

**Stop TB Partnership**



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To Fight AIDS, Tuberculosis and Malaria



THE  
**STOP TB**  
DEPARTMENT

***Promotion and Rationalization of Operational Research  
Activities in TB control***

**Workshop Report  
11-12 May 2010, Geneva, Switzerland**

**Objectives of the workshop:**

1. To identify research priorities in Operational/Implementation Research for improved TB control, with the view to contributing to the development of an International TB Research Agenda
2. To address the translation gaps for implementation of current and innovative technologies and service designs for TB control
3. To update the Operational/Implementation Research part of the Global Plan to Stop TB 2006-2015

**Methods:**

The workshop relied on a series of thematic *sessions* identified as key areas where evidence is lacking for proper implementation of current or novel technologies and novel service delivery models at the Expert Group Meeting in February 2010. In each of these thematic sessions, a broad overview of the situation was first presented by a designated speaker, followed by short presentations by 1 or 2 discussants who addressed key points and issues. These were followed by all group discussions in which participants were expected to identify the *gaps* and describe the *expected OR activities* to be carried out in order to improve programme activities with present tools and interventions and enhance uptake of new tools and interventions. For each of the thematic areas, participants were to define: (i) what research was needed, (ii) at what level (local, national, or multicountry/international), (iii) in which timeframe (short, medium or long-term), and (iv) the methods to be used. A designated rapporteur summarized the propositions from the audience and gave full feedback to the whole audience on the second day.

**DAY 1:**

The meeting was opened by Marcos Espinal, Executive Secretary, STP, who insisted on the importance of improved TB control to reach the objectives of the Global Plan to Stop TB and on the need to address gaps that hamper the improvement of interventions for TB control and uptake of new tools. There is a paucity of research to help countries developing their own guidelines for optimal TB control, and there is a need of evidence-base recommendations to be formulated on what does work and what does not work in TB control. Christian Lienhardt (CL) then described the Objectives of the meeting and presented the process currently undertaken by the Stop TB Partnership to revise and update the Global Plan to Stop TB. He also introduced the TB Research Movement (RM) that has been launched by the Stop TB Partnership and WHO.

***Session 1: From local to global scale: the spectrum of operational/implementation research***

After reviewing briefly the existing definitions of OR, CL showed how OR, in its broad sense, covers a *spectrum of research activities*, from local setting-oriented research to international policy guiding research. He observed that the type and scale of OR is largely dependent on the objectives of the research and its expected level of *impact*, that determine the relevance, replicability and generalisability of the results. On one end of the

spectrum, local setting-oriented research aims at improving local management and practices through audit-like approaches and local hypothesis generating studies (often qualitative but using properly defined methods). In order to ensure generalisability and replicability, local hypothesis testing studies would require significant attention to important methodological details (hypothesis, definitions, design, data collection, management and analysis, etc) and input from epidemiologists and statisticians, so as to be relevant well beyond the local setting. Other disciplines such as economic evaluation might also be useful. On the other end of the spectrum, is measurement of the impact of new interventions, or collection of information to guide international policies, for which capacity building is important to understand the different sorts of evidence needed and how reliable they might be.

Then, Frank Cobelens and Sanne Van Kampen showed the results of a Systematic Reviews (SR) of OR projects conducted on the areas of (i) clinical algorithms for diagnosis of smear-negative TB, (ii) implementation of IPT for contacts of TB cases, and (iii) implementation of IPT in HIV infected persons. These SR showed the variability of studies done and the variability of their results, and showed the difficulty to define criteria for relevance and generalisability of results. Furthermore, they showed clear gaps in OR with regard to their potential to inform policy decision, and the need for a coordinated action at global level.

### **Session 2: Funding Operational Research**

Jacqueline Bataringaya reviewed the GF-supported programmes and the place of OR in GF grants. Presently, within GF grants, OR is budgeted as part of M&E and is to the scale of 5-10% of the grant. Jacqueline presented the perspective for the GF in the near future, that include: (i) establishing a curriculum on OR in collaboration with key partners (WHO, IAS, PEPFAR, UNAIDS, WB); (ii) the development of a joint OR information system to make OR outcomes transparent and widely available; and (iii) the design of multi-centric OR proposals as part of GF multi-country application. She presented some key questions to moving forward (do we have a coordinated effort to mobilize funding for OR in TB control?), as well as some opportunities, such as PEPFAR Phase II, that states that "study proposals submitted in response to the FY2010 Public Health Evaluation call for concepts are encouraged to focus on bringing evidence into practice to improve service delivery and outcomes".

Then, participants examined the need for OR in 5 selected areas (see Report of the Expert Group on OR - 22<sup>nd</sup> February 2010):

- Access, Screening and Diagnosis of TB
- Developing sustainable collaboration with all practitioners for TB care and control.
- TB/HIV: prevention of TB in HIV patients and combined HIV and TB treatment
- Treatment of DS and M/XDR-TB: optimal access and delivery, community participation
- Capacity Building

### **Session 3: Access, Screening and Diagnosis of TB**

*see the Session specific reports in Annex*

**Session 4: Developing sustainable collaboration with all practitioners for TB care and control.**

*see the Session specific reports in Annex*

**Session 5: TB/HIV: prevention of TB in HIV patients and combined HIV and TB treatment**

*see the Session specific reports in Annex*

**DAY 2:**

**Session 6: Treatment of DS and M/XDR-TB: optimal access, delivery and community participation**

*see the Session specific reports in Annex*

**Session 7: Capacity Building**

*see the Session specific reports in Annex*

**Engaging in the Health Systems Research Agenda:**

Diana Weil (WHO/STB) and Shenglan Tang (WHO/TDR) stressed on the need to engaging health system research, so as to address potential constraints in the areas of management capacity, policy & regulation, service delivery, as well as drug and diagnostics logistics/supply systems. Financing systems (patient costs, social protection), as well as Human resources aspects need also to be considered. Links with potential institutions involved in HSR were presented. The challenge is also to understand the relationships between community and their health systems, which relates to locate situations.

Then, the rapporteurs from each session presented a feed-back and summary of the presentations and discussions, highlighting the potential OR priorities to be addressed in each of the thematic areas, categorized according to the level they have to be addressed (i.e. locally, nationally or internationally) and their expected timeline (short, medium or long-term). Discussions went on for each of the thematic areas - for example, the need to link what is taking place at local and international levels for IPT for PLHIV, or the need to link several countries to address issues related to implementation of new diagnostics recommendations and interventions. Participants agreed that the OR priorities identified have to be carried out at various levels and that these are not mutually exclusive. Novel and creative thinking is needed to address gaps between policy recommendation and implementation, from the local needs to the larger frame. There is scope for wide cooperation on this, as exemplified by the TUG initiative that groups countries from Eastern Europe to address issues related to the use and implementation of new diagnostics (supported by TDR, The Union and the Global Fund).

Finally, Mario Raviglione closed the meeting, emphasizing the importance of OR to improve TB control, and placing it into the larger context of the Stop TB Strategy. He mentioned the

importance of developing an Agenda for OR in TB that will be integrated into the overall international Research agenda that the Research Movement is presently developing and that will be shared with all major stakeholders.

**Next steps:**

The OR priorities identified in the 5 thematic areas are fully described in the Annex. They will be shared with the larger group of the Stop TB Partnership Working Groups for comments and amendment as appropriate.

The outputs of this workshop will serve the following 3 objectives:

1. Inform the update of the "Global Plan to Stop TB" in terms of OR activities to be carried out over the next 5 years;
2. Inform the GF on the necessity to carry out concerted OR projects within the frame of their support to countries;
3. Be included in the International TB Research agenda that is being prepared by the TB Research Movement

**Christian Lienhardt  
TB Research Movement  
10<sup>th</sup> June 2010**

***Annex 1: Operational Research Priorities identified in the areas of***

1. Access to screening and diagnosis of TB
2. Developing sustainable collaboration with all practitioners for TB care and control.
3. Prevention of TB in HIV patients and combined HIV/TB treatment
4. Treatment of Drug-susceptible and M/XDR-TB: optimal access, delivery and community participation
5. Capacity Building for Operational Research

## **I. Improving Access, Screening and Diagnosis of TB**

Andrew Ramsay, Afranio Kritski, Maarten Van Cleeff, Gillian Mann, Anne Detjen

**Goal of the session:** To identify and prioritize operational research needed to improve access to and use of diagnostic services, to increase early TB case-detection and improve the diagnosis of DS-TB, M/XDR-TB and TB/HIV

### **Rationale:**

TB control in most endemic countries relies heavily (if not solely) upon direct sputum smear microscopy, as this is the only simple test that can be used below reference laboratory level. Currently, however, only about 60% of all infectious TB cases are being detected with this test, and a proportion of those detected (i.e. listed in the laboratory registers as having at least one positive smear) do not come back to the clinic after submitting the first specimen, so do not receive appropriate treatment. In addition, among the estimated half a million cases of MDR-TB globally, only a tiny fraction are identified and treated appropriately. From the diagnostic perspective, this is largely due to services not being accessible to patients. Diagnostics services for drug-resistant TB are based on complex technologies that require sophisticated biosafe laboratories with highly-trained staff, and so are rarely available outside of national reference laboratories. As transport of specimens from the periphery to the centre is problematic, services are usually non- or dysfunctional. Similarly, since direct smear microscopy is less sensitive in HIV-associated TB, further testing using complex technologies in sophisticated laboratories is needed to reliably diagnose HIV/TB. New simple inexpensive tools are needed to identify the various forms of TB (including drug-resistant and HIV-associated TB) at the lower levels of health services. Current assessment of the present diagnostics pipeline suggests that these tools will not be available within the next 5 years. However, the WHO has endorsed the use of at least 10 new diagnostic tools (technologies or approaches) since 2007 that, if used wisely, could facilitate considerably TB control. There is, however, insufficient evidence available to determine which package of diagnostic tests would work best in a given set of circumstances, and there is little guidance available to countries on what new diagnostic tools, or combinations of tools, should be implemented in particular epidemiological/health system settings and at what level of the health service it should be done. Such provisional guidance could act as the starting point for implementation in an operational research context and for the collection of multiple country experiences to better guide regional or global policy in future. This requires the creation of a conducive environment for operational research around TB diagnostics and diagnostics services preferably using a multi-disciplinary approach, based on careful situation analysis.

**Identified outstanding questions for optimization of diagnosis for TB:**

### **1. Improving access to TB diagnosis:**

Based on the most currently used TB diagnostic test (sputum smear microscopy), what are the socio-economic and qualitative barriers that influence TB diagnosis at patients and health providers levels (in terms of timeliness of diagnosis, convenience and cost to patient, prevention of primary default)? Which interventions (decentralization to primary level facilities, decentralization into communities, use of mobile clinics etc) would be most effective in overcoming these barriers? How to bring diagnostic services closer to the community (decentralization, active case-finding, mobile systems, etc), and how to integrate them in the general health system, keeping in mind that the nature of the technology employed and how it is delivered will determine patients' access to the service ?

### **2. Improve suspects' and high-risk groups' screening:**

The major questions are: what should people be screened for, who should be screened, and how should they be screened? For this, we need to identify the high risk groups for different forms of TB at which to target intensive case-finding (PLWH, prisoners, vulnerable groups, MDR suspects, contacts), and define appropriate screening algorithms and test methods (eg. symptomatic, digital chest X-rays, LED and/or front-loaded and/or other laboratory tools). Similarly, reliable methods for ruling-out active TB need to be established, for IPT delivery for example. Such questions are context specific, and screening approaches may vary among risk groups and so will the yield of screening approaches.

### **3. Service delivery: using the introduction of new tools to improve practices:**

The WHO has recently endorsed optimized smear microscopy approaches (front loaded microscopy, LED microscopy), molecular diagnostic tests and a variety of commercial and non-commercial options for culture and drug-susceptibility testing (such as MODS, Colorimetric Redox Indicator, Nitrate Reductase Assay). How to introduce these new tools in current health systems ? What would be their contribution to improved case detection and treatment of DS and DR-TB ? How can TB diagnostics services be integrated with other diagnostic services for infectious as well as non-infectious diseases? What are the pros and cons? The delivery of these services will clearly depend upon the existence of a functional and interconnected tiered health system. OR must address the issues associated with dysfunction in specimen and patient referral systems, as well as the communication of and response to laboratory results.

### **4. Building accessible, effective and efficient diagnostic services with new diagnostic tools:**

*The MAJOR question across all the above areas is "what combination of diagnostic tools should be introduced and what determines the appropriateness of particular combinations to given national programmes/health services?"* Until we start addressing this question, most of the work in areas 1 - 3 above will remain unfocused. This needs a broad approach to either revise existent or develop new clinical algorithms incorporating the use of diagnostic tests, taking into account the prevalence of HIV and HIV-associated TB, the prevalence of multi- and extensively-drug resistant TB, as well as infrastructural issues such as transport and health systems assessment. Such changes would have major implications for the administration of the National TB Control Programme and the Ministry of Health.

Starting work in this area will require the identification of "provisional best-fits" packages of particular diagnostics that might be used effectively and efficiently in a given epidemiological and infrastructural situation.

### **Priority Areas for Operational Research:**

The research questions have been prioritized with a view to facilitating operational research that could lead to improvements in the accessibility, quality and scope of diagnostic services for tuberculosis. The same knowledge is needed at all levels from local to international and the research questions need to be asked at all levels. There may be different answers at different levels.

**1. Situation analysis:** this is the baseline assessment. Studies need to be conducted to *identify the local barriers to access to diagnosis of TB* in order to allow better use of *existing systems* for diagnosing TB (all forms) in various populations (including difficult-to-reach populations) and specific risk groups (TB suspects, DS-TB, re-treatment, DR-TB, HIV, children). Importantly, these studies need to be done carefully so as to deliver relevant and reliable results.

- level: local, national
- time frame : short-term - within next 6 months
- method: descriptive study, qualitative study

**2. Identification of new programmatic approaches,** including revised clinical algorithms for TB diagnosis, and definition of the proper use of new diagnostic tool(s) in specific settings and populations (i.e. screening or confirmatory, rule-in or rule-out, etc...) so as to maximize their impact. Examples of such approaches could be: (i) the development of improved clinical algorithms for smear-negative TB in high, medium and low HIV prevalence settings with and without access to (digital or conventional) chest x-ray; or (ii) the identification of specific risk factor profiles for MDR-TB in different settings, that could be used for the presumptive identification of suspect MDR-TB cases or identification of MDR-TB risk groups.

- level: local/national and international
- time frame : short-term - within next 6 months
- method: Expert Group Meeting based on systematic reviews. Comparative intervention studies. This also needs HSS approaches to build stronger management and supervision.

**3. Identification of "provisional best-fit" packages of diagnostic interventions and/or tools in different settings:** are infrastructure and delivery systems appropriate for implementation of the new test in the country? Are health care providers willing and able to utilize the new test? Does the new test facilitate equitable access to all patients? Will it reduce diagnostic delay ? What is the impact on patients' outcome, etc?

A ***progressive stepwise approach*** can be proposed, that relies first on existing tools (optimized smear microscopy and smear-negative clinical algorithms, the only methods that

can currently be utilized at the lower levels of health services in low and middle-income countries), and then builds-up on the introduction of new tools.

*(1). Improving technical performance of sputum smear microscopy services for TB:* The WHO has recently endorsed a more sensitive definition of a smear positive case and has endorsed tools to reduce the workload in smear microscopy labs (2-specimen approach) and increase sensitivity of sputum smear microscopy (LED-based fluorescence microscopy). Can a combination of these reduce the workload in smear microscopy labs and increase the number of sputum smear positive cases detected in routine settings? Does it increase the TB notifications and number of patients cured? How cost-effective is the approach?

*(2). Improving treatment access for sputum smear positive (SS+) TB cases detected.* Based on the above, can same-day smear examination (with or without same-day reporting and treatment initiation/referral) reduce initial default? Does it lead to improved access to treatment? How cost-effective is the approach? Are there opportunities for integrating infection control practice with reorganization of patient flow in waiting rooms?

*(3). Improving the presumptive (non-bacteriological) detection of smear-negative tuberculosis (including HIV-associated TB) through smear negative clinical algorithms.* With improved sputum smear microscopy services and access to treatment at baseline, can improved clinical algorithms be applied in routine settings to increase the number of TB cases detected and accessing treatment?

*(4). Improving the detection of smear-negative TB cases using rapid culture-based techniques and/or line probe assays.* Building on the existence and availability of improved sputum smear microscopy services and improved presumptive detection of smear negative cases, what will be the impact of the introduction of rapid culture or line-probe assays and rapid *M.tuberculosis* isolate identification or a combination of those? What proportion of newly detected cases will access treatment? How cost-effective is the new combined approach in routine settings? As these will highly depend on settings, Expert Group Meetings convened at global/regional level would provide guidance to countries in identifying the likely provisional best-fit packages for particular settings.

*(5). Improving the detection of MDR-TB cases using rapid culture-based techniques and/or line probe assays.* Building on the above (availability of improved sputum smear microscopy services and improved presumptive detection of smear negative cases) and the improved identification of MDR-TB suspects/risk group, what increase in confirmed MDR-TB case detection will result from the introduction of rapid culture-based techniques, rapid *M.tuberculosis* isolate identification and rapid DST? What proportion of detected cases will access second-line treatment? How cost-effective is the approach in routine settings. Here again, the situation will be highly dependant on

the prevalence of HIV-associated or drug resistant TB together with the level of laboratory and other infrastructure (including transport/communication infrastructure) available in different settings. Expert Group Meetings convened at global/regional level should provide guidance to countries in identifying the likely provisional best-fit packages for particular settings.

- level: national or international
- time frame: short term (6 months - 18 months)
- Method: expert group meetings setting-up simple model studies using real-life NTP situations as far as possible, with different epidemiological situations (high or low MDR-TB, high or low HIV prevalence, small/high density populations, urban/rural). This would imply identification of structures/partnerships to take the work forward, develop core protocols, identify national programmes willing to partner in the work, and secure funding. These would then be followed-up by intervention studies based on the results of the above.

**4. Evaluation of the scale-up impact of a new test or new package**, particularly the public health and societal consequences of scaling-up and rolling out new diagnostic test(s). These can be conducted using, for example, the Impact Assessment Framework (developed by the Liverpool School of Tropical Medicine, the New Diagnostics Working Group and TREAT-TB) that provides 5 layers of assessment: efficacy, equity, health systems, scale-up analysis and policy analysis (see Annex 2).

- level: national or international
- Time frame 2 - 5 years
- Method: quantitative and qualitative impact assessment studies; cost-effectiveness studies;

## **II. Developing sustainable collaboration with all care providers for TB care and control**

James Newell, Zafar Ullah, Nguyen Viet Nhung, Knut Lonroth and Mukund Uplekar

**Goal:** To achieve the targets of the Global Plan to Stop TB through fostering operational research for sustainable public-private mix and partnerships for TB care and control

### **Background:**

Globally, TB case detection has been stagnating at around 60% despite strengthened TB programmes. In many countries, a significant proportion of TB suspects and cases, including the poor and vulnerable populations, present themselves to a range of public and private care providers that are not linked to national TB programmes. These providers include informal and formal, commercial and non-profit, individual and institutional private sector care providers such as traditional healers, pharmacies, GPs, private clinics and hospitals, NGOs and FBOs, and employee health services by the business sector as well as public sector care providers such as general and speciality public hospitals, academic institutions, prison and military health services. The evidence shows that TB diagnosis and treatment practices of many non-programme care providers are inappropriate and that care seeking from diverse care providers hampers access to quality TB care, causes delays in TB diagnosis and imposes financial burden on patients. Furthermore, it is estimated that only about 5% of people with MDR-TB are managed within TB programmes. Several Public-Private Mix and Public-Public Mix (PPM) projects in diverse country settings have demonstrated the feasibility, effectiveness, cost-effectiveness and scalability of engaging non-programme care providers in TB care and control. In some settings, PPM has also been shown to improve access, enhance equity, reduce diagnostic delays and reduce costs of care for TB patients. Subsequently, WHO advises countries to undertake baseline and periodic national situation assessment (NSA) to determine the need and scope of implementing and scaling-up PPM. A tool to help conduct a NSA and guidance for PPM implementation is available and has been used effectively by many countries. By 2008, 58 out of 93 active global fund grants to countries had a PPM component amounting to about 5% of the total allocation.

### **Identified outstanding questions for optimization of collaboration with all practitioners:**

**1. The scale up issues.** While there are examples of PPM projects that are being taken to scale, the knowledge gaps for models or approaches for nationwide PPM scale-up do exist. Prioritizing providers for engagement remains unclear. More needs to be learnt also about specific models and approaches for scale up, such as the use of incentives and enablers, the use of regulatory approaches, the use of social marketing and franchising. Provider segmentation and adaptation of approaches to fit specific groups of providers who are targeted to provide specific services such as TB suspect identification and referral, TB treatment support, etc. need to be better understood and the role of PPM in the broader aspects of TB Intensified Case Finding (early and complete TB case finding) among respiratory symptomatic patients requires clarity. Effectiveness and feasibility of PPM implemented with the Practical Approach to Lung health (PAL) also need to be investigated.

## **2. Measuring the contribution of PPM to TB care and control.**

Measurement of the contribution of diverse care providers to a variety of TB control tasks poses problems and may put an undue burden on the recording and reporting systems. The components of PPM contribution (referral, microscopy, treatment, DOT, default retrieval) that need to be measured at different levels need to be tailored to country contexts. Tied to this is understanding the resource requirements, from the programme perspective for scale-up and thus the ability to weigh PPM outputs and outcomes against resource inputs which can help to monitor PPM cost effectiveness as initiatives are taken to scale.

**3. The TB Care and Control Quality Issues** as PPM initiatives are taken to scale using the International Standards of TB Care as the yardstick and also from the perspective of the patient

### **Priority Areas for Operational Research:**

It appeared essential to differentiate here the OR questions to be addressed either local/national or international level.

#### **1. Improve and scale up existing approaches to engaging all providers**

##### *At the global level*

- Develop an evidence base of different PPM models and approaches to scale up that includes contextualised analyses of reasons for success/failure as well as mechanisms to create demand for quality services. Methods include structured evaluation of existing models using methods such as Pawson's realistic evaluation approach; observational cohort studies; intervention cohort studies; cost-effectiveness studies.
- Assess enablers and incentives for different care providers. Methods include qualitative studies with providers; intervention cohort studies testing various enablers and incentives adapted to local context.
- Assess different mechanisms to fund scale up. Methods include costing studies.

##### *At the national/local level*

- Identify locally appropriate approaches to scale up, include PPM/PAL integration. Methods include situation analyses; qualitative studies with potential providers and users; intervention studies.
- Assess mechanisms to create demand for quality services. Methods include cohort studies, user satisfaction studies; rapid participatory appraisal<sup>1</sup> (or ethnographic mapping) to better understand health seeking behaviour; health systems mapping to better understand providers, services and quality.

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<sup>1</sup> Annett H, Rifkin SB. Guidelines for rapid participatory appraisal to assess community health needs. Geneva: World Health Organisation , 1995

- Assess quality of TB care and control, using the ISTC as the yardstick, as initiatives are taken to scale. Methods include analysis of routine cohort reports; observation, quantitative and qualitative studies with providers and users.

## **2. Measure the contributions of different provider groups to TB care and control**

### *At the global level*

- Assess contributions of different care providers to TB control. OR is needed to develop appropriate methods.

### *At the national/local level*

- Assess the abilities of different providers to improve user access, case detection and outcomes for underserved groups, and reduce diagnostic delays and costs of care. Methods include situation analyses; user and provider surveys; surveys of drug sales; analysis of information from pharmaceutical companies.
- Understand resource requirements for scale up. Methods include integrated costing studies and cost modeling for all providers.

## **3. Encourage involvement of as yet unengaged providers**

### *At the global level*

- Develop an evidence base of different models and approaches. Methods include review of existing approaches; observational cohort studies; intervention cohort studies; cost-effectiveness studies.

### *At the national/local level*

- Identify potential new providers that could provide accessible and effective services. Methods include mapping of large employers and organisations.
- Assess effectiveness of models involving new providers. Methods include qualitative studies with potential new providers; intervention cohort studies; cost-effectiveness studies; user satisfaction surveys;

## **4. Encourage involvement of private sector in MDR-TB management and TB/HIV collaborative activities**

### *At the global level*

- Develop an evidence base of different models and approaches. Methods include review of existing approaches (systematic reviews); observational cohort studies; intervention cohort studies; cost-effectiveness studies.

### *At the national/local level (depending on the local epidemiology)*

- Identify potential providers that could provide accessible and effective services for MDR-TB and TB/HIV management. Methods include mapping and review.

- Assess effectiveness of models for PPM for MDR-TB and TB/HIV. Methods include qualitative studies; intervention cohort studies; cost-effectiveness studies; user satisfaction surveys.

## **5. Develop and assess responses to changing involvement of diverse providers in TB care and control**

*At both global and national levels*

- Identify and assess ways to ensure rational use of new diagnostics and drugs in the private sector. Methods include structured evaluation of existing approaches; ethnographic mapping to better understand providers' practices.

## **6. Encourage introduction of regulatory approaches such as mandatory TB case notification, certification and accreditation, and restricting access to anti-TB drugs to collaborating care providers**

*At global level*

- Develop an evidence base of regulatory approaches that includes contextualised analyses of reasons for success/failure. Methods include structured evaluation of existing approaches; ethnographic mapping to better understand providers' practices.

*At national level*

- Develop locally appropriate regulatory approaches. Methods include situation analyses; ethnographic mapping to better understand providers' practices and willingness to comply with regulation; political analysis to assess ability of the state/others to encourage and ensure compliance with regulations.

### **III. Prevention of TB in HIV-infected patients and joint treatment of TB and HIV – Global update and Need for Operational Research**

Jonathan Golub, Alwyn Mwinga, Neil Martinson, Jay Varma, Soumya Swaminathan

#### **Goal of the session:**

To address priority operational research questions at global and regional level to improve implementation of joined TB/HIV control activities

#### **Background:**

The WHO 3 I's strategy recommends that all people living with HIV should be screened for tuberculosis, and, if tuberculosis is ruled out, isoniazid preventive therapy (IPT) should be provided. Despite this recommendation, less than 1% of people living with HIV were started on IPT in 2008 (WHO 2009). Among people living with HIV that develop TB disease, mortality remains unacceptably high. Early initiation of co-trimoxazole and anti-retroviral therapy can reduce mortality, but linking HIV-infected TB patients to HIV care and treatment has proven challenging.

#### **Identified outstanding operational questions:**

Operational research is needed in developing countries to optimize prevention and treatment of TB in people living with HIV.

#### *Barriers to TB diagnosis:*

Among people living with HIV who have not yet been diagnosed with TB, barriers to TB diagnosis include the lack of awareness by HIV care providers about why and how they should screen for TB disease, inadequate recording, reporting and monitoring of TB screening in HIV care and treatment settings, and limited access to TB diagnostics in HIV care and treatment settings.

#### *Barriers to IPT initiation:*

Among people living with HIV who have been screened and are deemed eligible for IPT, barriers to IPT initiation remain formidable, despite the presence of substantial clinical research to address these. For example, many programs remain unclear about whom they should prioritize for IPT, i.e. whether IPT should be offered to all HIV patients that do not have active TB disease or whether it should be restricted to those with specific tuberculin skin test results or to patients above or below a specific CD4 threshold. Similarly, there are questions about the optimum mode of delivery (e.g., in clinics vs. through home health; in HIV facilities or TB facilities), frequency and type of monitoring for adherence, toxicity, and breakthrough TB disease, and methods to train and motivate health care workers.

#### *Barriers to optimal joint TB and HIV diagnosis and treatment:*

Among patients who seek care in TB clinics, HIV testing has been scaled up rapidly around the world. Nevertheless, in many settings, particularly countries with concentrated or low-level HIV epidemics, major questions remain about whether or how to implement targeted, as opposed to universal, HIV testing of TB patients. When TB patients are diagnosed with

HIV infection, these patients should immediately be evaluated for HIV care and treatment, particularly co-trimoxazole and anti-retroviral therapy, to reduce short-term mortality. Nevertheless, the optimum models for joint TB and HIV diagnosis and treatment remain ill-defined at the patient and public health level, i.e. how to connect TB and HIV clinical services and how to conduct joint monitoring and evaluation of these services.

### **Priority Areas for Operational Research:**

#### **1. Optimization of linkages between TB and HIV programs:**

What forms of cross-referral, co-location of services, and community participation may increase the proportion of people living with HIV (PLHIV) who are screened for TB disease, in whom IPT is initiated, and who survive during treatment for TB disease? Specific attention should be paid to studying these questions in special populations, such as children, injection drug users, and prisoners. For this, it is necessary to carry out studies that would determine the best linkages between TB and HIV programs. In particular, the following questions need to be addressed:

- Determine best strategies and optimal models to integrate and deliver joint TB/HIV interventions, including antiretroviral therapy, at community and health sector level to HIV-infected TB adults, children and families
  - Determine the best models of community participation (i.e. effective, feasible, acceptable, sustainable) for enhanced TB case finding and early HIV detection to reduce delay in initiation of TB and HIV care, and their impact on reducing TB and HIV transmission
  - Determine cost-effectiveness of joint TB/HIV interventions delivered through community approach and through health facilities
  - Determine the best models of delivery of collaborative TB/HIV interventions to most at risk and special populations in all settings with different TB and HIV epidemiology and epidemic states
- Level: national, regional
  - Time frame: short-term
  - Method: observational studies, e.g. case-control clinics or communities or before-and-after interventions.

#### **2. Assess validity of TB screening algorithms in different settings**

In PLHIVs who attend health facilities, does implementation of the WHO recommended algorithm for TB screening increase the proportion of subjects screened for TB, reduce the proportion of PLHIV that develop TB disease during IPT, and reduce mortality during TB treatment compared with current policy or more intensive TB screening strategies (e.g. microbiologic evaluation of all PLHIV)? Specific attention should be paid to studying this question in different contexts in which TB screening might occur, such as HIV counseling and testing centers, HIV clinics, community-based case finding, and household contact investigations. The following questions need to be addressed:

- what is the best model to eliminate diagnostic delay, hasten treatment initiation for TB and reduce mortality, using existing tools including the efficacy of the revised WHO algorithm for smear negative TB among HIV infected TB suspects ?
  - what are the best strategies to promote and scale-up integrated screening of HIV-infection and TB infection and disease among household contacts of HIV-infected TB patients ?
  - What are the best operational models for enhanced case finding of TB among HIV infected patients in HIV service facilities and at community level in both high and low HIV prevalence settings ?
- Level: regional, national
  - Time frame: short-term
  - Method: Observational studies (before/after; stepped-wedge design)

### **3. Reducing mortality in co-infected patients:**

In people living with HIV being treated for TB, what factors are associated with death during TB treatment and, among those who die, what are the most common causes of death? Although use of ART and co-trimoxazole have been clearly documented to reduce mortality during TB treatment, specific attention should be paid to identifying whether the absence of such treatment is responsible for ongoing, high mortality rates or whether additional, modifiable risk factors can be identified.

- Level: local, national, multi-country
- Time frame: short-term
- Method: Descriptive studies, observational studies

### **4. Optimal timing of IPT in relation to ART:**

In people living with HIV and eligible for both IPT and ART, what is the optimal duration, safety, efficacy and cost-effectiveness of isoniazid preventive therapy alone or added with antiretroviral therapy in reducing the risk of active TB compared to antiretroviral therapy alone among people living with HIV, particularly under program conditions?

- Level: international, regional, local
- Time frame: short-term
- Method: observational data; propensity scoring methods for adjustment of unmeasured confounding

### **6. Models to improve adherence to IPT**

In people living with HIV initiating IPT, what models of medication delivery, clinical monitoring, and community support reduce rates of default during IPT, reduce the incidence of breakthrough TB, and reduce the occurrence of severe, adverse events? What are the best operational models to scale-up IPT in HIV care setting including frequency of symptom screening, monitoring tools and measures to maintain high adherence among patients and health workers

- Level: local, national
- Time frame: short-term
- Method: observational studies, cluster randomized trials

## **8. Optimizing infection control to reduce TB transmission**

In HIV care and treatment settings, does a standardized package of infection control (IC) interventions reduce nosocomial TB transmission compared with current policy and practices? Do selected IC interventions reduce nosocomial TB transmission? For both of these questions, the best recognized indicator to measure (in operational research studies) is TB infection rates in health care workers. Therefore, the following would need to be addressed:

- Determine the best infection control interventions that effectively reduce *M. tuberculosis* transmission (both drug susceptible and resistant) in health care settings, at home and in the community
  - Determine the best operational models, i.e. practical, feasible, easily reproducible and effective, to implement and monitor infection control measures in health facilities
  - Determine the best operational models to assess the impact of infection control measures in reducing the spread of *M. tuberculosis* to HIV-infected adults and children
- Level: local, national, multi-country  
-Time frame: medium-term  
-Method: cluster randomized trials

#### **IV. Treatment of Drug-susceptible and M/XDR-TB: optimal access, delivery and community participation**

C. Lienhardt, Anthony Harries, Matteo Zignol, Jennifer Furin, Rony Zachariah

##### **Goal:**

To investigate methods to improve access to and delivery of treatment for drug-susceptible, MDR and XDR-TB patients and encourage community participation

##### **Background:**

Access to health care is the cornerstone of TB control programs that must ensure that all detected patients receive a full course of treatment. This includes establishing effective treatment as well as effective strategies to support the process of care from detection of disease through the completion of appropriate treatment. Limited access and poor adherence to treatment remain, however, major obstacles in the global fight against TB. In 2008, 39% of TB cases were not reported or detected, 93% of MDR-TB cases were not diagnosed and even more were not treated with an approved GLC regimen, and 93% of HIV-infected TB patients were not started on antiretroviral treatment. Patient and health system factors contribute to these problems. Major diagnostic delays compromise the treatment outcomes and increase TB transmission. The 2008 WHO report presents a treatment success rate of 87% for new patients with smear-positive pulmonary TB, but this apparent success hides a number of operational challenges. For MDR-TB, only 30,000 (7%) out of the 440,000 (95%CI 390,000-510,000) MDR-TB cases estimated to have emerged in 2008 globally, were notified, and nearly 6,000 of them (1.4%) were put on treatment. Treatment success of a cohort of 4,500 MDR-TB patients treated under programmatic conditions in 2004-6 was 60%. Access to treatment for MDR-TB remains one of the major problems facing the world today. Only a small fraction of the tens of thousands of diagnosed patients are receiving care. Even among the 72,000 patients approved for GLC treatment, only 19,000 have actually been enrolled. OR is thus highly necessary to improve access to care of DS and MDR-TB patients

##### **Priority areas for operational research:**

**1. Identify reporting gaps:** Determine treatment outcomes of new smear positive PTB at different sources: compare sputum lab register with TB patient register. Also, compare TB treatment outcomes by treatment cards, registers and quarterly reports. This should also be done for patients enrolled in re-treatment regimens.

- Level: national /international level
- Time frame: short-term
- Method: cohort reporting

## **2. Avoiding irregular treatment and improve adherence**

Avoiding missed doses on treatment is beneficial, since not all who receive irregular treatment will default but may be at high risk for acquired resistance. Similarly, defaulting from treatment may contribute to drug resistance. Efforts are needed under programmatic condition in order to reduce irregular adherence or default from treatment (and hence reduce the risk of death and resistance among these individuals); and to reduce selective pressure for resistant organisms among patients who have irregular treatment, but do not default.

### **2.1 Do better “patient locators” at the time of identification or registration of TB suspects improve case holding and reduce default? (mobile phones of patients and relatives; better geographical addresses; other methods ?)**

- Level: national
- Time frame: short/medium term
- Method: case-control / observational studies

### **2.2 Mapping of primary defaulters (suspects, in lab register, in TB register) to understand geographic factors**

- Level: national
- Time frame: short/medium term
- Method: case-control / observational studies

## **3. Is there an association between drug stock-outs and default/treatment failure/death/acquisition of additional resistance?**

Better monitoring of national and local TB drug stocks and operational research studies to determine associations between drug stock-outs and case holding

- Level: national /international level
- Time frame: medium-term
- Method: retrospective cohort

## **4. Improve decentralized and fully integrated access to HIV testing and combined TB and HIV treatment.**

All HIV-infected TB patients should start ART early; the provision of TB drugs and ART drugs should be in the same facility. How can we provide joint treatment at health centres? How can we better engage communities (structures, support, links with traditional systems...)? Should TB programs have their own stock of tests, prophylactic or antiretroviral treatment ? Should they be able to place orders to HIV programmes for patients receiving TB treatment or, should they have to refer patients to HIV programmes for all the above?

- Level: national /international level
- Time frame: short-term
- Method: descriptive studies - cohort reporting

## **5. Re-treatment regimen and amplification of drug resistance**

How effective is the re-treatment regimen and does it amplify drug resistance?

- Level: national /international level
- Time frame: medium-term
- Method: cohort reporting - drug resistance studies

**6. PPM collaboration studies:** how to get realistic data on numbers of DS and DR-TB cases treated in the private sector and know about treatment outcomes ? Why do people use the private sector rather than the public sector? How to engage with the private sector (esp. in India, China) for the treatment of DS and DR-TB?

- Level: national/international level
- Time frame: short/medium-term
- Method: National surveillance tool; situation analysis; surveys; qualitative studies; cohort reporting.

## **7. Define and evaluate strategies for integration/scale-up of DR-TB management within TB control programs (what models ?)**

### **7.1 Develop algorithms for selecting patients eligible for DST and 2nd-line treatment in different settings (early identification of MDR-TB):**

It is necessary to develop optimal strategies targeting patients most at risk of developing or having MDR-TB. Also interesting would be the operational steps & time required to introduce new diagnostics for identification of drug-resistance. Note that different methods will require different technologies/infrastructure, but many processes will likely be identical.

- Level: national/international level
- Time frame: Medium/long-term
- Method: cohort reporting

### **7.2 Develop strategies for provision of 2nd-line treatment (including adherence and use of incentives and enablers, Community based ambulatory care and support)**

- Level: national /international level
- Time frame: Medium/long-term
- Method: descriptive cohort

### **7.3 Identify bottlenecks for scaling up access to MDR-TB treatment in different settings**

- Level: national /international level
- Time frame: medium-term
- Method: descriptive and observational studies

### **7.4 Evaluate the effectiveness of existing infection control measures and strategies for implementing infection control measures (communities, household and health facilities)**

- Level: national /international level

- Time frame: Medium/long-term
- Method: descriptive cohort

**8. Identify risk factors for drug resistant TB**

- Level: national /international level
- Time frame: short-term
- Method: observational studies

## **V. Capacity Building for Operational Research**

Tony Harries, Rony Zachariah, Marieke J. van der Werf, Frank Cobelens, Gurmit Singh

**Goal of the session:** to address issues related to capacity strengthening for operational research to ensure that countries have the capacity to perform Tuberculosis-related Operational Research to improve TB programme performance. For this session, operational research is defined as research that aims to improve the performance of the National TB Control Programme of the country

### **Rationale:**

Despite international interest in the subject of operational research, the reality is that very little research is conducted or published from resource-limited settings where the greatest burden of tuberculosis resides. Yet major funders such as the Global Fund to fight Against AIDS, Tuberculosis and Malaria explicitly state that up to 10% of country proposal budgets should include monitoring and evaluation and operational research. There is wide consensus that OR is important at local/national level to improve programme performance and at international level to guide for policy recommendations. Questions remain however on the where OR should be "located" (NTP, Govt. Institute, University, NGO, or partnership?), and on the sort of capacity to develop and how, as well as on the evaluation of outcomes of training. NTPs often lack expertise, infrastructure, staff, funds, policy cycle, and/or professional culture, and there might be a disconnection between programmers & researchers. Key aspect of capacity building/strengthening in OR at programme levels are that: (i) OR be embedded in Programme Strategy Plan, (ii), there must be an OR focal point in Programmes, (iii) OR projects should end-up with clear results to alter/improve programme performance

**The following ten key enabling factors for capacity building/strengthening in OR at programme level have been identified:**

- (i) OR should be embedded in a Programme Strategy Plan ,
- (ii) there must be an OR focal point (supported by other field staff) that supports the programme manager and who coordinates and sets the national research priorities,
- (iii) programme staff that engage in operational research should be encouraged and motivated through on-the-job training and supervision, being provided with dedicated time and opportunity for research activities, provided with opportunities to make presentations at national and international conferences, research bonuses and small grants,
- (iv) there should be adequate infrastructure (eg room space, computers, internet, stationary) and implementation support (eg motorbikes),

- (v) at country level there should be a paradigm shift towards a “partnership model” in operational research which is inclusive of academic institutions, Non Governmental Organizations and community based associations so that the comparative advantages of each group are taken on board,
- (vi) OR training should be based on strict selection criteria, must be output oriented, and should involve strong “mentorship”. The OR training model should be practical and geared to provide practical skills for both conducting and publishing research (eg the UNION-MSF OR approach to training (<http://www.theunion.org/fr/news/operational-research-training-programmes-launched.html>)),
- (vii) there should be long term career opportunities at programme level through operational research fellowships (junior and senior),
- (viii) OR projects should end-up with clear results that can influence or alter/improve programme performance,
- (ix) funding and resources for operational research need to be built into the programme so as to avoid foreign or academic institutions developing a monopoly on funding, time and mandate for research and consequently, the associated power of decisions, and
- (x) Program researchers should be represented on the Global Fund Country Coordinating Mechanism (CCMs) so that the rationale for and decisions on research funding are made at the highest level.

### **Priority operational research questions**

1. Models: What are the existing models of operational research capacity building and the lessons learnt (important to assess effectiveness of capacity/training programmes)

- Level: international
- Method: descriptive study

2. What is the impact of existing training models in terms of products/outputs & outcomes (number and type of publications; Impact indicators for policy and practice) ? Importance of defining accurate and reliable impact indicators to assess quality of OR project and capacity for translation in programme practice.

- Level: national / across-country
- Method: Evaluations + questionnaire surveys

3. Funding: what sort of efficient funding mechanism can be used or is needed for OR capacity building at national level, with an international/consortium community of practice of facilitators, mentors, standard curriculum and sustained mentorship?

4. Sustainability: what are possible ways of sustaining and retaining trained research staff within programmes? Link training with OR projects.

## ***Annex 2: Agenda of the workshop***

### **A Workshop on the Promotion and Rationalization of Operational Research Activities in TB control**

**11<sup>th</sup> - 12<sup>th</sup> May 2010, Geneva, Switzerland**

#### **Objectives of the workshop:**

4. To identify research priorities in Operational/Implementation Research for improved TB control, with the view to contributing to the development of an International TB Research Agenda
5. To address the translation gaps for implementation of current and innovative technologies and service designs for TB control
6. To update the Operational/Implementation Research part of the Global Plan to Stop TB 2006-2015

#### **Methods:**

*Plenary sessions* on a series of themes identified as key areas where evidence is lacking for proper implementation of current or novel technologies and novel service delivery models. Participants will identify the *gaps* and describe the *expected OR activities* to be carried out in order to improve programme activities with present tools and interventions and enhance uptake of new tools and interventions.

For each of the thematic areas, participants will define:

- what research is needed ?
- what level (local, national, or multicountry/international) ?
- under which timeframe (short, medium or long-term) ?
- which methods should be used ?
- which study population ?
- who should conduct the research

Sessions will be constructed around a broad overview of the situation by a designated speaker (20 mn). This will be followed by short presentations by 2 different discussants who will address key points and issues (10 mn each maximum). A general discussion will then take place, conducted under a designated chair, with the view to address the questions mentioned above. A rapporteur will take full notes of the discussions and summarize the propositions from the audience in a pre-defined format and report to the whole audience on the second day.

<b>DAY 1</b>		
		<b>Chair: Haile Getahun</b>
8h15 - 8h30	Welcome	Marcos Espinal
8h30 - 8h45	<i>Objectives of the workshop</i> The Global Plan to Stop TB and the TB Research Movement	Christian Lienhardt
8h45 - 10h00	<i>Session 1: From local to global scale: the spectrum of operational / implementation research</i>	Christian Lienhardt Frank Cobelens
10h00 -10h45	<i>Session 2: Funding Operational Research</i>	Speaker: Rifat Atun Discussant: Jacqueline Bataringaya
10h45 -11h00	Coffee break	
11h00 -12h45	<i>Session 3: Access, Screening and Diagnosis of TB</i>	Session Chair: Andy Ramsay Speaker: Afranio Kritski Disc 1: Gillian Mann Disc 2: Maarten van Cleeff Rapporteur: Anne Detjen
12h45 -14h00	Lunch	
14h00 - 15h30	<i>Session 4: Developing sustainable collaboration with all practitioners for TB care and control</i>	Session Chair: Jeremiah Chakaya Speaker: James Newell / Knut Lonroth Disc 1: Zafar Ullah Disc 2: N.V. Nhung Rapporteur: Zafar Ullah
15h30 -16h00	Tea break	
16h00 - 17h30	<i>Session 5: TB/HIV: prevention of TB in HIV patients and combined HIV and TB treatment</i>	Session Chair: Jonathan Golub Speaker: Neil Martinson Disc 1: Soumya Swaminathan Disc 2: Jay Varma Rapporteur: Alwyn Mwinga
17h30	End of day 1	

	<b>DAY 2</b>	
		<b>Chair: Frank Cobelens</b>
8h30 - 10h15	<i>Session 6: Treatment of DS and M/XDR-TB: optimal access and delivery, community participation</i>	Session Chair: Christian Lienhardt Speaker: Anthony Harries Disc 1: Matteo Zignol Disc 2: Jennifer Furin Rapporteur: Rony Zachariah
10h15 -10h30	Coffee break	
10h30 -12h00	<i>Session 7: Capacity Building</i>	Session Chair: Anthony Harries Speaker: Rony Zachariah Disc 1: Frank Cobelens Disc 2: Marieke van der Werf Rapporteur: Gurmit Singh
12h00 -12h30	Engaging in the Health Systems Research Agenda	Diana Weil and Shenglan Tang
12h30 -14h00	Lunch	
		<b>Chair: Christian Lienhardt</b>
14h00 - 15h45	Presentations by rapporteurs from each session	Rapporteurs, sessions 3 to 5
15h45 -16h00	Tea break	
15h45 - 16h45	Presentations by rapporteurs from each session	Rapporteurs, sessions 6 and 7
16h45 - 17h00	Summary and next steps	Christian Lienhardt
17h00 - 17h15	Conclusions	Mario Raviglione
17h15	<i>Adjourn</i>	

### ***Annex 3: List of Participants***

**Workshop on Operational Research in TB  
Geneva, 11-12 May 2010**

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