastes

Containment: within the laboratory there are two sorts of activity containment.
Primary Containment: protect worker and immediate laboratory environment: good microbiologic techniques, safety equipment, facility design.
Secondary Containment: protect the environment outside the laboratory: facility design, waste management, etc.

Biosafety Level (BSL)
Conditions under which an infectious agent can ordinarily be safely handled. These conditions are a combination of: laboratory practices and techniques, safety equipment, laboratory facilities.

Usually a BSL is agent and procedure specific, generic BSLs are available for many infectious agents however the procedure-specific BSLs is often missing.
GLI Biosafety Projects is to develop a BSL agent specific for TB.

1. Biosafety guidance for TB lab procedures
   Started with the Technical consultation in Sept. 2008 followed by Expert meeting in April 2009 and WHO and CDC were the lead agencies.

2. Specifications for a ventilated work station suitable for direct AFB-smear microscopy
   Expert consultation in Sept. 2009 and CDC and APHL were the lead agencies.

1. Biosafety Guidance
   Consensus recommendations for minimum biosafety requirements for
   AFB-smear microscopy
   Culture
   Drug-susceptibility testing
   Molecular testing
   Based on a risk assessment for each TB diagnostic procedure
   generation of infectious aerosols
   concentration of bacilli in those aerosols

Direct AFB-Smear Microscopy
Limited risk of generating infectious aerosols
- Work can be done on an open bench
  • separate bench for smear-preparation
- Facility: adequately ventilated enhanced BSL1 or basic BSL2 laboratory
  • natural or mechanical ventilation; 6–12 ACH
  • directional airflow
- Proper disposal of infectious material

Processing Sputum Specimens for Smear, Culture, Molecular Tests
Risk of generating infectious aerosols during centrifugation and specimen manipulation.
- Work with specimens should be done in a biosafety cabinet (BSC)
  • BSC class I or II may be used
- Facility: adequately ventilated BSL2 lab
  • directional airflow; 6–12 ACH
- Use aerosol-containing rotors or buckets
- Proper disposal of infectious material

Processing Cultures for Smear, ID, Subculture, DST, Molecular Tests
High risk of generating infectious aerosols during manipulation of liquid suspensions
- Work with cultures should be done in a BSC
  • class I or II BSC may be used
  • certified at least annually
- Facility: adequately ventilated BSL3 or enhanced BSL2 laboratory
  • directional airflow; not recirculated
- Use aerosol-containing rotors or buckets
- Proper disposal of infectious material
BSL3 – Secondary Containment
BSL2 secondary containment plus:
• Controlled access to a separate area
• Double door entry
• Single-pass air; 6-12 air changes/hour
• Enclosures for aerosol generating equipment
• Room penetrations sealed
• Walls, floors and ceilings are water resistant for easy cleaning

If a facility does not have all required BSL3 features (e.g. sealed penetrations, solid ceiling), an acceptable level of safety for conducting routine procedures, including culture, may be achieved in a BSL2 facility providing:
• Directional inward airflow is maintained and exhaust air is discharged to the outside
• Access to the laboratory is restricted when work is being performed
• The recommendations for BSL3 practices, procedures, and safety equipment are rigorously followed.

Next Steps for Work Group
• Finalize guidelines
• Distribute guidelines

2. Specifications for a ventilated work station suitable for direct AFB-smear microscopy

Why is a Ventilated Work Station Needed for Direct Microscopy?
Risk of Mtb infection with is 1.4-fold higher for TB microscopists than non-TB workers
Potential need for increasing BSL
• Increased vulnerability of HIV-infected staff
• Decreased treatment efficacy (M/XDR TB)
• Increased exposure (unreliable airflow)

Class I and II BSCs are expensive and require annual maintenance

What is Done in The Work Station: Open sputum cup, Smear (disposal sticks/loops, re-usable loops w/ flame/micro-incinerator), Air dry, Close sputum cup, Disposal of sticks, heat fix?, Stain?.

Objectives of Expert Consultation
- To assess the need for ventilated work stations in resource-limited settings
- To provide guidelines for design, materials, and construction of work stations
- To provide guidance on validating the recommendations to ensure the safety, reliability, and integrity of the work stations.

Issues Addressed
- General requirements to reduce risk of infection with AFB smear microscopy
- Balance need for safety with unintended messages about AFB smear microscopy
- Appropriate vs. non-appropriate use
  • not intended for TB culture, TB DST
- A guideline is not a standard and certification will not be available
Recommendations made for Minimum Requirements

- Materials
- Ergonomics
- Electric Components
- Design
- Validation
- SOP Checklist

Next Steps for Work Group

- Prepare report of expert consultation.
- Prepare guidelines in simple language suitable for an international audience detailing instructions how to construct a work station.
- Prepare specifications for materials, ergonomics, electric components, design, validation, and SOPs.

Implementation of New Diagnostic Approaches and Methods: Operational Considerations

Lucia Barrera, SRL, Argentina

As it has been shown earlier in this meeting, there are new proposed methods to increase case detection of TB and MDR TB,
- LED Microscopy
- MDR TB rapid screening by
  - Nitrate reductase assay (NRA)
  - Colorimetric redox indicators (CRI)
  - Line probe molecular assays (LPA)
- Rapid culture and drug susceptibility testing (DST) in (automated) liquid culture.

Adoption and selection of methods should be based on the analysis of initial investment but also on other issues such as:

- existing resources and organization of the laboratory network in the countries
- users acceptance and technical know-how
- long-term guarantee of: basic logistics, recurrent budgeting, maintenance of laboratory infrastructure/biosafety/equipment, quality of laboratory results.

Long-term interventions is needed to fight TB thus long-term sustainable diagnostics are needed in this fight. The issue is that long-term sustainability of new diagnostics has yet to be demonstrated in tuberculosis endemic areas.

In the meantime, fast growth of rapid diagnosis demand should be satisfied following a careful risk-benefit analysis of alternative approaches.
LED microscopy
The technology does not originate novel risks and can be employed in the biosafety level required for conventional microscopy.

Guidance on Bio-safety related to TB laboratory diagnostic procedures
Geneva, Switzerland 8-9 April 2009

Regarding Equipment
LED microscopes /attachments are available from several manufacturers that have already created a commercial space in the developing world. Gradual incorporation of this shared platform seems to be feasible during the processes of: continual renovation of microscopes/accessories and expansion of microscopy capacity.

Performance of LED modules depends on quality of the microscopes to which they are attached.

Regarding Supplies
Reagents are easy to procure
Quality of auramine is less variable than that of fucshin, which is an advantage
Stability of auramine solutions under field conditions has been questioned and should be further evaluated.

The critical point of LED microscopy seems to be the intensive training and QA activities are essential requirements for these technology; technicians are generally unfamiliar with fluorescence microscopy in developing countries.

Global guidance for fluorescence microscopy EQA is still required though challenges are the instability of stained smears upon prolonged storage and slides restraining practices.

Considering Rapid DST
MDR TB rapid screening by
– Nitrate reductase assay (NRA)
– Colorimetric redox indicators (CRI)
– Line probe molecular assays (LPAs)
Rapid first and second line DST in (automated) liquid culture systems.
Addressing common barriers for rapid DST implementation:
All these must be addressed before the implementation is taking place at the countries.

- The main constraint is the poor basic logistics connecting the DST laboratory to the health system.
- The availability and use of proper forms to identify patients that will benefit from the new test
- The appropriate shipping and labelling
- The regular transportation of specimens/isolates.
  - Contamination resulting from delays, it is relatively more critical for methods employing liquid media.
  - Reduce bacilli viability might result in invalid or even false results
- Telecommunication systems and information networking.

- Laboratory infrastructure / biosafety: Improvement is needed in most laboratories performing culture and/or DST in developing countries.

- To follow the Guidance on Bio-safety related to TB laboratory diagnostic procedures
  Geneva, Switzerland 8-9 April 2009

- Lack of policy and programme for health surveillance of laboratory personnel in developing countries, policy must be stablished
  Baseline assessment (tuberculin skin test)
  Medical history
  Monitoring of tuberculin skin reaction, respiratory signs & symptoms

- There are not clear actions to Incident and accident response
  Chemoprophylaxis
  Appropriate medical investigations
  Response after accidents with MDR or XDR strains is a matter of concern as they are not clearly stablished

- Established beliefs: there are no urgencies associated to tuberculosis, Inexorably DST results require at least 4 months since specimen is collected.
- Capacitation programmes should address not only technical issues but also basic topics such as: distinction of urgent cases/specimens/isolates and translation of delays introduced by batching, infrequent inspection of cultures and late communication of results to patient outcome.

- Choosing methods and the appropriate response in a particular scenario. If sustainability of high standards of biosafety is not ensured, the use of methods using liquid culture and eventually microplates should not be encouraged, as this is linked to high risk of aerosol creation, eventual spillage while handling repeatedly microtiter plates that are not tightly sealed.

- There is basic equipment for reagent preparation and specimen processing (water distiller, refrigerators, freezer, electronic balance, vortex mixer, centrifuge, BSCs, UPS, autoclave), but there are other type of equipment use for specialized methods mainly commercial.

<table>
<thead>
<tr>
<th>In-house methods</th>
<th>Commercial methods</th>
</tr>
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<tbody>
<tr>
<td>NRA</td>
<td>Liquid culture systems</td>
</tr>
<tr>
<td>Incubator</td>
<td>Automated system for incubation and growth detection</td>
</tr>
<tr>
<td>Inspissator</td>
<td></td>
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<tr>
<td>or 80 °C incubator (for media preparation)</td>
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### Approaches to increase DST capacity

(according to population, MDR-TB burden, geographical extension, accessibility) the DST can be established in one central lab or in several selected intermediated labs as shown below.)
Screening of MDR-TB by rapid methods does not eliminate the need of standard DST:
Screening of MDR-TB should diminish hands-on time in laboratory networks and running costs (if performed by an inexpensive method) compared to standard DST offered to all patients at risk of drug resistance.

Supply logistics for the NRA method:
- Reagents and consumables are: nonproprietary products, relatively cheap, locally available from several manufacturers/suppliers.
- All chemicals have long shelf-life, even in solution and are stable to temperature fluctuations during transportation and storage (except for antibiotics).
- Centralization of procurement and preparation of media/reagents is possible and may be convenient when NRA is performed at the intermediate level of the network.
- Refrigeration is required for delivery.
- Re-usable glass-tubes may be employed.

Supply logistics for (Automated) liquid culture-based tests and LPAs methods
- Reagents and consumables may be not available in scenarios performing conventional methods on egg-based media, but they should be easy to obtain from local suppliers. (some difficulties with NALC and alamar blue).
- Media and reagents procurement create dependence on one manufacturer and probably on one local supplier.
- Some antibiotics and media enrichment requires refrigeration during transportation.
- All chemicals have long shelf-life

Authorization
Importation and implementation of commercial tests require approval/registration & licensing processes.
In many developing countries these processes are not required for the introduction of in-house assays if they are endorsed by the NTP and the NRL.

Human Resources
The workload dedicated to each method is different as seen bellow
These assay characteristics are critical in health institutions where:

- Budgets are extremely low.
- Shipping and customs logistics are complex and time-consuming.
- Support for importation does not exist or is inefficient.
- Local distributors may be reluctant to license/import new items especially in markets that are not attractive.
- Cost of reagents may be 2-5 higher than catalog price.
- Procurement is unreliable and unstructured leading to stock-outs of key supplies.
- Special storage conditions are not available.

Technical considerations
Commercial tests employ simpler procedures
- Reagents/media are almost ready-to-use
- LPAs sample preparation is simple; culture-based methods require suspension dilutions
- Reading of MGIT tubes is simple

In house culture-based methods require repeated addition of reagents LPAs require meticulous interpretation.

It is important though to consider that the introduction of very sensitive methods (culture in liquid media/molecular tests) may result in high frequency of (cross) contamination and even misdiagnosis in some scenarios such as poor experience/implementation/manipulation of high proportion of positive specimens).

NRA is very easy to implement in scenarios using the proportion method on LJ and the nitratase test.

Important questions are:
-Which is the best low-cost and rapid ID method to complement DST rapid culture-based tests in low-resourced laboratories?
-Are commercial lateral flow tests for speciation of *M tuberculosis* applicable to complement in-house assays?
-Are they affordable in low-resource scenarios?
-Does an additional tube containing PNB work?

Regarding QC/QA
Internal quality control of drug-containing media and reagents.

(Automated) liquid media systems and CRI
Rigorous IQC is costly and impractical (media is prepared for each test plate-to-plate/tube-to-tube variation may occur).

NRA LPAs
Daily IQC tests may not be necessary, testing standard drug-sensitive/resistant strains with each new batch of media/reagents may be sufficient.

External quality control
No particular procedures need to be introduced at country or supranational level to evaluate regularly the competence of laboratories performing new culture-based methods.
Special panels of strains carrying different mutations are to be used for LPAs proficiency testing.
A Global guidance and support for the introduction of rapid DST would be helpful

Guidance for:
- Matching the choice of an appropriate method with strategies of NTP resources that are available and/or sustainable (even after withdrawal of donors support), laboratory level, and personnel skills.
- SOPs development
- Inclusion of the newly endorsed assays in the WHO training package for culture and DST of tubercle bacilli.
- Development of standardized protocols for validation at country level.
- EQA through on-going SRLs PT exercises.

Additional operational research would be helpful for
Comparative evaluation of alternative tests for rapid screening of MDR-TB
- Implementation and labour costs
- Feasibility of implementation in settings without DST and culture facilities
- Cost-effectiveness, impact on patient management
- Long-term sustainability

This under/ out of the umbrella of demonstration projects.
Essential Components of Integrated National Laboratory Plans
John Nkengasong, CDC-GAP

The above graph shows that for any support program in any given disease there aren't that many laboratory services as Serology, CD4, Culture etc.....however to implement them correctly within a Laboratory system, requires many aspects to run well within the laboratory systems as Quality, training, equipment etc to allow for the strengthening and sustainability of the lab systems thus to enable for the laboratory services.

Thus any of the intersections shown in the above graph represent a challenges to enable correctly laboratory services in different context.

Integration of the labs systems and services to address the needs of different diseases are a challenge since funding is given upon disease portfolios and thus comes from separated channels. There are silos of National Reference Laboratories where disease-specific laboratories are a common practice

There is a network of Neglected National Laboratory Systems where the NRL is in good condition but the regional and district laboratories are completely neglected.
An Era of Increased Resources: As many different donors have come together to fund projects and initiatives on public health including laboratory issues. Is this an Opportunity or a Challenge? Generosity can be a burden if this represents a risk of emergence of parallel lab networks.

This can happen if we don’t coordinate our efforts to enable for best usage of funding.

The above paper emphasize that strengthening the systems for the given infectious disease this strengthens the national healthcare systems and vice versa if weakened.

Thus is necessary as shown in the following graph, to establish country national policies in adaptation with the national strategic lab plans for an integrated laboratory approach; today the issue is that most countries do not have policies in place.

The following declaration was issued to support the integration of laboratory platforms, to tear down the walls between disease-specific laboratories

**The Maputo Declaration on Strengthening of Laboratory Systems**

Call on national governments to support laboratory systems as a priority by developing a national laboratory policy within the national health development plan that will guide the implementation of a national strategic laboratory plan. Governments should establish a department of laboratory systems within the Ministry of Health.

Call on national governments with support of their donors and partners in resource-limited settings to develop national strategic laboratory plans that integrate laboratory support for the major diseases of public health importance including HIV, tuberculosis, and malaria.
Diseases of Public Health Importance Whose Surge in Funding Can Drive Overall Laboratory Strengthening Efforts

National Strategic Plans Should Integrate Major Diseases

- Malaria
- HIV
- Tuberculosis
- Polio, Influenza
Since the Maputo Declaration many countries have established their National Laboratory Strategic plans and policies.

**Guidance for Development of National Laboratory Strategic Plans**

Produced with the collaboration of:

WHO-AFRO
WHO-GENEVA
U.S. Centers for Disease Control and Prevention
The Association of Public Health Laboratories
The American Society for Clinical Pathology
The Bill and Melinda Gates Foundation
The Clinton Foundation
The Global Fund
Development of National Strategic Laboratory Plan in PEPFAR-Supported Countries

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<th>Country</th>
<th>Country Engaged in Discussion</th>
<th>Coordinating &amp; Technical Committees Formed</th>
<th>Strategic Plan Developed</th>
<th>Strategic Plan Implemented</th>
<th>Strategic Plan Progress Reviewed &amp; Evaluated</th>
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After the plans have been built and policies set the challenge lies in the implementation.

Laboratory Network Guidance: A document issue to:
- Focuses on how to enhance multi-disease laboratory networks

For the laboratory plans to work is necessary that:
- Policy Makers and Managers Make it happen, the action of decision makers to allow for the train to move on.
- The integration of laboratories, strengthened Laboratory Infrastructure for HIV/AIDS is being use to combat other diseases as Reference Laboratory for HIV, TB, AI and Malaria.
- Training, Mentorship, and Retention Strategies
WHO AFRO Laboratory Accreditation – A Step-Wise Approach Towards Quality Improvement

It is important to acknowledge than none of this strategies would be really possible without partnership and commitment mentorship from the different institutions to make it happen.
As mentioned earlier by Dr. Raviglioni the global TB estimates 2007 and the significant proportion of cases of MDR TB being undetected.

<table>
<thead>
<tr>
<th>All forms of TB</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
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<td>9.27 million</td>
<td>1.77 million</td>
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<td>(139 per 100,000)</td>
<td>(27 per 100,000)</td>
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<td>Multidrug-resistant TB (MDR-TB)</td>
<td>511,000</td>
<td>150,000</td>
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<td>Extensively drug-resistant TB (XDR-TB)</td>
<td>50,000</td>
<td>30,000</td>
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<tr>
<td>HIV-associated TB</td>
<td>1.4 million</td>
<td>456,000</td>
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Overall problem: it is that the MDR-TB diagnostic and treatment levels under WHO - GLC standards care still far too low.

In regards of TB Laboratory scale-up

It is driven by

- Case detection moving towards universal access
- HIV-associated and drug resistant TB
Challenged by

- Weak health systems
- Inadequate human resources
- Insufficient programmatic and managerial capacity
- Inadequate infrastructure (biosafety)
- Problems of availability and access
- Slow technology transfer
- Lack of recognition of laboratory importance in TB control, weak communication between NTPs and laboratory services

There is an acceleration in recent developments:

- At least 20 new technologies in various stages of development and evaluation
- Distinct target areas for drug-resistant TB being addressed
- WHO policy formulation
  - Liquid culture, rapid speciation and line probe assays endorsed by WHO 2007-2008;
  - LED microscopy and selected non-commercial culture and drug susceptibility testing methods expected in 2009
- Expanded access to new diagnostics and laboratory strengthening

Why a Roadmap for TB?

Process that constructed the roadmap

- May 08: GLI CG meeting
  - GLI strategic objectives defined
- May 08: 1st annual GLI meeting
  - Consultant findings on stakeholder interviews and country fact finding visits
  - Break-out group discussions to identify gaps and next steps
- Oct 08: Dedicated TBCAP funding
- Oct 08 - Jun 09:
  - Conceptual framework defined
  - Country case studies pursued and common themes identified
  - Stakeholder interviews continued
  - WHO policy recommendations incorporated
- Jun 09 – Aug 09
  - Intensive revision by Writing Committee, GLI CG and external laboratory experts.

Purpose and scope of a roadmap

- **Structured framework** for TB laboratory strengthening based on WHO-GLI norms and standards, documented best-practices at country level, growing lessons from the field ('learning by doing')
- **Generic document** encompassing managerial, operational and technical aspects of TB laboratory strengthening within the context of national laboratory strategic plans. Main challenged of this document is to maintained updated as the scenarios changed. This document will be customized to be adapted at country level.
• Broad user base including NTP and NRL managers, technical agencies, donor agencies, implementing partners, programme budgeting and planning officers
• Living document, responsive to changes in TB diagnostic landscape and WHO policy frameworks
• Supported by resource list for tools and technical procedures

Roadmap capture all core elements:
• Laboratory infrastructure and maintenance
• Equipment validation and maintenance
• Specimen referral and transport mechanisms
• Policy framework for implementing new TB diagnostics
• Laboratory commodity and supply chain management
• Laboratory information and data management systems
• Laboratory quality management systems
• Laboratory human resource development

The following of the present talk will be based on point for of the core elements:

Policy framework for implementing new TB diagnostics

A Stepwise approach: this is as many countries cannot suddenly move from nothing to a universal access for this a step by step approach is required.

Policy change at country level, must consider first what is already there in the countries at try to work with what is found there towards improvement, this based on
  • Local epidemiology (TB, HIV, MDR-TB)
  • NTP priorities for case detection (risk groups)
  • Laboratory networks and capacity
  • Laboratory staff resources and skills base
  • Treatment policies for drug-resistant TB
  • Financial resources

Expansion of laboratory services based on
  • Tiered system (peripheral, intermediate, central)
  • Available technologies
  • Ancillary laboratory needs related to specialised treatment (eg. ART, second-line anti-tuberculosis drugs)
    – General microbiology, biochemistry, haematology, etc.
  • Integrated approach: important to realize that for HIV related TB is not only about diagnostics capacity but of the lab capacity to perform the test necessary

The following in the stepwise approach is the process that is followed:

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
  – Initiation of 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, supplies
- Validation of new tools and laboratory performance
- Adjustment of NTP policy based on local data

Phase 3: Impact assessment
- Continued mentoring, technical support and oversight
- Assessment of impact on NTP outcomes

Expansion of labs will have little value if we dont measure if it actually makes a difference for patients treatment and disease outcomes, thus as part of this process we need ongoing technical and oversight support and mentoring.

Together with the policy there is a need for a _Analytical process among NTPs and NRL to:
Quantify or estimate TB, TB-HIV and MDR-TB burden
Identify and target patient risk groups, eg.
  • Treatment failures
  • Non-converting patients
  • HIV+ individuals
Quantify or estimate diagnostic need to identify cases
  • 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 diagnosis and monitoring
  • Ancillary laboratory tests
Laboratory algorithm
Starts at the country level and uses the:
- Screening policy for suspects
- Microscopy services as entry point
This slide shows what are the advantages in terms of time safe:

**MDR-TB diagnosis using conventional 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 liquid culture and DST**

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

MDR-TB diagnosis after 3 to 5 weeks

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

- Microscopy: 24h
- Line probe assay: 24h
- Liquid culture: 2-3w
- 1st line DST: 1-3w

MDR-TB diagnosis after 3 to 5 weeks

**XDR-TB diagnosis using conventional solid culture and DST**

- Microscopy: 24h
- Solid culture: 6-5w
- 1st line DST: 3-4w
- 2nd line DST*: 3-4w

*Method not validated or standardised

XDR-TB diagnosis after 12 to 16 weeks

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

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

XDR-TB diagnosis after 4 to 9 weeks

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

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

XDR-TB diagnosis after 4 to 9 weeks
Policy considerations that national programs have to make

- Current technologies not mutually exclusive. There is not magical to change completely prior technology.
  - Conventional culture capacity required for SM- specimens
  - Conventional DST capacity required to detect XDR-TB
- Liquid culture and line probe assay as gold standards, to be phased in without loss of existing culture and DST capacity
- LED microscopy as alternative for both fluorescence and conventional light microscopy (pending STAG endorsement)
- Selected non-commercial culture and DST methods not alternatives for gold standards, but may provide interim solution (pending STAG endorsement).
Session 4: Expanding and Accelerating Laboratory Services through Innovative Pathnerships  
Chair: Paul Klaster

UN definition of “capacity”:
Capacity is the process by which individuals, organizations and society develop abilities to perform functions, solve problems and set and achieve goals premised on ownership, choice and self-esteem.

Key features of capacity building
1. Capacity should be treated as a goal in its own right, not merely as a means for achieving other development objectives;
2. Capacity strengthening should address the three dimensions of capacity: human, organizational and institutional capacity;
3. Supply, need and demand factors shape capacity constraints and capacity strengthening opportunities and outcomes.

Three dimensions of capacity

-Human capacity
Individuals with skills to analyze needs, design and implement strategies, policies and programs and monitor

-Organizational capacity
Groups of individuals bound by common purpose, clear objectives and internal processes, systems, staffing and other resources to achieve them

-Institutional capacity
Formal rules and informal norms that provide the framework of goals and incentives within which organizations work (societal context).

Laboratory capacity strengthening

Human capacity
- Pre-service training
- In-service training
- Post-graduate training
- Training materials
- Consultancy

Organizational capacity
- (Q)-management
  - SOPs
- Implementation of new Dx (platforms)
- Monitoring and evaluation
- Facilities
  - biosafety

Institutional capacity
- Country lab policy
- Accreditation and certification bodies
LabCap – International Laboratory Capacity Building Program
Keith Klugman, Chair- American Society for Microbiology (ASM) International Board

American Society for Microbiology (ASM) – is the oldest & largest life science organization in the world -1899-2009; with membership >43,000 worldwide (30% reside outside US)

The ASM International Board - mission is to ensure that ASM continues and expands its global activities in the field of microbiological sciences.

ASM International Board Committees
• International Education Committee (IEC)
• International Membership Committee (IMC)
• International Laboratory Capacity Building (LabCap) Committee

How LabCap began
• Resulting from a 2005-signed four-year cooperative agreement between ASM and CDC’s Global AIDS Program (GAP), ASM International Board fostered the creation of the International Laboratory Capacity Building (LabCap) Program
• Primary objective of LabCap – to assist CDC with improving laboratory diagnosis of HIV-related opportunistic infections in PEPFAR-funded countries
• In 2006 LabCap invited to support two PEPFAR African countries – Namibia and Zambia

Where LabCap is now
LabCap activities currently include 4 separate programs with differing funding mechanisms:
• Technical support to the CDC’s GAP & PEPFAR Initiatives
• Technical support to the CDC’s Global Disease Detection’s International Emerging Infections Programs (IEIP) – assisting with lab strengthening for the diagnosis of respiratory disease
• USAID-funded ASM-PATH (Program for Appropriate Technology in Health) Collaboration in India – assisting Indian Intermediate TB Reference Labs with obtaining national accreditation for performing TB culture and DST
• USAID-funded TB Indefinite Quantity Contract (IQC) led by PATH - providing extensive support to USAID operating units in the implementation of their TB control and prevention programs through the introduction and expansion of the components of the WHO-recommended STOP TB Strategy

LabCap is now – in 15 different countries, on 3 different continents – soon to add 4 more countries this year (DRC, Ethiopia, Guyana, and Vietnam).

What LabCap is doing
- TB lab strengthening
- Basic micro lab strengthening
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Major Collaboration – Case Study – Cote d’Ivoire (CI)

In line with GLI objectives – CDC-CI and ASM are leading a first-time multi-organizational collaboration in Côte d’Ivoire to improve TB diagnostics.

-Key partners involved: CI MOH (NTP, NTRL,NAP), ASM, CDC, FIND, WHO, UNITAID, EGPAF, BD, ACILT, CDC Lab Coalition Partners.

-Objectives – Partner coordination on the following key aspects:
  - AFB smear microscopy training & EQA
  - AFB smear microscopy specimen referral system
  - Implementation & training on TB liquid culture, DST, and molecular assays
  - Upgrading infrastructure of TB culture labs
  - TB infection control
  - Formulation of national strategic plan for the public health laboratory – including TB, HIV, Malaria, & other diseases
  - Integration of infectious disease laboratory services

-Achievements
  - Assisting MOH with development of National Laboratory Strategic Plans & Policy – CDC-CI, ASM, CDC Lab Coalition Partners
  - Near final upgrading of NTRL into a BSL3 facility – CDC-CI, ASM, EGPAF, FIND/UNITAID
  - Guidance on establishing national EQA for AFB microscopy – ASM
  - Preliminary plan for national specimen referral system – BD
  - Training & follow up technical assistance/mentoring plans for TB liquid culture, DST, and line probe assay – ACILT, ASM, BD & FIND
  - AFB smear microscopy technical assistance at largest regional TB facilities - ASM
  - Establishing of an MOU between FIND/UNITAID and CI MOH enabled by CDC-CI

-Challenges
  - Slow establishment of in-country Technical Working Group
  - Lapses in communication amongst Partners, now resolved with the identification of an in-country lead (CDC-CI) through which all communication is fielded
  - Funding mechanism set-up does not allow for much flexibility

New LabCap Developments

  - LabCap renewed a five-year cooperative agreement with CDC’s GAP
  - LabCap is participating in the newly developed WHO-AFRO accreditation scheme for public health labs in Africa
  - LabCap is developing standardized, customizable training packages containing modules based on LabCap’s field-tested best practices & enhancing the current structure of the LabCap mentoring program.
  - MOU signed with Universidad Peruana Cayetano Heredia (UPCH) –
    - Establishing additional South-to-South collaborations involving the sharing of evaluated, culturally appropriate, and highly effective strategies and programs
    - Fostering the expansion of Centers of Excellence as international and/or regional centers for quality assurance and training by providing both access to ASM educational and scientific resources and linkages to LabCap partners
  - LabCap continues to promote partnerships to maximize coordination of international lab capacity building efforts and optimize resource leveraging.
New ASM International Board Developments

- ASM International Board offered recommendations to the **Institute of Medicine (IOM) Committee on the US Commitment to Global Health**; report was released May 20, 2009 –
  - Recommendations included increased global support for the establishment and strengthening of quality-assured, integrated national public health laboratory networks as integral components of overall health systems in resource-limited and transitional countries
- ASM renewed its **formal relationship with PAHO/WHO**
- ASM has agreed to publish in its **Clinical Microbiology Reviews (CMR)** an article on TB diagnostic capacity building in resource-limited countries
- ASM has now extended discounted membership & resource opportunities to individuals from **mid-tier economy countries**; lower-tier continue to receive free membership & essential resources

PEPFAR and Laboratory Integration

**John Nkengasong, Chief - International Laboratory Branch, Global AIDS Program, CDC**

Laboratory System Strengthening Allocations by the Global Fund and PEPFAR

[Figure 1: Direct funding of health systems through Global Fund grants](#)

[Figure 2: PEPFAR planned investments in health-systems-related programmes and bilateral programme support in 15 countries in 2009](#)

Piot P et al 2009

Global Fund for AIDS, TB, Malaria
PEPFAR II $500 M in 2009

Number of PEPFAR-Supported Laboratories in Selected Countries as of September 2008 (N= 1,917)

PEPFAR Laboratory Program is a Critical part of Health Systems Strengthening Mission: To support countries to strengthen sustainable, integrated laboratory systems to provide quality diagnostic services for effective implementation of prevention, surveillance and treatment programs across diseases (HIV, TB, Malaria, OIs).

Strengthened Laboratory Infrastructure for HIV/AIDS is being use to combat other diseases: Reference Laboratory for HIV, TB, AI and Malaria

African Centre for Integrated Laboratory Training at NHLS/NICD Johannesburg

Vision

- A healthier Africa through quality laboratory practices that support efforts to combat major infectious diseases.

Mission

- To provide integrated hand-on training courses to expand laboratory capacity in Africa for diagnosis and monitoring of major infectious diseases including HIV, TB and malaria.
Partners in implementing TBCAP- the Tuberculosis Control Assistance Programme
Maarten van Cleeff, Director TBCAP

What is TB CAP?
Tuberculosis Control Assistance Program 2005-2010

- USAID’s main mechanism to support TB control
- Budget $169.8M
- Worldwide with Global, Regional and Country focus

Implemented by the Tuberculosis Coalition for Technical Assistance (TBCTA)
KNCV Tuberculosis Foundation: Prime partner.

8 TBCTA partners

Focus on 5 priority areas
1. Increased political commitment for DOTS
2. Strengthened and expanded DOTS
   - Lab strengthening
   - MDR and Infection control
3. Increased Public Private Participation
4. Strengthened TB/HIV coordination
5. Improved Human Resource Capacity

Focus on 5 priority areas
‘Core funds’: USAID Washington
   - Strategic policies, tools, global think tanks

‘Regional funds’: USAID regional bureaus
   - African, E&E

‘Mission funds’: USAID country missions
   - “proof of the pudding”
Key ‘Regional’ lab. projects
- Establishment of TB Supra National Reference Laboratories (SNRL) in Eastern Africa: Uganda and Tanzania
- Centre of Excellence for PMDT: Rwanda
- Guidelines and training on Infection Control including lab settings

Key ‘Core’ lab. projects
Toolbox with Lab tools + Dissemination
- SOP for smear, C/ST
- EQA training materials
- Guidelines for purchasing laboratory products
- MIS tools for TB laboratories
- (Roadmap)
- (Biosafety Manual)

Support GLI secretariat
Enhance functioning of SRLs in Africa

HRD
- C/DST courses
- Trained 40 lab consultants

**USAID**
*Dr Gavin Macgregor Skinner, Senior Laboratory Advisor for Tuberculosis*

USAID TB Priority Countries

<table>
<thead>
<tr>
<th>Category</th>
<th>Countries</th>
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<tr>
<td>Tier 1 (20) (64% of global burden)</td>
<td>Afghanistan, Bangladesh, Brazil, Cambodia, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Philippines, Russia, South Africa, Tanzania, Uganda, Ukraine, Zambia, Zimbabwe</td>
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<td>Tier 2 (20)</td>
<td>Angola, Armenia, Azerbaijan, Bolivia, Djibouti, Dominican Republic, Georgia, Ghana, Haiti, Kazakhstan, Kyrgyzstan, Malawi, Mexico, Namibia, Peru, Senegal, Southern Sudan, Tajikistan, Turkmenistan, Uzbekistan</td>
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Countries in italics are High-Burden Countries.

GLI Roadmap—TB Laboratory strengthening elements
- Laboratory infrastructure and maintenance;
- Equipment validation and maintenance;
- Specimen transport and referral mechanisms;
- Management of laboratory commodities and supplies;
- Laboratory information and data management systems;
- Laboratory quality management systems;
- Appropriate, adequate strategies and funding for laboratory human resource development.
DTLab - A Dutch partnership on worldwide strengthening of TB laboratory services
Linda Oskam, KIT – Royal Tropical Institute

DTLab (Dutch Tuberculosis Laboratory partnership) provides technical and system-services for international TB-control.

KIT - Royal Tropical Institute
  – quality laboratory systems and technologies

KNCV - Tuberculosis Foundation
  – linking TB control with laboratory systems

RIVM - National Institute for Public Health and the Environment
  – reference laboratory and technologies

Good quality and evidence-based laboratory services are mandatory for effective and efficient TB control.

Objectives
• Advocate the role of TB laboratory services in TB programs
• Improve the quality of national laboratory networks for sputum smear microscopy
• Strengthen the capacity to deliver reliable culture and DST services
• Strengthen managerial capacity of NRLs
• quality management, procurement, MIS, planning, biosafety
• Support the introduction of innovative diagnostic tools
• Support operational and translational research on laboratory issues.

Local ownership and sustainability are crucial to our approach.
Specific DTLab strategies

- Delivering leadership to international working groups
- Facilitating quality laboratory services
- Delivering services in line with the Stop TB Strategy
- Services based on state-of-the-art evidence
- Capacity building through pre-service and in-service training and knowledge exchange
- Use of existing tools as well as innovative lab and IT techniques.

How does DTLab work?

- One contact point for every client
- Client sends needs request to DT Lab front office
- One proposal from the three partners together
- Tailor-made proposal on how to address the needs
- Both technical and managerial support
- Advisors from the partner institutions or their network
- DTLab does not have funding available, but can advice clients on how and where they might find funding for our services.

Conducting Operational Research to Optimise New Tools and Approaches
Armand Van Deun, The Union

What is the value and need for operational research

- To define place and value of new tools
  - capacity limitations: is not everywhere same
  - differences between countries & within countries
  - yield: patients put on effective treatment / cured. Finally what does it help the new diagnostic tools.

Its a given method or diagnostic tool going to bring more patients towards effective treatment?

- Study requirements and pitfalls
  - “peripherals”: there is a need for a supply system, quality assurance...are they working right?
  - robustness and sources of error. Techniques might be very accurate but does not mean that this will be the case at the country sites and the basic conditions in the field.
  - cadre: strategies and algorithms

Advantages for Operational Research

- Oftentimes is more feasible to do operational than high level research for countries and partners
  - low-budget
  - lower expertise requirements
- Ownership, operational research is a
  - good way of introducing a new technique, tools
  - or early way for problem-solving
- Boosts job satisfaction
  - even without remuneration
Problems for Operational Research

- Conduct limitations
  - control lost more easily
    - low budget
    - difficulty to reach if happens in the field, maybe multi-centric
  - gold standard: i.e. culture?? To understand clearly what is the gold standard of reference.

- Credibility
  - can’t always be fully documented

Example: LED fluorescence microscopy

- First stage: proof of principle
  - evaluation in a SRL: proving that was not inferior to HBO
- Second stage: field application
  - performance under less ideal conditions
  - user acceptance
- Third stage: questions around application
  - best instrument?
  - best stains?
    - bulk preparation, shelf-life and distribution questions
  - EQA system?

Session 5: The Supranational Reference Laboratory Network – Time for Change and Innovation

Chair: Kai Man Kam
Co-Chair: Bereneice Madison

Achievements of the SRLN, 1994 – 2009
Armand van Deun, SRL Coordinating Centre, Belgium

SRL network: current status
- Little change since 1994
- Very few in low-income
- Map and database

http://glitblabs.blogspot.com

Selection and certification
- Original group: historical links WHO/Union
  - later too little formal: needs, opportunities,....
  - minimal requirements
    - participate in rounds
    - support at least 2 countries
      - TOR between country and SRL
- FAQ: how do we become a SRL?
  - unofficial status, no funds; yet much desired
  - certification process ill-defined
    - assessment visit
    - good scores in min. 2 successive rounds
Achievements
• Mainly: standardised use of DST (first-line)
  – annual rounds of proficiency testing among SRL

  Started second-line drug proficiency testing
  – rounds 14 & 15
  – looks quite good
    • Cm more problematic (some labs)
    • Km, Ak, Ofx: at par with FLD
    • but so far few resistant strains included

Regional networks and PT
  – European Task Force; L. American network; WPRO

Individual links SRL- NRL
  – incomplete and unclear
    • recent survey: 19/51 countries in Africa report 1 or more links
    • SRLs report 96 country links (duplicates excluded); variation+++
  – functionality? mainly DST and DRS

Ad hoc links: DR surveys
  – panels
  – limited TA and rechecking
Research
Has been very limited

RMP borderline strains
  – obvious problem from rounds
  – 9 volunteer SRL; special panel of strains
    • particular mutations: MICs close to the breakpoint
    • systematically missed by BACTEC
    • Importance? needs further research

Limitations
  • Few SRL in the south (Africa! Francophone!)
  • Links: organisation and continuity
  • Scope of the activities
    – support to existing / candidate SRL
    – SRL not supporting other countries
      • & support to countries often too narrow
    – operational research needs not addressed

Obstacles
  • Lack of a clear plan
  • Lack of TOR / enforcement
  • Lack of funding
    – salaries: additional staff needed to provide support
    – larger scale panel production, rounds conduct
    – TA visits, meetings
    – ad hoc operational research
  • Lack of suitable SRL (candidates)?
    – low-income: in-country needs still huge
    – industrialised: appropriate expertise; language
Beyond 2009: Changing the Role and Scope of the SRLN
Chris Gilpin, IOM

What should be the role the SRLN?
• The SRL network should provide technical assistance to countries in establishing national policy on culture and DST
• Build a cadre of skilled laboratory personnel
• Implement quality assurance mechanisms for smear microscopy, culture and Drug Sensitivity Testing (DST)
• Assist with implementation of new tools
• Ensure regular Drug Resistance Surveys (DRS)
• Provide laboratory support for MDR-TB diagnosis and treatment monitoring.
• Assist countries with operational research

What is good about the SRLN?
• 29 Laboratories across all six WHO regions
• The biggest technical resource of the GLI ...but is under utilised!!
• Laboratory network with excellent technical capacity and expertise
• Has good demonstrated proficiency in DST
• Has laboratory facilities for training
What is NOT so good about the SRLN?

- Concentration of SRLs in Europe.
- Only two SRLs in Africa.
- Not enough SRLs linked to francophone countries.
- Overlap between SRLs supporting different countries.
- Technical assistance not well co-ordinated.
- Some countries are not linked to an SRL.
- Not all SRLs have expertise in building microscopy networks in resource limited settings.
- The in-country support is not evenly shared across the SRLN.
- Some SRLs support several countries while others do not support any country.
- The level of technical support provided to countries by each SRL differs widely.

Funding the SRLN?

- Funding provided for the co-ordinating centre to perform DST QA for the SRLN.
- Limited quality assurance activities are funded through WHO regions as APWs.
  - Not uniform across all regions
- No funding for implementing or quality assuring new diagnostic tools.
- All SRLs indicate that despite capacity to expand existing activities funding is needed.
- Need for global co-ordination to avoid duplication of efforts.

The way forward

- Prioritise the SRLN as an essential component of TB laboratory strengthening efforts within WHO.
- Facilitate formal links between SRLs and NRLs.
- Develop clear TORs for the SRLs.
- Assist SRLs to develop work plans for sustained co-ordinated technical assistance and capacity strengthening beyond QA for DST.
- Build capacity in country for the establishment of new SRLs.
- Provide global co-ordination.
Strengthening TB laboratories through quality assurance and co-ordination

Locations of the SRL

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Session 7 & 8: Group Session - Scaling Up TB Laboratory Services at Country Level - Tackling Laboratory Strengthening into the Future
Chair: Vijay Gupta, GLI Core Group Community Representative
Co-Chair: John Ridderhof, CDC & GLI Chair

Each group discussed the following questions on each theme:
What are the three key activities necessary at country level to move forward?
What are the key barriers and possible solutions?

Group Presentations
Group I
Developing country policies and national plans for introduction of new TB diagnostics
Facilitator: Armand van Deun, Institute of Tropical Medicine, Belgium
Rapporteur: Tom Shinnick, CDC

Three Key Activities
• Engage countries to develop country-specific strategies with assistance from consultants, experts, WHO, GLI, etc
• Conduct needs assessment for each country
• Develop guidance on how to select which technologies to use and how to implement

Barriers
• Lack of knowledge of best uses of new technologies; impact on TB control and health system; how to implement and incorporate into country-appropriate plans
• Clinicians uncertain how to use results
• Lack of resources; sustainability
• Availability for long-term TA and guidance
• Availability of training tools and strategies
• Lack of engagement and coordination of all stakeholders, implementing partners, donors, WHO.

Solutions and Way Forward
• GLI to provide general guidance, roadmaps, ...
  • Best uses of technologies, testing algorithms, evidence basis, quality control and assurance, best practices, lesson learned, resource needs to implement and sustain
• Develop mechanism to coordinate assistance
• Develop cadre of long-term consultants to work in country to assist in assessments, planning, training, implementation
  • Lab capacity building/health sector strengthening
• Stepwise deployment, monitoring and evaluation
  • Operational research: effectiveness, feasibility, cost
• Prequalification of tests and equipment
• Training and capacity building at lab level

Group II
Coordinating and optimizing technical assistance for laboratory strengthening at country level.

Facilitator: Zhao Yanlin, China
Rapporteur: Gavin MacGregor-Skinner, USAID

Activities
• 7 common elements to lab strengthening
• TOR/SOW/Trip Reports
• Sustainable short, medium, long term TA
• Incentivize TA
• Reagent rental (lease and maintenance agreements)

Barriers
• Who, what, when, where
• Political will/leadership/advocacy/decision making
• Time and money
• Consultants and trainees – standardize training
• Loss of skilled staff
• Not utilizing non-TB resources and programs

Solutions
• Promote ownership
• Everything readily available/customize
• Networks, associations at all levels (tiered)
• Core competencies/skill sets/roles for consultants/lab staff
• Innovative approaches to training/mentor
• Portal for all TA e.g. GLI website
• Fellowship programs for next generation.
• Innovative coordination – lab steering group, sub regional, country, GANTT chart, calendar.
Group III
Measuring the impact of laboratory strengthening at country level
Facilitator: Gerrit Coetzee, South Africa
Rapporteur: Catherine Mundy, Management Sciences for Health

Key activities to move forward
• Assess the current stages of all essential systems (Infrastructure, Supply chain, QMS, HRD, Referral networks, LIS, Equipment maintenance) and use findings to identify requirements to meet country policies/plans/strategies
• Formulate specific output indicators and regularly measure progress (e.g. Patient access to lab services, No of patients tested/diagnosed, No of sensitive /resistant strains, No of labs accredited)
• Formulate impact indicators - Links between lab services, clinicians and patients (e.g. No of patients started on treatment, Client/stakeholder uptake and satisfaction)

Challenges
• How can we integrate/involve/capitalize the Private Sector?
• How can we ensure that countries have the capability, systems and accountability to collect, analyze and report data?
• How can we ensure that the information is used and acted upon?

Solutions
• Engage policy makers and stakeholders throughout
• Engage effective PPM (e.g. Egypt, Indonesia)
• Provide appropriate resources (funding, tools, HR and training)
• Ensure vertical and horizontal communication; make use visualizing tools (e.g. GIS).

Next Steps
John Ridderhof, CDC & GLI Chair

• Partnership
  – Accelerate and create technical WG activities (emphasize HR, accreditation)
  – Assure active/inclusive forums, finalize core group governance.

• Diagnostics
  – Expert consultations = WHO policies
  – Systematic reviews for the evidence base
  – Practical issues/reality check, operational research, country models/experience

• National laboratory plans for TB
  – Support national plans and develop TB roadmap (draft for feedback)
  – Strengthen partner coordination, country ownership

• SRL
  – TORs, shipping, M&E, accreditation.
  – Business plan and resource strategies to support and expand SRLs and activities.