Eliminating TB: The need for a Global Research Strategy

Bellagio, 15th - 16th March 2011

Meeting Report

Introduction:

Devising a creative research response to the global TB epidemic is one of the most pressing issues of our time. The Research Movement of the Stop TB Partnership, in collaboration with WHO, convened major donor agencies for TB research and development, together with key scientists and representatives from NGOs, patients and communities for an intensely focused gathering. The overall goal was to spearhead the necessary acceleration that is needed to increase our knowledge of human TB. This knowledge will be needed to be able to create new tools and strategies for improved TB control worldwide. Furthermore, research is also needed to ensure that these tools are being accessible and affordable to populations in low-income countries that bear the largest burden of human suffering due to TB. Increased attention to, and support of research will be critical to turn a page in the history of our efforts to control tuberculosis.

Objectives of the meeting:

1. To introduce and discuss the newly developed *Roadmap for International Research to Eliminate TB* ;
2. To agree on the key strategic areas to move research efforts towards elimination of TB;
3. To support the Roadmap's vision of synergistic global TB research efforts through the establishment of a mechanism to better coordinate action and funding of research towards TB elimination.

Meeting Outline:

The meeting took place on two consecutive days:

1. The **first day**, entitled *"A Roadmap for International Research to Eliminate TB: a vision for research beyond 2015"*, was focussed on presenting key areas of the Research Roadmap. It was open to participants and was intended to address the greatest research and knowledge challenges facing TB elimination (Objectives 1 and 2);
2. The **second day**, entitled "*Towards harmonized funding",* was structured as a **retreat for funders/donors only** to discuss the prospects for harmonisation and coordination of research support and strategy in TB (Objective 3).

The meeting was attended by 27 participants representing the top donors and investors for TB research, thought leaders in research representing the scientific community, NGOs and BRICS country representatives (Brazil, South Africa).

DAY ONE:

Opening session:
After an opening and welcome from Drs. Mario Raviglione (WHO/Stop TB Department, Geneva, CH) and Lucica Ditiu (Stop TB Partnership, Geneva, CH), Dr. Christian Lienhardt presented the objectives and expected outputs of the meeting. He went back to the proceedings of the STP CB meeting in Abuja in 2006, where a proposal to create a unified front, a "TB Research Movement", encompassing the continuum of research was first introduced. He described the developments to date, and activities carried out since the official launch of the TB Research Movement in 2007, leading to the preparation and writing of the TB Research Roadmap and the organisation of the meeting in Bellagio.

Session 1: Setting-up the scene (Chair: Mark Harrington, Treatment Action Group, New York, USA). This session outlined the state of the TB epidemic and current approaches, successes and future goals for TB control.

Dr. Mario Raviglione summarized the global burden of TB and indicators that would have to be met to reach elimination of TB as a public health concern. To reach elimination targets for TB, a combination of approaches will be needed that goes beyond the traditional use of diagnostics, drugs and vaccines. Dr. M. Jeremiah Chakaya (KEMRI Nairobi, KE) discussed research needs in endemic countries to improve TB control. He reminded that each setting presents with unique aspects and drivers for the TB epidemic and presents with different co-infections and co-morbidities that require targeted strategies for intervention.
Dr. Christine Sizemore (NIH/NIAID, Bethesda, USA) outlined how research efforts could be combined in a cross cutting, multidisciplinary manner to contribute to tools and strategies for improved global TB control. Currently many research fields operate in parallel structures and are not unified or combined towards a common goal. Creation of cross-disciplinary approaches, such as combining drug, vaccine, and diagnostic research with fundamental and operational/epidemiological science around focal areas of prevention or cure of TB, could drive the level of innovation needed to transform research in TB.
Dr. Lienhardt (Stop TB Partnership, WHO, Geneva, CH) concluded the session with a concise summary of the "Roadmap for international research to eliminate TB" that has been developed over the last 18 months with the contribution of more than 150 persons worldwide. He underlined that the roadmap is encompassing the overall *continuum of research* for TB, identifying priorities in *each* research area, and expanding beyond product R&D. This summary further highlighted the interconnectedness of scientific goals and strategies and how coordination between research disciplines can be facilitated through the research roadmap. He stressed on the value of networking

among scientists and the need for multi-disciplinarity and inter-disciplinarity so as to develop '*needs-driven, use-inspired*' innovation.

Considering the current state of the global TB epidemic, the present weaknesses in TB control worldwide, and the need for new and improved health care interventions and tools to increase the rate of decline of TB worldwide, discussions confirmed that research in TB is a crucial component of global control. Discussions highlighted the need for complementarity in funding and the promotion of innovation if elimination is to be targeted. The participants made a case for a *transformational research focus* that would be *outcome*- rather than tools-driven, and that would rely on coordination and fertilisation within and across areas of research to address the key scientific knowledge gaps. The research roadmap is proposed as a vehicle and framework upon which transformational and outcome oriented focus areas can be constructed. The discussants agreed that the roadmap or a framework that is focused on key gaps of an outcome-oriented strategy will have to be endorsed and embraced by the scientific community and their thought leaders, as well as other stakeholders, to engage new funders, especially in TB endemic countries, such as BRICS. It was articulated that in order for such a framework to be successful, it must be developed in an inclusive manner and must maintain independence and freedom to operate for scientific researchers. Key aspects of this process will include discussion and definition of what country/control needs can be addressed through focused, outcome oriented projects and/or research focus areas, that can leverage multidisciplinary engagement, community involvement and appropriate capacity building. It was recognized by the participants that in order to reach the requisite decline in TB incidence, transformational approaches in TB research need to be initiated. In this context, it was felt that the concept of "elimination" should be used with caution and be defined by concrete and feasible expectations. It is expected that a carefully focused research framework that is based on outcome-oriented and feasible goals towards TB elimination and endorsed by the TB research and control community and by civil society will be attractive to new donors.

Session 2: Fundamental research (Chair: C. Sizemore, NIH/NIAID, Bethesda, USA).
Dr. Stefan Kaufmann (Max Planck Institute for Infection Biology, Berlin DE) initiated the session with a presentation on the need to maintain a close focus on the essential goals of fundamental research that are deeply rooted in high quality science and emphasis on a precise definition of the research questions. Dr. Kaufmann advocated that novel concepts need to be developed that leverage state of the art approaches and systems integration, and are outcome oriented. A thorough understanding of heterogeneity of TB at the population, patient and also molecular level will be paramount to making necessary gains in our understanding of the causalities underlying host-pathogen interaction, bacteriological persistence and the spectrum of infection to disease. Furthermore Dr. Kaufmann also explained that translation of basic research findings through applied science into implementation is not unidirectional, and that continuous feedback is needed between disciplines, including back translation of clinical findings to inform fundamental research hypotheses. Understanding the interrelatedness of host

and pathogen systems has the promise to build connections between what may currently be perceived as isolated scientific disciplines.

Dr. Douglas Young (Imperial College, London UK) summarized key issues and fundamental, outstanding questions in latent TB infection. He highlighted the need to develop approaches for the characterization of the spectrum of human responses to infection and identify what host/pathogen factors are of greatest importance along the continuum of infection to disease. Dr Young also articulated the importance to recognize and study the heterogeneity of immune responses in persons infected with Mtb to identify bio-signatures and markers that identify those individuals who are not able to naturally contain the infection and progress to active disease. He argued that heterogeneity in response to Mtb infection has to be studied at the population, patient and also cellular level alike, so as to gain an appreciation of the factors that underlie differential responses to infection and the ability to contain it.

The discussion following Dr. Young's presentation focused on the importance of building a continuum between basic research and implementation research to assure that innovations and biomedical knowledge is readily available to endemic countries and that care, control and implementation needs articulated by endemic country programmes and practitioners influence how basic science findings are translated into applications. For this, the creation of multidisciplinary teams in research institutions and in endemic countries, coupled with research investors/donors who are sensitized to cross-disciplinary research needs, will be crucial.

Session 3: New tools for TB control (Chair: Dr. Kenneth Castro, CDC, Atlanta, USA)
Three presentations summarized key strategic goals and questions in product development research.
Dr. Tom Evans (Aeras, Rockville, USA) summarized key challenges and opportunities in vaccine development, discussed target populations for highest vaccination impact, as well as immune strategies and the need to consider integrating vaccine/therapeutic approaches for the treatment and prevention of TB disease. One of the key aspects in development of new vaccines against TB is to determine what stages of the continuum from infection to active disease are most tractable by vaccines and what role a vaccine could play in reducing *transmission* of TB. He emphasized the need to evaluate the effect of candidate vaccines on reducing incidence in populations rather than focusing on individual immune responses only. He also questioned whether it is feasible to develop one vaccine that will be able to provide protective efficacy in all settings, age groups and/or stages of infection/disease and that different types of vaccines may be needed to provide the best public health benefit for the prevention of transmissible TB.

Key opportunities and question in diagnostics were presented by Dr. Madukar Pai (McGill University, Montreal, CA) who highlighted the need for implementation research as part of diagnostic development to assure new tests and strategies are appropriate and targeted to specific programmes and control needs. He articulated that

development pathways for diagnostics have to be tailored to what is needed for approval and endorsement of a new diagnostic tool for TB and also to deliver information that is needed at the country level to provide confidence that adoption of the diagnostic tool will be cost effective and improve TB care. He also reminded the group of the need to develop incentives for partnerships and participation of the private sector to contribute to TB control tools and strategies, since this sector, if integrated properly, will serve to increase the market value of diagnostic tools.

Dr. Mel Spigelman, (TB Alliance, New York, USA) focused his presentation on the need to study the phenomenon of bacterial persistence in humans. Persister populations are thought to be a major reason for the prolonged therapy that is needed in TB. Persisters being a natural bacterial phenomenon require a targeted approach that may have to include multiple modalities, such as drug and vaccine combinations. This approach will greatly benefit from combining host immune studies with pharmacology based intervention and discussions for new strategies to improve cure that go beyond the traditional focus on drugs alone.

The discussion then focused on the importance of coordinating clinical trials to assure limited resources and funding are used for the most critical and/or informative clinical trials, and on the importance of transferring new technologies to endemic countries as rapidly as possible. A recent example of how coordinated science and funding can lead to rapid technology transfer is the multi-partner development, endorsement and rollout of the Xpert MTB/RIF diagnostic test. Collaboration between fundamental/basic researchers, product developers and clinical scientist, as well as implementation researchers was instrumental in the success of this project and high quality research and clear product development and implementation goals were at least in part responsible for attracting new investors and researchers. Furthermore, the example of rapidly rolling out a technologically advanced diagnostic test for identification of drug resistant TB also highlighted downstream issues of increasing programme capacity for treating newly identified cases of drug resistant TB, and the need to re-adjust programmatic policies to managing increased case loads. The importance of attracting industry in the development of new tools continues to be paramount, and the various mechanisms allowing financial investments (advances-market commitment, patent transfer, patent pools, etc.) need to be further investigated.

Session 4: Clinical and operational research (Chair: Dr. Gwen Malegwale Ramokgopa, Deputy MoH, Pretoria, ZA)

This session was opened by a statement from Dr. Ramogkopa on the need for operational research in TB control programmes and how involvement of civil societies and health care providers, as well as researchers is paramount from the earliest stages and at all steps of clinical research and implementation of new tools, strategies and policies. She also applauded the integration of research and product development/programmatic care for TB and encouraged the group to increase research investments in high burden countries.

Clinical and operational research needs in HIV/TB and MDR-TB were presented by Dr. Richard Chaisson (Johns Hopkins University, Baltimore, USA). Dr. Chaisson summarized the current challenges in the management of TB in these two situations and highlighted the need to target interventions to specific patient populations and to provide alternatives for specific clinical needs and co-morbidities to address all forms of TB in all age groups. While development of new drugs against TB is a critical R&D goal, he cautioned that new drugs will have to be provided to patient in appropriate regimens and drug combinations and that a better understanding of the best use of existing drugs against TB is paramount. In this context, he also argued that preventive chemotherapy remains underutilized, particularly in HIV/TB co-infected population. In order to manage the spectrum of HIV associated co-morbidities, new TB therapies need to be evaluated not only in the context of antiretroviral therapy but also drugs used to manage the multitude of other conditions, to provide adequate "menu" options for health care providers.

Dr. Frank Cobelens (Amsterdam University, NL) presented on epidemiological and operational research in TB and how this can help guide overarching outcome oriented science goals. He argued that currently, only a limited number of studies are conducted that assess the performance or impact of newly implemented tools and strategies, and that these impact studies are critical to provide feedback to biomedical researchers and discovery and development scientists. He noted that in order to develop a relevant and progressive development pathway for new health care interventions, impact evaluation studies are thoroughly needed, and that continuous feedback from end users is required. This feedback can only be obtained through tight collaboration and dialogue between operational/epidemiological researchers and discovery and development scientist. He also cautioned that many epidemiological models of TB that have served as the guide for scientific studies have not been re-evaluated in modern times and are not taking into consideration how other co-infections, environmental and social factors and co-morbidites are affecting the traditional models of TB infection, latency and disease.

In the discussion, participants agreed on the need to develop a *research framework* or *action plan* that would allow for joint, cross disciplinary and outcome oriented projects to address complex issue in TB and how to leverage and solicit funding for impact evaluation. The discussion concluded with a reminder that a clear agenda was needed that can guide countries in their choices of research and engagement, and *the roadmap could play a critical role in articulating these choices*.

Day 1 concluded with a summary by Mr. Mark Harrington of the most recent TAG report on current R&D investments in TB (issued in November 2010). The ensuing discussion highlighted the need for funder and donor coordination in light of the current economic situation and the expectation that available support by the current major donors for TB research may be decreasing in the immediate future. To meet funding needs articulated in the research roadmap, it will be critical to increase the *number* and *diversity* of

donors for TB research. This donor base should include BRICS countries and should recognize the need to reduce the dependence on a few funders currently providing the majority of financial support for R&D.

Dr. Lienhardt summarized the key finding s of the day, particularly that the scientific community must define priorities and the strategic agenda towards outcome-oriented R&D in TB to provide donors with a framework and consensus of support needs. The research roadmap was considered a comprehensive summary of research needs and it was agreed that an action plan will have to be developed to guide cross-disciplinary research projects.

DAY TWO

The second day was designed to facilitate conversation among donors and investors only (16 people) to discuss possible strategies for harmonization of funding for research. Dr. Lienhardt opened the session with a summary and key take-home messages from the first day of the meeting:

(i) Research is an essential driver of success towards elimination of TB;
(ii) Crucial importance of encompassing the overall *continuum of research,* expanding beyond product R&D;
(iii) Value of networking among scientists across disciplines;
(iv) Coordination within and across areas of activity;
(v) Multi-disciplinarity and inter-disciplinarity required for sustainable "*needs-driven, use-inspired"* innovation;
(vi) The *TB Research Roadmap* is a clear draft document, well written, reflecting the research priorities in TB across the continuum – inclusive and outcome driven;
(vii) Prioritization based on the roadmap will serve to attract other constituents to the field, especially from BRICS countries;
(viii) Research-control interface is critical – questions built in programmes;
(ix) Importance of capacity building at all stages;
(x) The Research Roadmap is an *architecture* – actions are needed to adapt it to "*all geographical and weather constraints",* so an action plan is needed;
(xi) Promote organization of cross-disciplinary scientists around demonstration projects;
(xii) Clear call from countries and donors to receive guidance from scientists for projects.

Dr. Lienhardt then provided the group with suggested outcomes from discussions:
(i) better understanding of how funders operate – flexibility/constraints in funding mechanisms and peer-review;
(ii) Understanding of timelines from ideas to implementation of funding;
(iii) What do funders need from scientists to support investments in TB;

(iv) How to focus cross-disciplinary discussions among scientists to provide priority areas of support and is the TB Research Movement the appropriate umbrella;
(v) What are the next steps for funders' coordination?

The second day was organized around three successive round table discussions (chaired by Dr. Christine Sizemore, Dr. Peter Small and Dr. Lucica Ditiu, respectively), that addressed the following sequential issues:

1. What are the roles and operating models of the top funders in TB R&D funding and where are current investments focused?
2. How to identify research gaps?
3. How to facilitate future interaction and continued coordination among funders?

The discussion was opened by the statements of the deputy ministers of health of South Africa and Brazil, applauding the strategic move to recognize research as an integral part of a global TB control agenda and confirming their commitment to a TB research focus that should help guide national efforts. It was recognized that a framework for defined, outcome oriented and cross disciplinary research will be a valuable tool for donors to prioritize and focus funding and to create “success stories” that are necessary to maintain donor involvement in research.

Representatives of donor agencies (NIH, Welcome Trust, EC, BMGF, CDC, DFID, USAID, and Tibotec on behalf of the IFPMA) summarized their respective missions, operational models and current investment areas in TB and gave examples of collaborations or “handoffs” that are presently leveraged to assure translation of research findings into field implementation. The ensuing discussion allowed clarification about areas of emphasis, flexibility and timelines in strategy and funding and the feasibility of establishing and coordinating multi-donor projects. Participants shared ideas for cross cutting programmes, necessary scientific frameworks and the possible role of the Stop TB Partnership and a research framework to facilitate these interactions. The concept of *diversification of donors* (seeking out to other donors than those represented at the meeting) and their *coordination* appeared to be of crucial importance and was discussed by participants. It was felt that the roadmap and a research framework that is focussed on critical overarching gap areas that are cross cutting and require participation by a various number of stakeholders, disciplines and funders could serve as a focal point for coordination. Participants used examples of various existing funders networks that may be used as models for larger coordination. It was felt that there was adequate understanding by the funder community on the respective areas of emphasis and that, to increase funding for TB, the pool of donors need to be expanded since, due the current global economic situation, it is unlikely that investment by individual agencies will increase in the near future.

To frame donor investments in the context of a larger outcome oriented research framework, the group debated several key areas of concern. As was mentioned on day one, a target of “TB elimination” as a focal area for future investment has to be used

with caution. While a critical advocacy tool, discussants felt that shorter term, more tangible and feasible goals have to be established to provide opportunities for success and continuous opportunities for dialogue, process development and critical feedback. This will be important to assure funding agencies that their investments have resulted in gains in TB research and that changes in strategy relying on evidence-based science are not only needed but encouraged. In this context, the group also discussed suggestions on how restructuring at the Stop TB Partnership may provide a vehicle to bring scientist and health care professionals together and focus the research field on measureable, outcome oriented gap areas. An outcome focussed structure would facilitate discussions among disciplines that currently do not intersect - e.g. parallel development of drugs, vaccines and diagnostics - while integrated strategies require combinations of drugs, vaccine and diagnostics to treat and prevent TB. Furthermore, it would recognize that in order to transform TB care and control, a combination of stakeholders and scientific disciplines are needed at each step and give donors and scientists the opportunity to identify with larger projects and successes achieved within cross-disciplinary teams.

The meeting concluded with suggestions for continued dialogue and the establishment of mechanism for donor harmonization. Emphasis was placed on *developing demonstration projects* that are focused within BRICS countries and that could be implemented in a short period of time, leveraging existing donor investments in science, endemic country infrastructure and human capital, and has a reasonable chance of success. To continue the momentum of enthusiasm and dialogue that was created during the 2 day meeting, the participants summarized the proposed next steps as follows:

"The participants at the Bellagio meeting encourage the Stop TB Partnership to endorse the TB Research Roadmap, publish it promptly as an independent document, and facilitate the execution of the following Action Plan:

(1) Elaborate key areas of emphasis from the research roadmap to define an action plan for global TB research (including research advocacy);
(2) Initiate consultations with countries, especially BRICS countries, researchers, policy makers, the private sector, and civil society to explore the key areas of emphasis/action plan and build ownership;
(3) Match existing funded research with areas of emphasis to avoid unnecessary duplication, leverage existing resources and infrastructure to catalyse more effective collaborations;
(4) Funders will establish a harmonization and coordination mechanism for research support;

The participants at this 2 day meeting wish to commend Dr. Christian Lienhardt for the leadership in coordinating the roadmap and convening the HLM. Furthermore we wish to commend Ms. Gloria Haselmann for effectively organizing the meeting logistics."