

TBNET – COLLABORATIVE RESEARCH ON TUBERCULOSIS IN EUROPE

C. Giehl¹, C. Lange^{2*}, R. Duarte³, G. Bothamley⁴, C. Gerlach⁵, D.M. Cirillo⁶, D. Wagner⁷, B. Kampmann⁸,
D. Goletti⁹, T. Juers¹⁰ and M. Sester¹¹

¹European Research and Project Office GmbH – Eurice, Saarbrücken, Germany

²Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany

³Departamento de Epidemiologia Clínica, Medicina Preventiva e Saúde Pública Faculdade de Medicina da Universidade do Porto, Porto, Portugal

⁴Department of Respiratory Medicine, Homerton University Hospital, London, UK

⁵Tuberculosis Network European Trialsgroup Office, Borstel, Germany

⁶Emerging Pathogens Unit, TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Milano, Italy

⁷Centre for Infectious Diseases and Travel Medicine and Centre for Chronic Immunodeficiency, University of Freiburg, Germany

⁸Academic Department of Paediatrics, Imperial College, London, UK

⁹Translational Research Unit, National Institute for Infectious Diseases, Rome, Italy

¹⁰Betriebs- und Steuerberatungsgesellschaft SHBB mbH, Bad Oldesloe, Germany

¹¹Department of Transplant and Infection Immunology, Saarland University, Homburg, Germany

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Networking is a key feature of scientific success. The Tuberculosis Network European Trialsgroup (TBNET) was founded in 2006 as a non-profit, non-governmental peer-initiated scientific organization to collaboratively address research priorities in the area of tuberculosis in Europe. Today, TBNET is the largest tuberculosis research organization in Europe with nearly 500 members from 22 EU countries and 49 countries worldwide (www.tb-net.org). Apart from small multicenter basic research studies, a particular strength of TBNET is the performance of large collaborative projects, pan-European multicenter studies and database projects. In recent years, research from TBNET has substantially contributed to the understanding of the management, risk and prognosis of patients with multidrug (MDR) and extensively drug-resistant (XDR) tuberculosis and led to a better understanding of the clinical value of novel tests for the identification of adults and children with tuberculosis and latent infection with *Mycobacterium tuberculosis*. In 2009, two branches of TBNET were founded to specifically address tuberculosis in the pediatric population (ptbnet) and non-tuberculous mycobacterial diseases (NTM-NET). In addition to the research activities, TBNET is developing expert consensus documents for clinical management and provides training and capacity building especially for members from Eastern European countries, where tuberculosis is still a prevalent health problem.

Keywords: *Mycobacterium tuberculosis*, TBNET, NTM-NET, ptbnet, tuberculosis, Tuberculosis Network European Trialsgroup

Introduction

Tuberculosis is a leading cause of morbidity and mortality worldwide, being in 8th position out of all causes of death (Fig. 1) [1]. Probably a third of the world is latently infected with *Mycobacterium tuberculosis*, and this represents an enormous pool from which active and infectious cases of tuberculosis can arise. Although the incidence of tuberculosis has decreased steadily in most Western European countries over the past decades, an opposite trend has been observed in many Eastern European countries. In addition, the emergence of multidrug (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis* constitute a real threat for tuberculosis control and challenges the likelihood of attaining the Millennium Development Goals set out by the United Nations.

The Tuberculosis Network European Trialsgroup (TBNET) aims to promote clinically oriented research in

the field of tuberculosis in Europe by sharing and developing ideas and research protocols among the members of the network. TBNET members are spread throughout Europe, including Eastern European countries with a high burden of this disease. TBNET activities include three major areas, namely research, training and capacity building, and networking. In addition, two branches that focus their activities on tuberculosis in children (ptbnet) and on diseases caused by non-tuberculous mycobacteria (NTM-NET) were recently founded.

History of TBNET

New immunodiagnostic tools used to detect latent infection with *M. tuberculosis* and advances in understanding of the molecular biology of tuberculosis by the middle of the last decade provided the foundation for the idea of a

*Corresponding author: Prof. Dr. Christoph Lange, MD; TBNET Chairman; Division of Clinical Infectious Diseases, Research Centre Borstel, Borstel, Germany; E-mail: clange@fz-borstel.de



Fig. 1. Tuberculosis is a leading cause of morbidity and mortality worldwide and is still an important healthcare problem in many parts of Europe

pan-European network on tuberculosis research. A self-organized group of pulmonologists, epidemiologists and specialists in infectious diseases first discussed this possibility at a WHO meeting on tuberculosis diagnostics in Geneva in spring 2006. During the summer of that year interested colleagues visited the EUROSIDA headquarters in Copenhagen, a European study group on HIV-infection, in order to learn from their experience, how to build a similar clinical network for tuberculosis in Europe. On November 9th and 10th of 2006, 41 physicians and allied colleagues from related scientific disciplines, representing 12 European countries, gathered at the Research Center Borstel, Germany, to share ideas on how to build a network for tuberculosis research in Europe in general, and to discuss and prioritize suggestions for collaborative research projects. After two intense days of elaborating organizational issues and discussing 20 research proposals, a governance structure was designed, the main proposals were combined into six projects to

be performed with combined efforts, and TBNET was founded. The first collaborative research projects on the diagnosis of tuberculous pleurisy [2] and on the emergence of *M. tuberculosis* drug resistance in Europe [3, 4] were published the following year. In April 2009, the Pediatric Tuberculosis European Trials Group (ptbnet) was founded as a first branch of TBNET, followed by the Non-Tuberculous-Mycobacteria Network (NTM-NET) as the latest TBNET branch in September 2009.

Today, TBNET has nearly 500 members which include clinicians, epidemiologists, and research scientists from 22 EU countries and 49 countries outside Europe. With more than 30 peer-reviewed publications to date, TBNET has become the largest pan-European clinical research network on adult and pediatric tuberculosis, and non-tuberculous mycobacterial (NTM) infections. In addition, TBNET is established and recognized as a Clinical Research Collaboration (CRC) of the European Respiratory Society (ERS), the largest respiratory diseases society worldwide. TBNET

Table 1. TBNET at a glance

Name	Tuberculosis Network European Trialsgroup (TBNET)
Profile	Largest collaborative tuberculosis research group in Europe
Founding year	2006
Legal status	Non-profit non-governmental organization (Bad Oldesloe, Germany)
Membership	471 (August 2012), 22 EU, 2 EEA/EFTA countries, 47 non-EU or EEA/EFTA
Membership fee	None
Activities	Research, training, networking
Research focus	Prevention, diagnosis and treatment
Governance	A chair, a secretary, and one representative each for the fields of diagnostics, microbiology, pediatrics, NTM-diseases, translational research, epidemiology and statistics, clinical tuberculosis and a treasurer serve on the steering committee (3-year one time renewable mandates)
Branches	ptbnet (pediatrics), NTM-NET (non-tuberculous mycobacterial diseases)
Cooperations	BMBF, ECDC, ERS, EU-FP7, Stop TB Partnership (WHO)
Annual meeting	The day before the ERS conference at the same location
Website	www.tb-net.org

has been validated as a non-profit research organization in the central register of the European Commission and is a member of the WHO Stop TB Partnership. Key features of the network are summarized in *Table 1*.

Branches of TBNET

ptbnet

Childhood tuberculosis still remains under-appreciated and under-researched. The fundamental differences between adult and pediatric tuberculosis have significant implications for diagnosis and epidemiology: the disease is mainly paucibacillary, which makes bacteriological confirmation the exception rather than the rule, and disease-manifestations are age-dependent with higher susceptibility and extrapulmonary manifestations in the younger hosts, who are exposed to *M. tuberculosis* through adult index cases in the household.

Most guidelines for tuberculosis management are currently deducted from adult recommendations with little collaborative research conducted within the pediatric field. On this background, the pediatric branch of TBNET (ptbnet) was set up in 2009 by pediatricians already active within TBNET to address the issues arising in tuberculosis in children specifically. The main goal of the network, which now has members in 23 European countries, is to enhance the evidence base for diagnosis and treatment of tuberculosis in children through collaborative research and to provide clinical expertise and advocacy.

The ptbnet has made significant contributions to the child tuberculosis advocacy work at the European Center for Disease Prevention and Control (ECDC), to new case definitions for research and the understanding of the use of IFN-g release assays (IGRAs) in children and to the TBNET consensus documents. The ptbnet holds an annual meeting and is currently setting up a shared database system, which will facilitate epidemiological studies and clinical trials for children and families affected by tuberculosis in Europe.

NTM-NET

Diseases due to non-tuberculous mycobacteria are a differential diagnosis to tuberculosis both in pediatric as well as in the adult patients. In countries with decreasing tuberculosis incidence, pulmonary NTM-infections are of increasing importance in patients with pre-existing lung diseases, but still are considered rare diseases. Because its importance has only been perceived in the past two decades, little clinical research has been performed and treatment regimens have a very limited evidence base. Furthermore the exact pathogenesis of NTM lung disease as well as the interplay with the immune system also remains largely unknown. The need for international cooperation in basic and clinical research is evident in rare diseases like NTM-infections, and this was the motive for founding NTM-NET in 2009 as a branch of TBNET – an initiative of researchers from Freiburg University. Since then the NTM-NET has expanded across the world with strong bonds across the Atlantic with researchers from United States and Canada, but also to South East Asia and Australia. The NTM-NET now has about 150 members in 41 countries, and formal meetings are held biannually. Several studies have been launched, including a retrospective analysis of the worldwide distribution of NTM-species in respiratory secretions as well as a prospective treatment trial for pulmonary *M. xenopi*-disease. Future plans include the start of further treatment trials, establishment of a NTM-disease database and the revision of international guidelines.

Governance and organizational structure

TBNET is a non-governmental research organization registered at the court of Lübeck in Germany. TBNET is recognized as a non-profit charitable organization and has a VAT number. Membership is free for all participants, and registration is possible on-line. The TBNET office is lo-

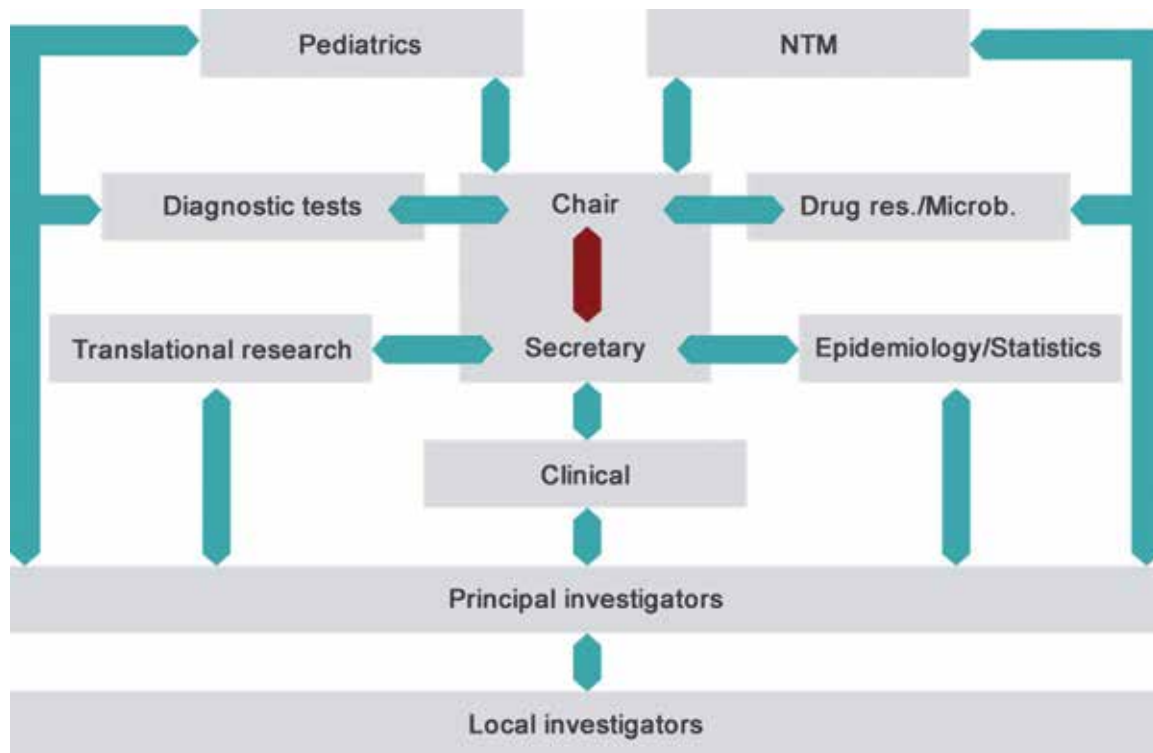


Fig. 2. TBNET governance and organizational structure. The steering committee is democratically elected and closely collaborates with principal investigators and members of the network to develop projects, training and teaching activities, and fundraising

cated at the Research Center Borstel, Germany and currently staffed with a part time manager. The steering committee consists of a chairman, a secretary, and representatives of the main areas of TBNET activity which include epidemiology and statistics, diagnostics, clinical tuberculosis, microbiology/drug resistance, translational research, pediatric tuberculosis, and non-tuberculous mycobacteria (Fig. 2). All positions are democratically elected for three-

year terms and one time renewal in office is possible. The treasurer is currently a professional certified accountant. The positions in the steering committee do not involve financial compensation. The steering committee closely collaborates with principal investigators and members of the network to develop and endorse new collaborative projects, to plan and implement training and teaching activities, and for fundraising (Fig. 2).

Announcements of ongoing projects, events and meetings are provided through the official TBNET webpage. Access is divided into a public and a restricted section. The public section is open to all interested individuals and provides information about the organization and the activities of TBNET. The restricted area is password-protected and accessible for TBNET members only. This section provides information about ongoing, finished, and future studies, including study protocols and overview tables on cooperating centers. In the near future, a TB consilium will be implemented within the TBNET webpage to allow registered clinicians to ask for essential collegial and professional help regarding appropriate treatment protocols for patients with tuberculosis.

TBNET activities

Activities within TBNET and its branches include three major areas, namely tuberculosis related research, training and capacity building, and networking (Fig. 3).

TBNET The Tuberculosis Network European Trialsgroup		
Research	Training	Networking
<ul style="list-style-type: none"> • Large pan-European cohort studies • Conducted in a collaborative approach by scientists from different disciplines & clinicians • Regular publications in peer-reviewed journals • Supporting EU-wide harmonization through recommendations and consensus statements 	<ul style="list-style-type: none"> • Provided by international experts for international audiences • Passing on specialized knowledge • Tailored specifically to young scientists • Multidisciplinary • Structured (TBNET Academy, summer-schools etc.) • Guided by recognized mentors 	<ul style="list-style-type: none"> • Taking place at annual meetings or continuously, in the context of projects, studies, and other TBNET activities • To exchange information • To get or give advise • To quickly integrate young scientists into the community

Fig. 3. Main areas of TBNET activities

Table 2. Important TBNET research findings

Finding	References
1 Unfavorable outcome in MDR tuberculosis with capreomycin resistance	Migliori et al. 2008 [15]
2 Favorable outcome of MDR/XDR tuberculosis under optimal medical care	Eker et al. 2008 [11]
3 Rapid identification of AFB-smear-negative tuberculosis by BAL-ELISPOT	Jafari et al. 2009 [7]
4 Limited effect of IGRAs for the diagnosis of active tuberculosis	Sester et al. 2011 [19]
5 Protective effect of BCG-vaccination against infection with <i>M. tuberculosis</i>	Basu Roy et al. 2012 [9]

Research

Research in TBNET has focused on the evaluation of novel methods for the rapid diagnosis of active tuberculosis and latent infection with *M. tuberculosis*, and more recently, on the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in Europe.

Important research findings published by TBNET are summarized in *Table 2*. Among them, diagnostic studies include the evaluation of novel biomarkers for the diagnosis of active tuberculosis and latent infection in adults [2, 5–8] and in children [9, 10]. TBNET is currently performing a pan-European study in a large cohort of immunocompromised individuals, including HIV-infected

persons, candidates for tumor necrosis factor (TNF) antagonist therapy, solid organ and stem cell transplant recipients, and patients with chronic renal failure to evaluate different methods for the diagnosis of latent infection with *M. tuberculosis* in a head-to-head manner. In addition, TBNET is closely monitoring a cohort of almost 4500 contacts of patients with active tuberculosis from 22 European Centers to evaluate the role of IGRAs to predict the development of tuberculosis in this risk group. Results from both studies will be formed in 2013.

In the field of *M. tuberculosis* drug resistance, TBNET was the first group to describe the epidemiology and clinical outcomes for patients with MDR/XDR tuberculosis in Europe [4, 11–13]. The group was the first to identify the



Fig. 4. Sites of hospitals for the care of patients with MDR/XDR tuberculosis in Europe that participate in the TB PAN-NET database research project

Table 3. Consensus documents

Topic	References
1 Definition of latent infection with <i>Mycobacterium tuberculosis</i>	Mack et al. 2009 [21]
2 Tuberculosis contact investigations in low prevalence countries	Erkens et al. 2010 [22]
3 Risk of tuberculosis related to the use of TNF antagonists	Solovic et al. 2010 [23]
4 European standards of tuberculosis care	Migliori et al. 2012 [25]
5 Risk of tuberculosis related to solid organ and hematopoietic stem cell transplantation	Bumbacea et al. 2012 [24]

importance of *M. tuberculosis* drug-resistance against fluoroquinolones [14] and injectable aminoglycosides/polypeptides [15] on treatment outcome in MDR tuberculosis. TBNET has also evaluated the safety and tolerability of second line anti-tuberculosis drugs, e.g. linezolid [3], and provided important information about adverse events on long-term drug treatment against tuberculosis.

Following the identification of substantial gaps in the clinical management of patients with MDR/XDR tuberculosis in Europe [16–18], TBNET is currently collating a prospective database in collaboration with the EU funded FP7 consortium TB PAN-NET with detailed information on the risk factors, diagnosis, treatment, adverse events and outcome of patients with MDR/XDR tuberculosis across Europe. Results from this large database project will provide guidance to improve the management for patients with MDR/XDR tuberculosis in the future (Fig. 4).

Formal systematic reviews and meta-analyses have addressed the value of the IGRAs in clinical practice [19, 20]. A systematic review of XDR tuberculosis emphasized the need for a standard definition and the use of quality assured laboratories to provide meaningful data on drug-resistance. Using the “wisdom of the commons” approach, consensus statements have been published (Table 3) regarding the nature and definition of latent infection with *M. tuberculosis* [21], contact tracing in low incidence countries [22], the risk of tuberculosis with TNF antagonists treatments [23], and the risk of tuberculosis in candidates and recipients of solid organ and hematopoietic stem cell transplants [24]. In addition, members of TBNET participated in the development of European standards for tuberculosis care [25]. A consensus statement on the management of patients with MDR/XDR tuberculosis is underway.

Europe is well placed to conduct clinical trials in latent infection with *M. tuberculosis* and in tuberculosis caused by drug-resistant mycobacteria. Adequate resources mean that immunological tests for latent infection with *M. tuberculosis* are accessible, and the low incidence of tuberculosis in Western Europe ensures that re-infection is less likely to affect the results as compared to high incidence regions of the world. Drug-resistance is an enormous problem in Eastern Europe, and the definition of effective new regimens to treat tuberculosis will be an important outcome of clinical trials. Again, access to quality controlled laboratories and molecular typing of drug-resistant strains is more readily accessible through collaboration between the different regions of Europe than it might be the case elsewhere in the world.

Training and capacity building

Activities in training and capacity building include training support of individual TBNET members as well as the implementation of TBNET schools and TBNET academies. Individual training is performed by the annual provision of grants for the attendance of a WHO supported course on the implementation of the Stop TB strategy. In addition, TBNET has developed a tuberculosis training course in collaboration with the ERS and TB PAN-NET that was held for one week in 2010 in Borstel, Germany.

The TBNET academy has been created as a new forum for young clinicians and researchers in the field of tuberculosis to exchange ideas and to learn from each other under expert guidance and mentorship. This academy is aimed at young residents, fellows, doctoral students, and post-docs within 3 years of their university degree, who are members of TBNET. In March 2011, the first TBNET academy took place in St. Leonhard in Austria. Eighteen young and talented clinicians and scientists were selected to meet international experts. The TBNET academy provides an excellent forum for the communication of young scientists to peers and experts within and outside each person’s field of expertise. The program includes keynote lectures by the experts in the field, review lectures provided by individual groups of participants, and discussions of clinical cases in an open format where everyone is invited to participate (Fig. 5). Special features such as how to write a manuscript, how to give a winning presentation, how to form a research network, how to obtain funding, and on the role of the mentor are part of the curriculum. Before the start of the Academy, the participants form individual groups with expertise in the areas of microbiology, molecular biology, epidemiology, immunology, and clinical research and are guided by a mentor during the preparation of the review lectures. The reviews aim to be comprehensive, explain and discuss recent developments or problems in the field, always supporting the work with clear evidence. The next TBNET academy will take place in spring 2013 in Chisinau, Moldova.

Networking – annual meeting

The annual meeting of TBNET is traditionally held on the Friday before the annual congress of the European Respiratory Society starts in the same city. A local TBNET member organizes an appropriate venue for about 100

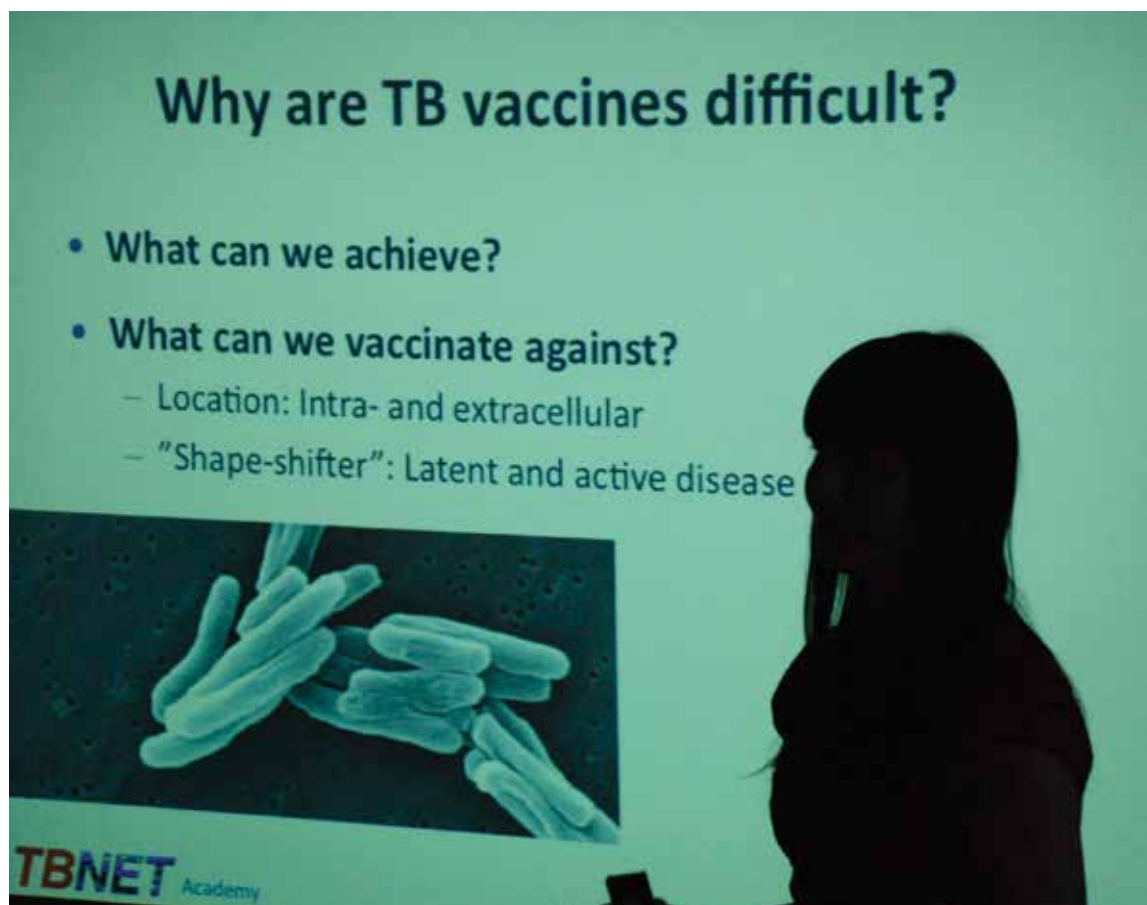


Fig. 5. TBNET academy. A young scientist is presenting an overview of tuberculosis immunology to other fellow participants



Fig. 6. Attendants of the TBNET meeting in Amsterdam 2011

participants, and the organization of this meeting is supported by the TBNET coordinating office. In addition to the legal requirements to inform the members about fiscal and administrative issues and the development of the network, the one-day agenda covers a scientific program reflecting the broad spectrum of research activity within TBNET. Preliminary findings and the results of ongoing TBNET studies as well as recently finished and published studies are presented followed by lively and productive discussions. The annual meeting offers also a platform to discuss new ideas and to build interregional networks

across multiple disciplines. This meeting is the major networking event to open new avenues for promoting clinically oriented research on the basis of a large number of cooperating centers in Europe and partnerships from abroad (*Fig. 6*).

As a result of several visits to the annual meetings by colleagues from Japan, a Memorandum of Understanding between the Japanese Society for Tuberculosis Diagnosis and TBNET was signed in 2012.

In addition to the annual meeting, the steering committee holds a two-day work meeting in spring.

TBNET projects

Up to now, TBNET has endorsed a total of 45 research projects, of which 32 are completed and 13 are ongoing. Proposals for TBNET projects may be submitted to the steering committee by all members at any time on a structured form. Formal criteria to be fulfilled include scientific novelty, sound statistical analysis, ethical approval, secure funding plans, and participation of TBNET members from at least three different institutions. Both the submission and the review procedure are based on formal predefined criteria to reach a structured presentation and impartial review process. Each proposal is reviewed by at least two experts in the field. All proposals that successfully pass the review process are endorsed as TBNET study. All newly endorsed studies including study protocols are placed on the TBNET website and presented at the annual meeting by the principal investigator. All TBNET members who are willing to participate in a given project are in direct contact with the principal investigator.

On the occasion of the World TB day 2012, TBNET initiated a photo contest entitled “Imagine a day with TB”. This activity was aimed at giving a visual impression of the varying effect of tuberculosis in the different geographic regions. All submissions were reviewed by a jury which selected the best photos to be used for raising public awareness of tuberculosis. Dissemination means will include illustrated books, calendars, and photo exhibitions in the public as well as on scientific meetings.

Financing of TBNET activities

In the years since its foundation, TBNET has benefited from both “in-kind” and “in-cash” support. The recognition by the ERS as an official Clinical Research Collaboration and related financial support was a first critical step and allowed TBNET to co-fund its administration. Similarly, ptbnet received some initial core funding from the European Society for Pediatric Infectious Diseases (ESPID). Clearly, the largest part of TBNET activities so far has been realized through significant in-kind contributions. Industrial cooperation partners have provided free test kits for the implementation of independent studies performed by TBNET, thus reducing the cost of research studies. However, the most significant in-kind support has been provided by individual TBNET members who have dedicated their time and efforts to TBNET activities without receiving financial reimbursement. TBNET gratefully acknowledges these valuable and significant contributions “from within”, by scientists and clinicians who contributed to studies without receiving any monetary reimbursement and their institutions who granted them the freedom to engage in TBNET activities, those who helped set up infrastructure such as the secretariat or the website, those who serve on boards, and those who participate in meetings at their own cost. The combination of these in-kind and in-cash contributions has enabled the foundation and

strengthening of TBNET as a pan-European community with significant expertise.

To take this initiative to the next level and help transforming TBNET into a sustainable platform, additional funding is now needed for three different types of activity:

- **Coordination and streamlining of individual, nationally funded research activities** to maximize European synergy and added value in clinically-driven tuberculosis research. TBNET members as individuals are represented in a variety of research initiatives that are funded nationally or e.g. under the 7th Framework Programme by the European Commission (FP7). A targeted approach to systematically coordinate and manage this portfolio of individual projects could be realized through a set of activities funded, for example, under the COST scheme and would lead to a significant leverage effect. COST funds open network initiatives that foster interdisciplinary collaboration and support the integration of early stage researchers into the scientific community.
- **Reimbursement for research and development (R&D) services** which are in line with TBNET aims and objectives. This important pillar of funding for TBNET activities has been performed successfully in the past, such as through replying to tenders by the ECDC, or through service delivery under a subcontract in the BMBF funded German “TB or not TB”-consortium, and needs to be continued and expanded.
- **Additional, own research activities driven by TBNET.** The network is now at a stage where it has proven its ability to design and implement large multi-country research studies leading to recognized peer-reviewed publications. TBNET has the potential to contribute to the education and support of the next generation of scientists in the field, and has established itself as a reliable partner for key European institutions. Furthermore, TBNET is formally ready for the direct participation in EU funded initiatives, with its registration in the EC database and validation by the Commission Services recently completed.

The next step is now to look at international research funding programmes such as FP7, the upcoming next EU Framework Programme Horizon 2020, or the European and Developing Countries Clinical Trials Partnership (EDCTP), and initiate their own TBNET-driven projects in the future.

Initial training networks under the FP7 PEOPLE programme for example aim to encourage international mobility of young researchers, improve their research skills, enrich those through complementary training, and foster interdisciplinary and intersectorial collaboration – objectives that are fully in line with the TBNET policy for training and capacity building and would thus and perfectly extend and complement ongoing activities such as the TBNET academy.

Large international research initiatives could be implemented as a collaborative project under the COOPERATION programme within FP7, or as an approach to respond to the societal challenges addressed in Horizon

Table 4. Future activities of TBNET

Research	Epidemiology and databases <ul style="list-style-type: none"> – Outcome of latent infection with <i>M. tuberculosis</i> where re-infection unlikely – Effectiveness of different second line regimens – Frequency of adverse reactions to second line drugs Multicenter diagnostic studies <ul style="list-style-type: none"> – Evaluation of new diagnostic tests for tuberculosis – Evaluation of human markers of inflammation – Predictors of the development of active tuberculosis after infection Multicenter drug trials <ul style="list-style-type: none"> – New drugs in MDR/XDR tuberculosis – New regimens for preventive treatment
Training	TBNET academy European training course on tuberculosis
Capacity building	TBNET consilium TBNET research center Fellowships for young investigators

2020. In the framework of such a project, TBNET with its unique combination of basic and clinical researchers could directly contribute to the translation of research for human health and help optimize the delivery of healthcare to European citizens.

Lastly, TBNET with its dual focus on clinical trials and capacity building could be a most valuable partner for projects funded by the EDCTP, a partnership between European and African partner countries that aims to fight poverty related infectious diseases by supporting the implementation of clinical trial activities in Sub-Saharan Africa, strengthening clinical trials capacities, and improving the research environment and infrastructure in Africa.

Future outlook

TBNET remains committed to fostering collaborations among those who are engaged in the management of patients with tuberculosis. The goals of TBNET are intended to bring advances in research into clinical practice and create a cycle of innovation and progress. Key areas of interest are summarized in *Table 4*. Our reasoning is that without rapid progress in the development of new drugs for tuberculosis and an understanding of latent infection, we will be overwhelmed by untreatable, drug-resistant tuberculosis. To prevent this, we need a network that encourages patient participation in research during the routine clinical care. In the 1970s, the Medical Research Council began its first national collaboration in the treatment of leukaemia. After expecting 10% of patients to participate, within 10 years enrollment was 82% and instead of one in five surviving, four in five now have disease-free survival. Similarly, our aim is that every patient with tuberculosis and every contact is successfully treated and contributes to the research progress by participating in a clinical trial. This requires that tuberculosis physicians start collecting standard data, to achieve standards of good clinical practice sufficient for clinical trials. This is important to allow randomized controlled trials of the best vs. the likely “bet-

ter than best” treatments, beginning with drug-resistant disease. TBNET will promote standard simple techniques so that different regimens can be evaluated, e.g. for early bactericidal activity of novel antituberculosis drugs. The TB PAN NET database can be simplified and modified to capture sputum smear and culture conversion, outcome and rate of relapse as a standard of care. The UK MDR tuberculosis Advisory Group has given advice on the management of drug-resistant tuberculosis [26] and is a model for a similar European advisory service, the TBNET Consilium, by physicians for physicians to manage drug-resistant tuberculosis in the best possible way. This forum already exists within the ptbnet and has found to be valuable for patient management and educational purposes.

Latent infection with *M. tuberculosis* must be tackled effectively and efficiently in order to consider the prospect of elimination of *M. tuberculosis* as a human pathogen [27]. The modern epidemiology of latent infection with *M. tuberculosis* is unknown, and rates of relapse have been affected in the past by the much higher likelihood of re-infection. In Europe, these important data can be easily obtained because the incidence of tuberculosis is sufficiently low to make repeated infection unlikely and because the molecular typing can confirm identity of the strain of tuberculosis in the contact with the original index case. Currently, many contacts are treated who will not develop active tuberculosis (number needed to treat to prevent one case of tuberculosis is 72 (95% confidence limits 50 to 143) [28] and treatment lasts at least 3 months. The low rate of active disease in contacts after the initial assessment requires studies that enroll more than 10,000 subjects to have sufficient power to distinguish between different preventive treatments and obtain sufficient numbers of patients who will develop tuberculosis, a feat that only an active network such as TBNET will be able to achieve. The collection of strain typing of the index, documentation of contacts in a standard manner including the use of new immunological tests and follow-up has begun. The use of blood samples from these contacts which remain after tests

performed in routine patient management have been completed can, after obtaining an informed consent but without extra costs to the patient in terms of time or additional blood tests, be used to explore predictors of relapse, especially in the majority who decline preventive treatment or whose older age limits the use of potentially hepatotoxic drug regimens.

The application of “omics” research in the microbiology and human immune response to tuberculosis is at an early stage [29]. The clinical studies will provide valuable material for collaborators in basic science to pursue an understanding of latent tuberculosis and the mechanisms by which drug-resistance arises. From these, fruitful collaborations should spring new diagnostic tests, new drug targets and their treatments, and new tests to focus the limited resources in health care on those who will benefit most.

In order to encourage the links between basic science and clinical practice, TBNET started the TBNET academy. For in-depth research in drug-resistant tuberculosis, we plan a TBNET Research Center in an area of high incidence. This center can pilot the new diagnostic tests, the application of molecular biology and immunology to patient management and test out the forms and processes that can then become part of a larger network of randomized controlled trials of treatment.

The expertise of those in basic science needs to inform physicians so that progress can be accelerated and hopefully prevent our health systems being overwhelmed by untreatable, drug-resistant tuberculosis, and a burden of latent infection which will take many years to overcome. TBNET has an ambitious programme, which remains dependent on the enthusiasm of clinicians to make research part of normal clinical practice and the expertise of basic scientists to realize the potential of the clinical material that such a network can afford.

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