

Brazilian Tuberculosis Research Network - REDE-TB

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Abstract

Despite the significant progress of tuberculosis (TB) and nontuberculous mycobacteria research in Brazil, at the beginning of the millennium there was still a weak cooperation among the various actors in this area: industry, universities, research institutes, civil society and health services, including the National TB Program (NTP). In 2001, REDE-TB - the Brazilian TB Research Network - was created as a multidisciplinary group of Brazilian researchers, students, civil society and health services representatives working with TB and HIV/AIDS throughout the country. REDE-TB helped build the necessary bridges between these different actors to promote research and educational activities in an integrated manner. Recently, REDE-TB prepared the National Tuberculosis Research Agenda. We identified gaps and priorities for research and innovation platforms focused on national demands. These platforms will be based on the integration of basic/clinical/translational research with the industrial park in order to expedite the availability of new technologies and new management strategies for the health system. These technologies will be evaluated with operational research within the current Brazilian healthcare system in order to analyze its impact from the individual and collective perspective.

Keywords:

Research & development, nongovernmental organizations, tuberculosis, nontuberculous mycobacteria.

The Brazilian context before the REDE-TB was established

In the 1970s, the country experienced a positive mood due to innovative actions implemented by the National Tuberculosis Program/ Ministry of Health (NTP/MoH) coordination. These actions included a pioneer incorporation of the shortened therapeutic regimen (six months of rifampicin/ isoniazid/ pyrazinamide) and the closing down of most existing sanatoria. Thanks mostly to the introduction of the new regimen, it was thought that TB control would be effective. As a result, the fight against the disease suffered some demobilization across various sectors, including academia and the biomedical societies, with a weakening of nongovernmental organizations (NGOs) which promoted advocacy and diffusion of the issues related to TB. It was then that the Brazilian Tisiology Society was fused with the Brazilian Pneumology Society, resulting in the Brazilian Society of Pneumology and Tisiology (SBPT).

Against this background, the Unified Health System (Sistema Único de Saúde – SUS) was introduced in the late 1980s, having as pillars the principles of equity, universality and comprehensiveness. From this point on, SUS's organization stipulated that basic attention would be the entry door to the system and, therefore, actions against TB were decentralized. This recommendation brought on a slow restructuring of the NTP/MoH, with migration from a vertical structure to a horizontal one.

In the 1990s, after a long period of military dictatorship, the elected president, Fernando Collor, adopted as his political guideline cutting down state expenditures and public salaries. As a result, a considerable drop in the NTP/MoH's performance took place. In spite of this, a few initiatives implemented by the NTP occurred over this period, such as the creation of the Society of Fine Chemistry of Tropical Diseases (QTROP), in partnership with teachers of fine chemistry at the Federal University of Rio de Janeiro (UFRJ). However, this initiative resonated little at the national level, probably because of its restricted scope. Despite the advances in basic research in Brazil, the need to bridge gaps between basic research and translational research has been identified since then, with the aim to broadening the frontiers of knowledge, the main obstacle towards developing scientific and technological innovation in the country.

At the end of the 1990s, a new National TB Control Plan was drawn up, based on bringing an end to agreements between the federal government and the states, since they did not add value to the services, nor did they promote a restructuring of health care providers with a view to overcoming operational problems. It has been proposed to health care providers that they: a) analyzed their results as to the compliance of TB control targets, taking into account their structure, processes and results; b) adopted a

new method to transfer financial resources to the municipalities, based on their results; c) gave priority to introducing the Directly Observed Therapy Short course (DOTS) strategy across the whole nation. Following this decentralization trend, the Sanitary Pneumology technical area was incorporated to MoH's Department of Basic Attention from January 2000.

The lack of political commitment to control TB throughout different government terms was an ongoing pattern along the following years. Decisions were made without any technical grounds, nor any participation of the social and academic sectors to plan and carry out actions both locally and regionally. Against this backdrop, two seminars on TB Investigations were held on the Federal University of Rio de Janeiro (UFRJ) campus. The installed capacity, proven technical and scientific competence were evidenced in Brazil, but there was still an ineffective articulation among the major players – government, academia and industrial base. As a by-product of the seminars, a network was consensually created whose mission was to face the challenge of reducing the gaps to other sectors, such as enterprises and civil society, endeavoring to include and undertake efforts which could lessen this scourge to humankind.

REDE-TB's inception, its organization and initial activities

In its initial stage, the REDE-TB was formed by researchers drawing from different regions of the country, who carried out investigations both in basic and operational research, integrated by partnerships.

The innovation consisted of a strategy to:

- a) regard the REDE-TB as a self-organizing organism, as conceived by Immanuel Kant in his *Critique of the Power of Judgment*: to prioritize the systematic thought (contextualized) and avoid a merely analytical approach, preventing fragmentation;
- b) identify leaders in different areas/disciplines who were willing to coordinate these connecting points (coordination areas), with a view to acting in different platforms, in which each subject can both act on and champion processes, whose key mission would be to control TB;
- c) regard this procedure as an essential strategy which might identify gaps and partnerships, and to facilitate control actions both on national, state (provincial) and municipal levels.

In May 2001, the Ministry of Science, Technology & Innovation's (MCTI) National Council for Scientific Research and Development (CNPq) launched a request for applications for the creation of Research Networks, the so-called Millennium Institute. Under the guidance of Professors Afrânio Kritski and José Roberto Lapa e Silva, from UFRJ; Antonio Ruffino Netto and Célio Silva, from University of São Paulo (USP), Ribeirão Preto; and Diógenes Santos, from Pontifical Catholic University (PUC)-RS, a proposal

was submitted in the area of TB, entitled "Integrated Strategies towards the Study and Control of Tuberculosis in Brazil: New Drugs, New Vaccines, Diagnostic Tests and Clinical-Operational Evaluation". In October 2001, of 260 proposals submitted to CNPq, the REDE-TB one was shortlisted among the 17 approved proposals. Of these, only three were in the biomedical area, and none had as comprehensive a scope as the one proposed by the REDE-TB. This achievement has been a landmark in the biomedical history of the country, not only because of the scientific merit recognized by the funding body, but chiefly for the acknowledgment that developing knowledge and transferring it may be undertaken in a collective, integrated, multidisciplinary and decentralized way. There is no doubt that the funding played a crucial role to put in practice the activities which brought together researchers and further REDE-TB players, obtained both on that request for applications and on the following ones issued by the Millennium Institutes in 2003 and 2005.

The guiding idea for the project was the synergy between research centers which competed independently for the same resources, heightening the research and reducing their time frame, especially by the recruiting ability which arose at the collaborating centers where REDE-TB's coordinators were present. This proposal also contemplated interaction and promotion activities of operational research, in which a liaison with SUS would be crucial.

Initially, the REDE-TB consisted of the following coordination areas: Drugs, Diagnostics, Vaccines, Basic Research, Clinical Research, Epidemiology/Clinical-Operational, Human Resources, and Interaction with the Industry. Further coordination areas were later created. Currently, the REDE-TB also encompasses the following areas: TB/HIV, MDR-TB, Pediatric TB, TB in Prisons, TB in Indigenous Populations, TB in the Homeless Population, Quality Management, Social Mobilization, TB Infection Control, and Non-tuberculous Mycobacteria.

The following years were marked by the REDE-TB's consolidation. Eight national workshops were held from 2002 in Rio de Janeiro (Southeastern Region), Manaus (Northern Region), Fortaleza, Recife and Salvador (Northeastern Region), and Campo Grande (Central-Western Region). São Paulo, Rio de Janeiro and Vitória (Southeastern Region).

At the REDE-TB's First National Workshop, which had 800 participants and took place in Rio de Janeiro in September 2002 (<http://www.faperj.br/?id=6.2.4>), the following priorities were consensually identified:

a) Creating a legal society from the concept of REDE-TB. This society would constitute a corporate entity, with its own statutes and by-laws, and a board of directors elected every 2 years by universal suffrage in general meetings.

b) Including members of the REDE-TB should occur through requests made to the professional with interest to undertake and/or take part in research projects in TB and other mycobacterioses. Creating different subject areas with a coordinator and vice-coordinator, whose key mission would be to make the connections among researchers of their respective areas, to improve viewing and management of the REDE-TB.

c) Creating new areas in addition to the existing subject areas: Social mobilization and TB/HIV.

d) Promoting actions to help create TB-related NGOs at the local, state and national levels.

e) Promoting regional seminars to locally facilitate liaisons among government/services, academia and civil society.

f) Promoting seminars in the areas of Pharmaceuticals and Diagnostics, focusing on the Interactions among Industry, Regulatory Bodies (ANVISA, CONEP), Science, Technology and Innovation in Health Secretariat (SCTIE), MCTI's CNPq/Finep, the Social Development Bank (BNDES), and the REDE-TB.

g) Holding REDE-TB's National Workshops, interspersed with other activities, such as the National TB Meetings, which should be coordinated by the REDE-TB, together with key partners: NTP, Ministry of Health's STD/AIDS National Program (currently Department of STD/Aids/Hepatitis), Medical Societies (i.e. SBPT, Brazilian Infectology Society, Brazilian Tropical Medicine Society), as well as the representation of the International Union against Tuberculosis and Lung Diseases (UNION) and of the Pan American Health Organization.

Another priority was to identify NGOs and International Cooperation Agencies which could take part in this process.

h) Creating a website for the REDE-TB, to optimize everyone's efforts, substantiating the existence of a virtual, articulated and updated NETWORK (www.redetb.org).

i) Stimulating the certification and/or accreditation of laboratories and/or 'clinical sites' whose coordinators are members of the REDE-TB.

Over the ensuing 14 years, the REDE-TB coordinators have endeavored to attain these goals. Among these goals, completion of the process of the REDE-TB's registration as a corporate entity, on July 1, 2003. In August 2003, some REDE-TB coordinators helped create ONG-TB in Rio de Janeiro, and in November 2004, they took active part in the creation of the Brazilian Partnership against TB, linked to the STOP TB Initiative. Over the following years, the Brazilian Partnership against TB has been voted academia's representative at the Executive Committee.

The First National TB Meeting took place in Brasília in 2004, under the joint coordination of the REDE-TB, the NTP and SBPT. This meeting brought together efforts by academia, government and civil society.

Since then, 5 other national TB meetings have taken place in São Paulo, Salvador, Rio de Janeiro and Brasília. From the Fourth Meeting, civil society joined the event's Organizing Committee. Brazilian Stop TB Partnership's First and Second Forums took place at the same time as the Meetings.

From 2007 on, under new management by the NTP/MoH, a higher level of interaction in research has taken place between the REDE-TB and the government. Representatives of the REDE-TB started to participate in NTP/MoH's National Technical Advisory Committee (CTA) which, in its twice-yearly meetings, discussed TB control priorities and policies. Acting as consultants, these representatives took part in the review of the *Manual de Recomendações para o Controle da Tuberculose (Recommendations Manual for TB Control)*,¹ published at the end of 2010, after 20 years without undergoing any reviews. The NTP made recommendations which included a regimen with four pharmaceuticals in combined fixed dosage, then used across nearly the whole globe, except for five countries – Brazil included, the only one with a high TB burden.

Still in 2007, the REDE-TB joined Tuberculosis Global Fund Project's Executive Secretariat, with active participation to draw up and monitor projects together with the Country Coordinating Mechanism's (CCM) meetings.

As soon as the Millennium Institutes' requests for applications were completed, in late 2008, the REDE-TB coordinators, professors Diogenes Santos (PUC-RS) and Afrânio Kritski (UFRJ), received approval for the project submitted to MCTI's CNPq, which set out the creation of the National Tuberculosis Science and Technology Institute (INCT-TB), headquartered at PUC-RS and at UFRJ-RJ. The goal was to develop anti-TB medications and/or vaccines in the mid- and long-term, and diagnostic tests, either molecular or not, in the short term, to control TB, MDR-TB and HIV-associated TB, employing the so-called 'from workbench to the shelf' approach (Cf. Process – CNPq /INCT 573548/2008-0, available on http://www.medicina.ufrj.br/noticias.php?id_noticia=351).

In 2009, the REDE-TB was invited by the World Health Organization (WHO) to take part in the Task Force for Movement Research. Although the research was reintroduced by WHO in 2006 as a recommended global TB control tool, there has been so far no evidence of its being incorporated into Tuberculosis Control Programs in high-burden countries. The REDE-TB has taken active part in the debates in progress among representatives from the WHO, UNION, the Bill & Melinda Gates Foundation, FIND, NIH and the University of Liverpool about which appropriate indicators should be used to analyze the impact of incorporating new technologies in the fight against TB. The REDE-TB, through the National Committee for the Incorporation of Technologies (CONITEC), has then submitted to the

NTP/MoH's CTA a platform to evaluate the incorporation of new technologies which were included in the government proposal.²⁻⁴ CONITEC, similarly to the UK's National Institute for Health Care and Excellence (NICE), is the MoH's body that analyzes the inclusion to or removal of technologies from SUS, based on safety, efficacy and cost-effectiveness evaluations. In this scenario, other process indicators should be used to analyze the clinical and economic impacts of innovations, not only the usual indicators drawing from epidemiology.

In 2009, the REDE-TB took part in putting together and coordinating two nation-wide projects, whose aims were, through pragmatic clinical trials (under routine conditions), to analyze the use of new molecular tests to be employed in the diagnosis and therapy of TB and MDR-TB, respectively, in primary health care (Xpert MTB/Rif – funded by the Bill & Melinda Gates Foundation), and in secondary and tertiary health care (Xpert MTB/Rif and MTBDR plus – funded by USAID/UNION) in different cities across the country. The Quality management courses promoted by the REDE-TB were key to qualifying the professionals involved in carrying out these TB pragmatic studies. Xpert MTB/Rif was incorporated to SUS in 2014, after approval by CONITEC. It currently serves as the basis for diagnostics of approximately 65 per cent of the cases in the country.

In 2011 new debate needs at the REDE-TB were identified and the areas dedicated to neglected populations were created: TB in indigenous populations, TB in freedom-deprived people, TB in homeless populations and pediatric TB.

In 2013, as a response to a request by WHO's Task Force for Movement Research, various interested parties in TB control convened in São Paulo to discuss and identify movements which could stimulate interactions among academia, research institutions, the industry, regulatory bodies, government institutions, NGOs and civil society, with the following basic targets:

1. identifying the most relevant TB research areas in Brazil;
2. developing a plan to outline and prioritize a national TB research agenda in Brazil;
3. identifying strategies to put in practice the National TB Research Agenda, to comply with the Third Pillar, as debated by the WHO.

In 2013, the National Institute of Allergy and Infectious Diseases/National Institute of Health (NIAID/NIH) requested REDE-TB's help to identify clinical sites in Brazil to carry out case-cohort studies and contacts in the TB area – the REPORT project. The aim of this project, undertaken in partnership with India, Africa and Indonesia, was to collect clinical and laboratory (clinical samples) data for later use in studies related to basic and translational research. Inclusion of sites in Rio de Janeiro, Manaus and Salvador was made possible through joint

funding by NIAID/NIH and the MoH's Department of Science and Technology, at the Science, Technology and Strategic Supplies Secretariat (Decit - SCTIE-MoH).

In 2014, as a result of the debates held at Movement Research, WHO signaled that the REDE-TB might be a good example of integrated efforts in TB research, since research started to feature as one of three pillars in the 2015 Global Plan to Stop TB.

In 2015, the REDE-TB launched a survey among representatives from different institutions, either in government, academia, research, and civil society about which TB research priorities should be indicated for Brazil, in response to the demands posed by the new Global TB Plan, as proposed by the WHO and the STOP TB Initiative. In late 2015, the REDE-TB, with the help of the NTP/MoH and Fiocruz, coordinated the consolidation of the National TB Research Agenda, to be adopted by public policy makers and funding bodies.⁵

The activities described above show the close collaboration among researchers, different sectors of government and civil society, and the importance attributed to the REDE-TB by the international funding and research bodies.

Current REDE-TB activities

Some of the REDE-TB's coordination areas are consolidated, while others are still looking for the best way to actively take part in the REDE-TB (Box 1). One of the firm convictions which has become a consensus among researchers in the basic and translational areas is the steadfast need for interaction with national and international industry. This movement has arisen especially in the diagnostics area, since there was a consensus about the requirement that the new diagnostic methods developed by the Brazilian Academy would only be made available to society if they had a high level of reproducibility, as a result of the standardization obtained through industry developed kits.

Basic/translational research

The clear and solid objectives, as well as the correct model adopted in the methodological strategies, may not be sufficient to prove the hypotheses conveyed by a basic science project. However, the qualification and experience of researchers may comply with Louis Pasteur's statement: *"In the fields of observation chance favors only the prepared mind."* Standing before the unknown, they may devise new hypotheses, set up new experiments and go ahead in their search for knowledge. Given the urgency of TB control, which is further aggravated by neglect on the part of those who hold financial resources and political power to carry it out, it is imperative that knowledge be transferred from a basic area to another, closer to the patient and society. It may be said that in few areas of scientific knowledge the gap

between generating it and applying it is so short and quick to transpire.

Vaccines

The REDE-TB and the Tuberculosis Research Center of the Medicine College, Ribeirão Preto - USP have been adopting various innovative strategies to develop new preventive and therapeutic vaccines to control TB.

Different experimental models for vaccine may be outlined:

(i) DNA vaccines; (ii) subunit vaccines, which use secreted and/or recombinant antigens; (iii) vaccines vectorized by live microorganisms, such as BCG and Salmonella; (iv) vaccines vectorized by controlled release systems, such as microspheres, liposomes and monoolein systems; (v) attenuated mycobacteria, saprophyte and recombinant BCG vaccines. Of these strategies, a DNA vaccine (DNA_{hsp65}) has shown the ability not only to prevent infection by *M. tuberculosis* but also therapeutic activity against the established disease. Results obtained in mice, guinea-pigs and monkeys have shown that the DNA_{hsp65} vaccine might cure chronic cases, disseminated disease, latent infection and MDR-TB. It also prevents disease reactivation in immunosuppressed animals and, when used jointly with chemotherapy, it is able to reduce TB treatment times.⁶⁻¹³

To undertake vaccine research and development, a spin-off company has been founded by REDE-TB researchers, whose aim it is to establish an important link between basic research and the productive sector in biotechnology in Brazil. The company, Farmacore Biotecnologia Ltda, has produced pilot batches for some of the vaccines being developed, to start the clinical trials.

Pharmaceuticals

The REDE-TB's Pharmaceuticals area has been dedicated to looking for new anti-TB agents along two different fronts: rational projection of pharmaceuticals from defined molecular targets, and phenotypical screening linked to new strategies to identify new anti-TB acting compounds. Among the identified pharmaceuticals, mention should be made of the IQG-607 compound (pentacyano (isoniazid) ferrate(II)), analogous to isoniazid (INH) and able to inhibit wild *Mtb* InhA *in vitro* activity as well as the activity of mutant varieties associated with resistance to INH from clinical isolates. Furthermore, this compound has been proved safer than INH. Thanks to the collaboration with the industrial laboratory SSK Biosciences Pvt Ltd at Pilani, Hyderabad Campus, Jawahar Nagar, it has been possible to arrange for a staggered synthesis of the IQG-607 compound (15kg/batch). Pre-clinical studies in mini pigs are under way and their results are quite favorable. Studies in human beings (stage I) should start soon. New derivatives in the chinoloxycetamide class were planned from the GSK358607A compound, identified

by the GlaxoSmithKline (GSK) group through screenings, in assays involving intact cells from their collection of molecules. This compound caused a powerful inhibition of *M. tuberculosis* H37Rv cell growth (MIC=0.70µM), low cytotoxicity to HepG2 cells (IC₅₀>50µM) and an acceptable therapeutic index (I.T.=HepG2 IC₅₀/H37RvMIC>50 times). In order to explore the relationship between the chemical structure and biological activity (SAR – structure-activity ratio), a series of 22 new analogs from the chinoloxycetamide class was synthesized, making this a promising new approach.

Diagnosics

Among the new diagnostic tests developed by REDE-TB researchers, interaction with national industry was made possible to market molecular (Detect TB, Q3) and phenotypical tests (recombinant PPD, Nitratase kit),¹⁴ developed by FEPPS-RS, Fiocruz-Tecpar-PR, FURG and UFMG researchers, respectively. The Detect-TB test and the SIRE Nitratase kit were approved by Anvisa and are being traded in the country.

Decit – SCITE funded the analysis of the clinical and economic impact of Detect TB across different regions of the country, the results of which were similar to the ones obtained with Xpert® MTB/Rif, manufactured by an American company. The other diagnostic tests are currently in the development, laboratory validation and/or efficacy studies stages.

The REDE-TB researchers also analyzed the clinical impact of using MGIT960 under routine conditions,¹⁵ and new molecular tests already traded as MTBDR plus and MTB Rif in the diagnostic approach of suspected MDR-TB patient, in reference centers of four states of the country (PROVE IT project, funded by USAID).¹⁶

REDE-TB researchers also undertook the Xpert® MTB/Rif implementation, acceptance and cost-effectiveness studies in an NTP project (InCo-TB project, funded by the Bill & Melinda Gates Foundation). Thanks to these analyses, the test was incorporated into SUS in 2014.¹⁷⁻²³

Clinical research/clinical trials

REDE-TB researchers are taking part in several multicentric clinical assays to test new regimens and new pharmaceuticals to treat sensitive, resistant and latent TB.^{24,25} The bedaquiline study and the comparison between the 4RIF and 9INH regimens for latent TB are examples.^{26,27} We are also undertaking a pragmatic clinical trial in primary health care units in the cities of Recife, Manaus and Rio de Janeiro, with the aim to compare different operational approaches to boost detection and diagnosis of latent TB. Public health actions will be implemented which are based on the initial situational diagnosis and the solutions proposed by the health units themselves.

Operational research

Activities in the areas of Epidemiology and Operational Research were put in practice in tandem until 2014. Epidemiological research sought new knowledge about the frequency and distribution of TB/HIV nosological conditions, the determining factors and the geoepidemiological condition. Operational research, on the other hand, was generally related to tracking knowledge displacement, technology transfer, technological practices for clinical use, evaluation of the implementation success of new interventions in prevention, therapeutic instruments, population based interventions, barriers to applying this knowledge and its implementation, studies about how to generalize interventions, and their efficacy. Where these two research fields meet, dozens of papers were published both in the national and international press.

The REDE-TB supported the establishment of ten operational research groups in tuberculosis in Brazil between 2001 and 2016: EE-UFRN-Natal; EE-UFPB-João Pessoa; EE-UNIRIO; UNIOeste-PR Foz do Iguaçu; FM-UFTM-MG Uberaba; State University of West Paraná-UNIOESTE/Foz do Iguaçu; EE-UFRS Pelotas; EE-FAMERP São José do Rio Preto-SP; EE-UFSCar São Carlos – SP; and EE- UFRS Santa Maria-RS, in partnership with USP RP.

The following contributions in operational research by the REDE-TB in the impact analysis of management/evaluation of health services are worth mentioning:

a) development and validation of an assessment questionnaire for the organization and performance of health care providers in dealing with TB, based on the Primary Care Assessment Tool (PCAT), which was adopted in over 30 municipalities across different regions of Brazil,²⁸⁻³² with citations on the Web of Science (25), Scopus (31), Google Scholar (78), and Scielo (92); and

b) evaluation of health care technologies through the creation and introduction of a TB support information system (SISTB) among health care providers with PCT in the Ribeirão Preto municipality (São Paulo State), in partnership with PCT coordination of the State of São Paulo 2014-2016.

Quality management

Since 2009, when the Quality and Technology Transfer area was created, approximately 12 courses were offered in Clinical and Laboratory Good Practices, aimed at health care professionals involved in clinical and operational research.

From 2016, the REDE-TB's aims are:

a) to help review the Policies of Public Health Laboratories and Collaborating Centers (linked to universities and research institutes), seeking allocation of the financial and human resources necessary to implement the Quality Management System; and

b) to obtain accreditation by INMETRO (via ISO 15189 or ISO 15025) at least for Reference Laboratories and Collaborating Centers which agree to effectively take part in the national TB research agenda in Brazil.

Infection control

Coordinators in the TB Infection Control area have helped carrying through national TB meetings in hospitals, from 2007 on. They also took part in the Inter-professional Seminar: "Health Care Worker Safety in the Context of Drug-Resistant Tuberculosis in Low and Medium Income Countries", coordinated by the World Medical Association (WMA). These activities were key to include TB infection control actions in the *Recommendations Manual for TB Control*.¹ Recently, the REDE-TB, together with the NTP/MoH, took active part in the review of TB infection control indicators to be disclosed in 2016 by the WHO and by End TB Transmission Initiative (ETTI), UNION's Working Group.

Human resources

In 2004, the SCTIE-MoH assigned to the REDE-TB the task to help in Research Qualification for the control of TB. The qualification course developed by the REDE-TB focused on areas of Clinical and Operational Research, and Health Systems. Preliminary results of the research qualification course were auspicious. This made funding of this approach possible by the National Institutes of Health (NIH), from 2005 to 2010, in a request for applications named International Implementation, Clinical, Operational and Health Services Research Training Award for AIDS and TB (IICOHRTA AIDS/TB) Program, TW 006883, coordinated by professors José Roberto Lapa e Silva, Afranio Kritski and Antonio Ruffino-Netto, in collaboration with three US universities. The IICOHRTA program comprised courses in four levels.

Fifty different types of level 1 courses and events were organized, which were attended by 1216 individuals. These activities consisted of courses in critical reading of scientific papers, scientific writing, good clinical practices, good laboratory practices, research ethics, collection and management of epidemiological data, research methodology for laboratory professionals, as well as data analysis and database creation based on software packages such as SPSS and R.

On level 2 courses, the aim was to qualify SUS's health professionals to develop and discuss operational and epidemiological research projects, especially in Tuberculosis and HIV. Twenty-one courses in Principles of Scientific Investigation Methodology took place between 2004 and 2012, 20 across different cities in Brazil and one in Maputo, Mozambique. At the end of the course, students presented their research projects and the five best ones were granted funding. 260 projects (56 per cent) by 462 students in total who took part in the courses were developed between 2004 and 2012.

Twenty level 3 courses were offered to 88 students in the American institutions taking part in the IICOHRTA: Johns Hopkins Bloomberg School of Public Health (JHSPH), University of California School of Public Health, and Division of International Medicine – Weill Medical College of Cornell University.

Sixty-one students took part in level 4: 28 finished the master's degree, 29 the doctor's degree and four finished the post-doctoral degree.

Publications by mid- and long-term trainees (level 3 and 4 courses) linked to research qualification amounted to 227 scientific papers until present.

Epidemiology

A closer interaction between the REDE-TB coordinators and NTP/MoH has developed from 2010 on. Thanks to the MoH's request for applications, with approval of the '*Spatial analysis of tuberculosis epidemiological data in Brazil's metropolitan regions*' project, the Epidemiology Laboratory at Federal University of Espírito Santo (UFES) gained access to SINAN-TB's nominal database and, therefore, several analyses could be carried out nationally by REDE-TB researchers. From 2012 on, REDE-TB researchers, together with the WHO and the London School of Hygiene and Tropical Medicine took part in studies related to social factors determining tuberculosis.³³⁻³⁹ Still in 2012, at the Fifth National TB Meeting, social factors determining tuberculosis started to be considered important for maintaining the disease indicators. In that year, projects led by REDE-TB researchers were approved at the CNPq's requests for applications which focused on studying the social factors determining neglected diseases.

In April 2013, in response to a WHO request, together with NTP/MoH, the REDE-TB took part in the Seminar 'Eliminating Tuberculosis' Economic Onus: Universal Health Care Coverage and Opportunities for Social Protection. In this event, it was possible: a) to bring together researchers and government representatives from high tuberculosis burden countries, multilateral and bilateral agencies, and civil society organizations, b) to nationally foster collaborative work to eliminate the economic onus related to treatment of the disease and c) to discuss social protection strategies to people living with tuberculosis and their families (http://www.who.int/tb/Brazil_TB_consultation.pdf?ua=1).

In March 2016 the REDE-TB's epidemiology area was invited to participate in the Technical Advisory Group on Tuberculosis Research Investment, which will study the establishment of models to assess intervention impacts on specific groups with higher TB risks in Brazil, South Africa and Vietnam. In Brazil's case, we will adopt the Case Reporting Information System (SINAN)-TB to establish parameters for the END TB strategy's indicators.

TB in Indigenous Populations

The TB in Indigenous Populations area was created as a result of the review process prompted by the Recommendations Manual for TB Control in Brazil.¹ Chapter 13 of this manual, which has been revised by the technical advisory group, highlights the need to look more closely into the TB situation in special populations, so that the disease control may be successful in the country. Similarly to other new areas, its creation followed a demand which arose during the Fifth National TB Meeting and the Second Forum of the Brazilian Partnership Against Tuberculosis, which took place in Brasília in 2012. Since then the TB in Indigenous Populations area, in partnership with national and international research institutions and with the participation of post-graduation students, has been undertaking studies

and research, both in the fields of scientific and technological innovation and in the operational area, with a view to boosting knowledge about clinical and epidemiological aspects of TB in different indigenous groups in the country.

Recent projects include: a) Traditional remedy practices and most prevalent medicinal plants in the Guarani-Kaiowá ethnic group, in the Mid-Western Region, and in the Munduruku, in the Northern Region, approved by SCTIE/MoH; b) Social inequalities and tuberculosis: dynamics and transmission, life conditions, and interfaces between biomedicine and traditional indigenous medicine, c) Social inequalities and tuberculosis: spatial distribution, risk factors and pharmacogenetics from the perspective of ethnicity, both funded by Fiocruz; and d) Life and work conditions and risk of tuberculosis among the Guarani-Kaiowá at Amambaí, Mato Grosso do Sul State, funded by the Coordination for the Improvement of Higher Education Personnel (CAPES).

Box 1 – REDE-TB area coordinators. 2014-2016 term.

Coordinator	Area	Lattes CV
Afrânio Kritski	Diagnostics (Coord.)	http://lattes.cnpq.br/0008770194107817
Ana Paula J. Kipnis	Basic Research (Vice-coord.)	http://lattes.cnpq.br/1252262903952987
Anete Trajman	Human resources (Vice-coord.)	
	Clinical trials (Coord.)	http://lattes.cnpq.br/7932066626042090
Andrea Maciel de O. Rossini	Pediatric TB - (Coord.)	
Antonio Ruffino Netto	Epidemiological studies (Coord.)	
	Human resources (Coord.)	http://lattes.cnpq.br/2736824113286715
David Jamil Hadad	Non-tuberculous mycobacteria (Vice-coord.)	http://lattes.cnpq.br/1780085142505190
Diógenes Santiago Santos	Medications (Coord.)	http://lattes.cnpq.br/0429581079142101
Eduardo Martins Neto	Audit committee	http://lattes.cnpq.br/1091943838920616
Ethel Leonor Noia Maciel	Epidemiology (Vice-coord.)	http://lattes.cnpq.br/3761398932271892
Ezio Tavora dos Santos Filho	Social mobilization (Vice-coord.)	http://lattes.cnpq.br/1272548109483604
José Uereles Braga	Epidemiology (Coord.)	http://lattes.cnpq.br/6027675934625064
José Roberto Lapa e Silva	Human resources (Coord.)/Audit committee	http://lattes.cnpq.br/3174288202051647
Laedi Alves R. dos Santos	Infection control (Coord.)	http://lattes.cnpq.br/0916177001823470
Luis A. Basso	Medications (Vice-coord.)	http://lattes.cnpq.br/3431777523511296
Margareth Maria Dalcomo Pretti	MDR-TB (Coord.)	http://lattes.cnpq.br/6650724547603081
Martha Maria de Oliveira	Quality management and technology incorporation (Coord.)	http://lattes.cnpq.br/2592177955634335
Moíses Palaci	Basic research in immunopathology (Coord.)	http://lattes.cnpq.br/2602694352713051
Monica Kramer de Noronha Andrade	Infection control (Coord.)	http://lattes.cnpq.br/8736776794939379
Nadja Faraone	Social mobilization (Coord.)	
Paulo Cesar Basta	TB in indigenous populations (Coord.)	http://lattes.cnpq.br/8095789908940383
Pedro Eduardo Almeida da Silva	Diagnostics (Vice-coord.)	http://lattes.cnpq.br/4577337828511155
Regina Célia B. Zuim	Vulnerable populations (Coord.)	http://lattes.cnpq.br/4366154226968574
Reynaldo Dietze	Clinical trials (Coord.)	http://lattes.cnpq.br/1727805739693861
Sylvia Luisa Pincherle Cardoso Leão	Non-tuberculous mycobacteria (Coord.)	http://lattes.cnpq.br/0390661714924664
Teresa Cristina Scatena Villa	Operational research (Coord.)	http://lattes.cnpq.br/7463185969200419
Valéria Cavalcanti Rolla	TB/HIV (Coord.)	http://lattes.cnpq.br/0311400155430166
Vera Maria Neder Galesi	Operational research (Vice-coord.)	http://lattes.cnpq.br/5497155242135960

Pediatric TB

The creation of the Pediatric TB area in the REDE-TB also took place in 2012, during the same meeting. Between 2012 and 2015 the area of pediatrics undertook investigations linked to post-graduation courses (master's and PhD) in two Brazilian cities: Rio de Janeiro and Curitiba. Clinical research was undertaken in the following fields: diagnostics through interferon gamma release assays (IGRA) to detect TB latent infections, contact control and development of clinical scores for the diagnosis of pediatric TB among HIV-infected and non-infected patients. Partnerships with researchers from other institutions were established, aiming at developing multicentric studies: Fluminense Federal University (Niterói, Rio de Janeiro State) and University of California, Berkeley (USA) to study biomarkers in the treatment of pediatric TB, and with Ghent University (Belgium) to study the diagnostic method and investigate M. tuberculosis resistance adopting the string test.

Non-tuberculous mycobacteria

The Non-tuberculous mycobacteria area was created in 2008 with the following objectives:

- 1) to study the diseases caused by these microorganisms in human beings,
- 2) to establish the clinical, microbiological and image criteria to diagnose the disease, transient colonization or contamination of clinical material by these microorganisms,
- 3) to track treatment of disease cases caused by these microorganisms; and
- 4) to create a non-tuberculous mycobacteria strain collection in different research centers across Brazil.

As a strategy to attain these objectives, a debate has been started with clinicians, biomedical doctors and radiologists, in order to draw up a document to record information about the clinical history, physical exam, image reports (for radiographies, CT scans and nuclear magnetic resonance images) and drug treatments, to standardize collection of information related to the disease by non-tuberculous mycobacteria across different regions of the country.

The creation of a strain collection of non-tuberculous mycobacteria isolated from human beings, animals and the environment (air, soil, water) aims to ensure microbiological and molecular studies are undertaken in different centers across the country, which would include the development, standardization and multicentric assessment of tests to identify, characterize and analyze susceptibility to biocides and antimicrobial drugs.

This approach resulted in several publications of national and international interest.⁴⁰⁻⁴³

Concluding remarks

The REDE-TB is more than a corporate entity divided in subject areas and coordinated by a small group of

directors. It is a novel concept of collaboration, in which the synergy of its complementary aspects paves the way to transferring knowledge to society. According to this concept, the hierarchy gives way to productivity and the ability to solve problems, attempting to meet the demand to link governments, academia, organized civil society and the industry for the sake of a single cause: the end of TB. The model that integrates and articulates efforts, as well as the process of creation, funding, maintenance and objectives observed at the REDE-TB may easily be extended to other areas of health care and other countries.

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