Implementing a molecular test to diagnose pulmonary tuberculosis in Brazil: a case study

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Table of Contents

List of acronyms and abbreviations

AIDS	Acquired Immunodeficiency Syndrome
BMGF	The Bill & Melinda Gates Foundation
BRL	Brazilian Reais (national currency)
CAB	Community Advisory Board
CAPES	Coordination for the Improvement of Higher Education Personnel
CBO	Community Based Organization(s)
CCM	Country Coordinating Mechanism
CD4	Cluster of differentiation 4 of T helper cells
CDC	Centers for Disease Control and Prevention
CEP	Research Ethics Committee
CFM	Federal Council of Medicine
CGLAB	General Coordination of Public Health Laboratories
CNPq	National Council for Scientific and Technological Development
CNS	National Health Council
CONEP	National Committee on Ethics in Research
CONITEC	National Committee for the Incorporation of Technologies on the SUS
CSO	Civil Society Organization(s)
CTA	Technical Advisory Committee
DALY	Disability Adjusted Life Years
DECIT	Science and Technology Department, MoH
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Strategy
DOU	Federal Official Gazette
DR	Drug-resistant
DST	Drug Sensitivity Test
ENSP	National School of Public Health
FAP	Ataulpho de Paiva Foundation

FDC	Fixed Dose Combination
FHS	Family Health Strategy
FIND	Foundation for Innovative New Diagnostics
FIOCRUZ	Oswaldo Cruz Foundation
FMT	Tropical Medicine Foundation
GAL	Laboratory Environment Management System
GDF	Global Drug Facility
GDP	Gross Domestic Product
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GHS	Global Health Strategies
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
IAS	International AIDS Society
IEC	Information, Education and Communication Programs
IMS	Social Medicine Institute
InCo.TB	Tuberculosis Control Innovation Project
INS	National Health Institute of Mozambique
IRI	Institute of International Relations
JHU	Johns Hopkins University
LACEN	Central Public Health Laboratories, State level
LPA	Line Probe Assay (Hain DNA-strip)
MCTI	Ministry of Science, Technology and Innovation
MDR	Multidrug-resistant tuberculosis
MEC	Ministry of Education
MGIT	Mycobacteria Growth Indicator Tube
MS	Ministry of Health, MoH
MSH	Management Sciences for Health
MTB	Mycobacterium tuberculosis
NGO	Non-governmental Organization
NTP, PNCT	Brazilian National Tuberculosis Control Program
OAB	Brazilian Bar Association

PAHO	Pan American Health Organization
PALOP	African Countries of Portuguese Official Language
PCR	Polymerase Chain Reaction
PCT	Tuberculosis Control Program, State level
PDSE	PhD Sandwich/Internship Program Overseas
PEPFAR	President's Emergency Plan for AIDS Relief
PHU	Primary Health Unit
PLWHA	People Living with HIV & AIDS
PPV	Positive Predictive Value
PR	Principal Recipient
PUC	Pontifical Catholic University
R&D	Research and Development
REDE-TB	Brazilian Tuberculosis Research Network
rGLC	Regional Green Light Committee
RIF, Rif	Rifampicin
RTR-TB	Quick Tuberculosis Testing Network
SCTIE	Science, Technology and Strategic Supplies Secretariat, MoH
SES	State Health Authority
SIASUS	SUS's Outpatient Information System
SINAN	Case Reporting Information System
SMSDC-Rio	Municipal Health and Civil Defense Authority of Rio de Janeiro
SSM	Sputum Smear Microscopy
STAG-TB	Strategic and Technical Advisory Group for Tuberculosis
SUS	Unified Health System
SUSAM	Health Authority of the State of Amazonas
SVS	Health Surveillance Secretariat, MoH
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TBTC	Tuberculosis Trials Consortium
UERJ	State University of Rio de Janeiro
UFES	Federal University of Espírito Santo

UFF	Fluminense Federal University
UFRJ	Federal University of Rio de Janeiro
UN	United Nations
UNAIDS	Joint United Nations Program on HIV/AIDS
UnB	University of Brasília
UNION	The International Union Against Tuberculosis and Lung Disease
USAID	The United States Agency for International Development
USP	University of São Paulo
WHO	World Health Organization

Executive Summary

Tuberculosis is still one of the main public health problems in the world, as well as in Brazil, where approximately 70 thousand new cases are notified every year. After decades of low levels of investment in research and development (R&D), very few advances in methods for diagnosis and treatment have been made available to health care workers. The current scenario in the fight against tuberculosis is distinguished by the mobilization by international governments and institutions to develop and introduce new technologies. The innovations which have resulted from this process may bring on key opportunities to change the epidemiological picture by leading to tools which enable a more prompt and accurate detection of tuberculosis, as well as a more effective treatment.

The aim of the case study, which is briefly outlined here, is to document the pioneering experience of introducing a molecular test to diagnose pulmonary tuberculosis in Brazil's Unified Health System (SUS), with a view to replacing sputum smear microscopy (SSM). To that end, this document reviews a case study for the project 'Pilot study to implement Xpert®MTB/Rif to diagnose pulmonary tuberculosis in two municipalities in Brazil', its antecedents and some of its offshoots, up to September, 2013. This document also refers to three other correlated studies which add to it, involving acceptability, economic assessment of the new method and evaluation of the laboratory infrastructure. This series of studies opens up possibilities to attain knowledge of various aspects involving the incorporation of technology. Each of these studies was undertaken as part of a cooperation agreement among the Brazilian Ministry of Health's National Tuberculosis Program, the Bill & Melinda Gates Foundation, which has funded the project, and the Ataulpho de Paiva Foundation, which has implemented it.

This case study seeks to record how the planning, execution and the results of the aforementioned studies took place, and how they have contributed to a successful experience. Deadlocks and challenges to sustainable adoption of this technology in the scope of tuberculosis control in Brazil are also discussed.

Following an analysis carried out by the authors, this study seeks to provide suggestions to guide future initiatives that adopt new health technologies which may prove to be relevant to public health. Information supporting the analysis was collected through interviews with several involved actors, as well as through document reviews.

The case study comprises four axes, which are described below. Along each of these axes, the authors seek to identify contextual and process aspects which were key to carrying out the study.

1. Context and preparation of the pilot study:
   Some aspects which were key to meeting the targets outlined by the initiative stand out. These aspects include: close consultation with managers at different levels, to set targets and scope; establishing political leadership to undertake the implementation across different levels; developing flexible funding mechanisms to avoid the known limitations of state bureaucracy.

2. Undertaking the pilot study and correlated studies:
   Positive factors observed include adequate planning and training of the health care workers involved, who were duly supported by adequate levels of technical and financial resources; management of the studies by notably capable professionals, who were selected based on their technical skills; management of the project, which was supported by an advisory committee with renowned expertise in tuberculosis. The observed challenges included the need to previously set up an adequate information system that can ensure quick access to test results by the professionals and duly manage the patients in shorter periods of time. After the study, the use of the molecular test by the participating services was interrupted due to disruptions in the supply of cartridges, which frustrated participating professionals and local managers.

3. Study results and adoption of Xpert by SUS:
   The introductory pilot study was successfully carried out on schedule and has produced significant evidence that will favor the future adoption of the method across the country. The new method has increased notification rate of tuberculosis cases with bacteriological confirmation by 59 per cent. The interval between sample processing and start of treatment of drug-susceptible TB has been reduced, from an average of 11.4 days to 8.1 days. Complementary studies have also indicated that this technology may be cost-effective in the Brazilian context and that the test has been positively accepted by health care, laboratory and management professionals. Though the process of technological assessment and the final decision by CONITEC on adopting the test have taken into account data produced in the studies, political factors were decisive in the early announcement, by the Minister of Health, about the adoption of Xpert, just as the study had been started.

4. Conclusions, remarks and recommendations.
   Several key lessons have been revealed by successes and difficulties faced by the team in charge of the study and the managers. These findings may bring about the success of future similar interventions. To that end, we sought to highlight the main challenges which have been identified along the described process, as well as some recommendations.

First Challenge: Adjusting the health information systems

Recommendations: To promote and ensure the early introduction of the Laboratory Environment Management System and of its interfaces with the Case Reporting Information System and other existing information systems, as well as to directly involve local management in planning to introduce and scale up the method.

Second Challenge: Ensuring adequate training and support to the professionals and technicians

Recommendation: To provide adequate support, both technical and financial, so that local managers may ensure the necessary training is available and support efforts of health professionals and technicians on the use of the new method. It should be emphasized that in order to extend the reach of the method, some joint planning and execution is necessary among different administration levels, going beyond mere recommendations by central management.

Third Challenge: Ensuring procurement of supplies

Recommendation: To ensure that emergency stocks of supplies and parts are kept, to meet demand if and when regular supply levels are disrupted for any reason.

Fourth Challenge: Establishing technical assistance to be provided by the manufacturer

Recommendation: To outline, together with the manufacturer, every condition which ensures the fulfillment of interests and needs of the Unified Health System, in order to attain an adequate provision of machinery and supplies, as well as to provide technical assistance.

Fifth Challenge: Managing dependence on a monopolized technology

Recommendations: To create ongoing mechanisms of operational assessment, at the Unified Health System, of new molecular tests which may become available at the domestic and international markets. These mechanisms would promote ways to reduce dependence on exclusive technologies which may weaken the national ability to negotiate; to create purchasing mechanisms which may enable the renegotiation of prices and flexible conditions.

Sixth Challenge: Ensuring reliable culture data

Recommendations: To expand laboratory capacity to carry out culture and sensitivity tests; to help states and municipalities to set up accurate information flows which ensure the quick availability of data about growth media and sensitivity tests to health care practitioners seeking adequate management of cases that point to resistance.

Seventh Challenge: Setting the algorithm(s) in the country: improving management of symptomatic and suspected drug-resistant TB patients

Recommendations: To define the algorithm(s) to introduce the new method, which optimize the benefits of managing patients, taking into account regional differences, evidence produced by different studies presented herein (among which are bottlenecks in the laboratory structure), as well as evidence produced by other studies commissioned by the National Tuberculosis Program.

Eighth Challenge: Reviewing the use of 'quick testing' terminology

Recommendation: Bearing in mind that the term has generated some frustration by patients and professionals in some units, it is advised that

the use of the term 'quick testing' be reviewed and changed, replacing it with 'the method', since it usually does not produce as immediate or speedy a response to the patient as HIV or pregnancy tests.

Ninth Challenge: Broadening the discussion with society players about the adoption of the method

Recommendation: To foster discussion with civil society, especially with users, about incorporating new technologies, including representatives of these users in the planning and surveillance stages of introduction.

Tenth Challenge: Broadening and sharing experiences gleaned from the study, in order to introduce the method across other countries and contexts

Recommendation: To broaden international collaboration, especially with African Countries of Portuguese Official Language (PALOP), about the introduction of health technologies in TB.

Final Remarks

In spite of all difficulties and obstacles, adequate planning and engagement of a wide network of partners have led the study to a successful outcome.

The Xpert®MTB/Rif method represents more than a new diagnostic technique. It imparts the feeling to the collective imagination (among managers, health care practitioners, laboratory personnel and users) that progress is being made. It is therefore essential not to frustrate the expectations associated with its introduction and to ensure satisfactory progress.

The experience obtained through this study indicates the importance of seeking agreement and mutual recognition of the genuine interests that inspire different actors. It should be emphasized that lining up the timescale prevailing in politics and in science may benefit all: data produced in the context where a new technology intends to be introduced helps boost the decision-making process. This agreement certainly empowers national institutions and ensures safeguarding of the best public interests.

Other operational pilot studies should also be recommended to enable the evaluation of new technologies under circumstances similar to SUS's routine, in the same manner as those which are managed by the InCo.TB project.

This experience is encouraging for new initiatives to introduce technologies, and it is hoped that these recommendations may contribute to a successful introduction of Xpert®MTB/Rif.

Foreword

Over the last ten years, Brazil has promoted various efforts to accelerate the improvement of its TB indicators. These nation-wide initiatives include the expansion of the Directly Observed Treatment Strategy (DOTS) project, together with The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the introduction of a new treatment scheme with four anti-TB drugs in fixed dose combination (4:1 FDC), and the implementation of studies to adopt new technologies for TB diagnosis.

The aim of this report is to document the pioneering experience of introducing a molecular test to diagnose pulmonary tuberculosis in Brazil's Unified Health System (SUS), with a view to replacing SSM. To that end, this document reviews a case study for the project, 'Pilot study to implement Xpert®MTB/Rif to diagnose pulmonary tuberculosis in two municipalities in Brazil', its antecedents and some of its offshoots, up to September, 2013. This document also refers to three other correlated studies which add to it, each involving acceptability, economic assessment of the new method and evaluation of the laboratory infrastructure. This series of studies opens up possibilities to attain knowledge of the various aspects involving the incorporation of this technology.

The consultants who are the researchers responsible for this document wish to state their involvement, since they have followed or even took part, at some stage, in the decision-making process to plan these studies. However, since they have not been involved in the execution of the studies, the consultants feel at ease attempting to describe the development and offshoots of the studies in the most impartial way possible.

This report was completed in mid-October, 2013, reflecting the state of affairs up to the previous month. Reviewing and editing tasks were completed in May, 2014 and take into account the latest data reviews, which took place in 2014.

Methodology

This report aims to round up experiences by several technicians, researchers and managers involved in the various sections of the pilot study to introduce Xpert®MTB/Rif in Brazil to detect pulmonary TB ('pilot study', hereinafter), its antecedents and some of its offshoots, up to September, 2013. The analysis carried out on this report also comprises correlated acceptability studies,[1] an economic assessment[2] and an evaluation of the laboratory infrastructure,[3] which were developed to provide evidence of different aspects involving the incorporation of technology. This documentation was based on individual and collective interviews, document analyses (reports, PowerPoint presentations, notes), as well as observation of collective events, such as workshops, seminars, meetings and congresses. This report also records impressions by the consultants.

Choice of respondents was done deliberately. Initially, an attempt was made to interview those responsible for the different studies, as well as some key individuals who were related to these studies. In some cases, when it was possible to contact people involved in the study, some consultations were also carried out, especially with some health care practitioners in the States of Rio de Janeiro and Amazonas. Some federal-level technicians and managers were also interviewed.

Quotes were sent to their authors prior to report publication, so that they were validated.

This report was written in collaboration with InCo.TB's senior consultant and with Global Health Strategies's Vice-president in Brazil, meticulously reviewed and approved by them and by the NTP's coordinator.

Epidemiological Scenario

Because some components of the pilot study are concerned with epidemiological data, this case study does not aim to dwell on these aspects. It is notoriously known that TB is an extremely important public health problem in Brazil, which is still among the 22 high-burden countries, and that various efforts have been made to alter this picture.

This report aims to focus on process, contextual and political aspects of the pilot study and correlated studies.

However, it should be stressed that in the Brazilian epidemiological scenario, a significant percentage (about 35 per cent)[i] [4] of new TB cases start undergoing treatment without bacteriological confirmation, and 70 per cent of re-treatment cases are not associated with culture or drug sensitivity tests (DST). The Brazilian NTP aims to introduce universal culture by 2015. However, while that does not translate into reality, it is vital to obtain an assessment of the potential impact, the acceptability and the cost-effectiveness of the diagnostic molecular test.

Brazil has a moderate TB-HIV co-infection rate (9.7 per cent),[ii] a low prevalence of multidrug-resistant tuberculosis (MDR), and a 1.4 per cent rate of resistance to isoniazid and rifampicin,[iii] [5] according to data in the last National MDR Enquiry (2006-2009). However, the WHO has recommended the test for HIV infected people who are suspected of harboring co-infection or MDR. Even so, the NTP has chosen to evaluate the test for detection of pulmonary TB at the primary care level, regardless of any suspected resistance.

[i] According to page 4 of the NTP's 2013 Epidemiological Bulletin, of approximately 86 per cent of diagnostic tests carried out on diagnosis about 74 per cent of the samples are positive.
[ii] *Ibid*, p. 5.
[iii] NTP's default presentation, 2012; slide 94.

Introduction

Some evidence seems to indicate that, in the future, the current years should represent a 'watershed' in the history of TB fight in Brazil,[6] according to the NTP's view.

Obviously, two of the symbolic – and palpable – elements of this period are the introduction of 4:1 FDC, in December, 2009 and the adoption of the molecular method to diagnose TB (Xpert®MTB/Rif, 'Xpert' hereinafter) in more than 60 cities in Brazil, initially scheduled for 2013.

A complex implementation study, also known as roll-out, executed at the same time as other previously mentioned complementary studies, was developed with a view to providing evidence to help decisionmaking regarding the adoption of this diagnostic technology in the country.

The development of the pilot study has not proceeded without some drawbacks and polemic; however, one may state in advance that it was a success story. We shall examine below the reasons which have helped to make this a successful experience. However, describing the conditions which backed the study is as important as reporting its successful execution.

Besides describing and reporting this experience, the specific aim of this document is to provide a roadmap for future initiatives on incorporation of new health technologies, as well as some conditions to be considered, either in Brazil or overseas. This experience may benefit other areas besides tuberculosis.

Format of this Report

This report comprises four axes:

1. context and preparation of the pilot study;
2. undertaking the pilot study and correlated studies;
3. study results and adoption of Xpert by SUS;
4. conclusions, remarks and recommendations.

1. Context and Preparation of the Pilot Study

The focus of this first point is to present some of the variables which have helped the development and construction of this study.
To this end, it will be separated into the following sections:

- a brief historical background and some technological antecedents;
- engaging actors around common interests; initial arrangements;
- factors which determined the viability of a project of this nature.

1.1. A Brief Historical Background

In the history of fight against TB, the development of molecular diagnostic methods for the TB causing pathogen, *Mycobacterium tuberculosis* (MTB) is certainly the most notable legacy of the first decade of the new millennium. In a spectacular technological leap, the SSM diagnostic method devised by Heinrich H. R. Koch finally finds a quality alternative, after nearly 150 years of waiting.

In Brazil, the fight against the disease falls into some fairly clear historical periods. Five are suggested here: the first period was the popular mobilization at the end of the 19th Century, led by the lawyer Ataulpho de Paiva, who attempted to orchestrate a response to tuberculosis, one of the serious public health problems which plagued the country. Subsequently, from the 1920's to 30's, the second stage occurred with the initiative, by the State, to provide hospitalization through the creation of sanatoria with public funds, which had been supplied by civil society up to that point. The third period was the 1950's, when initiatives to control tuberculosis used up more than half of Brazil's public health resources,[iv] [7] indicating its magnitude. Over this period new drugs were introduced, in a slow homogenization process across Brazil.

The fourth period started at the end of the 1970's and early 1980's, when Brazil undertook a major, pioneering reform, introducing the three-drug

[iv] Santos Filho, Ezio Távora dos. TB Policy in Brazil – A Civil Society Perspective. p. 47.

regimen, which included rifampicin. This public health measure intended to make treatment across the country more uniform. The era of self-administered outpatient treatment was started then, marking the decline of hospitalization. This was the end of sanatoria, which had left their marks in the collective memory, as well as the leprosaria. The new treatment scheme was provided free of charge for the patients, at very high costs for the public health system which, at that time, was based on a contributory approach. These reforms were not done without strong controversy, criticism, and disapproval, both within Brazil and abroad.

The fifth period of this history started at the end of the 1990's, with the attempt to establish in Brazil a policy of TB control which followed closely the international standards. This period was marked by the introduction of the DOTS strategy in some regions across the country, in which various isolated initiatives by states and municipalities with high TB burdens stood out, in a weakly articulated federal administration. The guidelines from the National Plan to Control Tuberculosis, launched in 1999, were only adopted as a national policy from February, 2004.[v]

The beginning of the 21st Century was marked by the resumption of revitalizing initiatives in the TB policies, notably with the attempt to broaden TB chemoprophylaxis in the city of Rio de Janeiro and in the State of São Paulo, and a 'new wave' of social mobilization, this time stimulated by governmental initiatives with support from international agencies, again in the States of Rio de Janeiro and São Paulo, in 2002 and 2003. Another important initiative of this period was the creation of the Brazilian Tuberculosis Research Network (REDE TB) in 2001, which aims to promote collaboration to generate scientific knowledge among different areas – academia, civil society and the different governmental levels.

It is safe to say that, historically, the fight against tuberculosis in Brazil has profited from a close cooperation between international bodies and institutions. The most recent stage in the Brazilian context has been no exception. The strong mobilization in the international scene has directly influenced the latest stage of the Brazilian response against tuberculosis.

In 2001, the Stop TB Partnership was founded in Washington D.C., as a multilateral initiative to promote cooperation and hasten new processes and techniques against the TB pandemic. WHO's Department of Tuberculosis itself adopted the name Stop TB Department, aiming to raise the profile of the new global policy against the disease. As a result of wider efforts and initiatives, an exponential increase has been noted in R&D investments in new treatments, vaccines and diagnostic methods for TB. Non-governmental organizations and international foundations came into existence to boost and speed up the R&D process together with industry, such as the Global Alliance for TB Drug Development (TB Alliance)[vi] for drugs, Aeras for vaccines, and FIND (Foundation for Innovative New Diagnostics).[vii]

The Brazilian Stop TB Partnership (*Parceria Brasileira Contra a Tuberculose*) was founded in a ceremony that took place in Brasília, in

[v] Ibid, p. 42.
[vi] http://www.tballiance.org/
[vii] http://www.finddiagnostics.org/

November, 2004, as part of the new national policies against TB, in tune with international efforts.[8]

Although the WHO sounded the alarm about the global scale of TB in the early 1990's, it was only in the early 2000's that international R&D efforts converged towards new technologies against TB. Rapid advances towards new alternative therapies were attained and new TB diagnostic methods were developed, stirring the international TB scene, which had lain dormant for decades.

Over the last few years, some new MTB diagnostic methods have been recommended by the WHO's Strategic and Technical Advisory Group for Tuberculosis (STAG-TB), starting from the adoption of the recommendation, development and assessment grade by evidence of benefits (GRADE system) at the reference laboratory level. The first diagnostic method was the bacteriological exam of liquid culture, MGIT960® Bactec®, in 2007. Subsequently, the molecular method, Line Probe Assay (LPA) GenoType® MTBDRplus Assay, also known as the Hain Strip, was launched in 2008.[9] Since these methods require medium or highly complex laboratories (levels 2 or 3), they have been indicated to detect resistant MTB.

When Xpert was registered in 2009, it seemed the dream had finally come true for health care practitioners and TB managers, who wanted to have access to a quick, simple, easy-to-use molecular test in the health unit laboratories (point-of-care), without any significant biosafety requirements. Xpert could, therefore, replace SSM efficiently and effectively in large scale MTB diagnostics.

The New England Journal of Medicine published data which validated the Xpert method in September, 2010.[10] After reviewing other evidence, WHO's STAG made political and technical recommendations. After a Global Consultation by the WHO, this organization endorsed the recommendation to use Xpert in suspected cases of multidrug-resistant tuberculosis (MDR) and for TB diagnostics among HIV cases.[11]

On the domestic scene, the potential of this new technology has introduced a challenge to health managers, health care practitioners and to the health system as a whole. Is it possible to definitively replace SSM as a diagnostic method for pulmonary TB under the circumstances prevailing in Brazil's SUS? What are the necessary conditions to implement a new diagnostic technology across the country?

1.2. Engaging Actors around Common Interests

Brazil was already making efforts to align itself with international policies to control TB, attempting to break free from the country's isolation and to resort to the new available techniques.

As from 2004, under the leadership of the NTP, Brazil has committed itself to expanding the DOTS strategy and to raising TB's profile in the country, with the GFATM-funded project tailored to TB high-burden metropolitan areas. This project, the execution of which started in 2007, typified a moment of engagement of various actors around a common agenda, involving domestic and international institutions.[viii]

The Brazilian Government, represented by the SVS, took part in the Executive Board of The Stop TB Partnership in 2007, in an effort to attain some visibility among global decision makers in TB. In that year, the Third Global Forum for Stop TB's Partners was scheduled to take place in 2009.[12] The city of Rio de Janeiro was chosen to host the event. This decision helped NTP-SVS-MoH attain some recognition for its efforts to improve its bad reputation due to feeble performance indicators in TB control, in contrast with the excellent global reputation earned over the previous decade by the AIDS program.

This is the background against which the first conversations were initiated around evaluating Xpert in Brazil. Some weeks before the event in 2009, FIND proposed scheduling an Xpert validation study[ix] to a group of UFRJ researchers.

At that time, the Bill & Melinda Gates Foundation (BMGF) was already established as the most important philanthropic financing agency for health in the world. As a significant donor to the GFATM, and directly supporting various actions proposed by the WHO, BMGF already has given support to multilateral actions that fought the major endemic infections. It also endeavored to draw closer to the new global leadership. In this scenario, the connection should be emphasized with emerging countries with high TB burdens, such as India, China and South Africa. Under these conditions, Brazil came up as a new cooperation possibility, with specific features, such as its political leadership, which was committed to reversing the TB indicators, the coverage of its public health services and its interest in research to guide public health policies.

1.2.1. Convergence of interests

The Third Global Forum for Stop TB's Partners, which took place in Rio, facilitated a bringing together of interests among different domestic and international actors.

[viii] Especially as regards the technical and political support by PAHO, and the financial support by USAID.

[ix] On August 22, 2013, Prof Afrânio Kritski, by email, reported that he had been looked for by Dr Mark Perkins, from FIND, who proposed an Xpert validation study in Brazil.

At the event's opening, in front of the major global partners who are involved in the fight against TB, the Minister of Health[x] reiterated the government's commitment to strengthening the policies against the disease, revealing the country's willingness to make advances in technological innovations.

On the first meeting during the course of the Partners' Forum, some avenues of cooperation started to be discussed, taking into account the various agendas and priorities of the institutions involved. Representatives from the following agencies attended that meeting: REDE-TB, NTP, Prof Helio Fraga Reference Center (CRPHF-ENSP-FIOCRUZ), Municipal Health and Civil Defense Authority of Rio de Janeiro (SMSDC-Rio), the Brazilian branch of Management Sciences for Health (MSH), Global Health Strategies (GHS),[xi] and BMGF.

From June 2009, consultations between the Gates Foundation and the Brazilian government stepped up. Ongoing dialog between the aforementioned partners has favored broad participation in the decisions regarding the activities outlined in the cooperation project.

Over the course of roughly one year of negotiations between the BMGF and NTP-SVS-MoH, a cooperation platform was agreed upon, based on three targets: (i) to strengthen the actions involved in the implementation of the 4:1 FDC regimen in the treatment of sensitive TB across the whole country; (ii) to strengthen cooperation actions with African Countries of Portuguese Official Language (PALOP), especially between Brazil's and Mozambique's NTPs,[xii] [6] which were already well under way, and (iii) to develop a pilot study to introduce the molecular method to detect pulmonary tuberculosis. The pilot study was initially scheduled to take place after the Xpert validation study in Brazil. The validation study, negotiations over which had started earlier with FIND and UFRJ researchers, was then planned to be carried out by FIOCRUZ.

1.2.2. Arrangements and definitions

In early 2010, cooperation between the BMGF and the Brazilian government was finally settled; enforcement procedures were set forth. The NTP assigned the Ataulpho de Paiva Foundation as recipient and manager of the international funds; the international funding agreement was signed in August, 2010. According to this agreement, the procedures would be developed as part of a separate project, named InCo.TB.

InCo.TB was then created to implement the actions agreed on as part of the partnership between the Ministry of Health and the Gates Foundation. At first, the project initiated collaboration with the NTP to put in place training strategies for health care practitioners across Brazil and to introduce 4:1 FDC, with the establishment of the intervention model and educational and informational materials.

[x] Minister José Gomes Temporão.

[xi] Consultants and representatives of the Gates Foundation in Brazil.

[xii] This initiative sought to boost the cooperation between Brazil and Lusophone African countries, as reported in an interview with Dr Draurio Barreira.

At the same time, Rio de Janeiro and Manaus were confirmed as the municipalities where the pilot study was to take place for the introduction of Xpert in Brazil. It was decided that the study would be managed and carried out at SMSDC-Rio's Primary Care Superintendency,[xiii] together with the Doutor Heitor Vieira Dourado Tropical Medicine Foundation (FMT), the Amazonas State Health Authority (SUSAM). The Amazonas study was developed in partnership with the Federal University of Espírito Santo (UFES), which, at the time, was completing some research at State and municipal health care units in Manaus.

The principal investigators were subsequently appointed for the qualitative acceptability studies,[xiv] the economic assessment,[xv] and for the studies on laboratory network capacity,[xvi] as well as those studies assessing epidemiological aspects, with a view to widening the analysis spectrum of the pilot study. The objective was to provide robust scientific evidence on the effectiveness (or lack thereof) of using Xpert as a substitute method for SSM in the diagnosis of pulmonary TB in high-burden areas across the country.

The study did not include an informed consent term (TCLE), and was thus approved by the National Committee on Ethics in Research (CONEP),[xvii] [13] because the pilot study was scheduled to assess the introduction routine use of a new technology at the laboratory level, using a methodology already approved by the National Health Surveillance Agency (ANVISA).

Over the course of setting up the pilot study and its components, between 2011 and 2012, it was evident how the proposal to carry out a validation study of the Xpert method in Brazil had become obsolete, as proposed by FIND in negotiations with FIOCRUZ.[xviii] Moreover, the results of similar studies in other countries were already about to be published.

As stated previously, the Xpert method had been approved by ANVISA in October 2009.[xix] [14] [15] This molecular diagnostic method was already being used by various private laboratories and in some research sites. The validation study's aim was therefore not to confirm the use of the molecular diagnostic technique in Brazil, but to evaluate its performance in the routine of the public laboratories, which was a purpose to be fulfilled by the pilot study.

Other elements have certainly contributed to the validation study not being performed, such as the slow negotiation on its details and the agreements to make funds available for its execution. At that time (2012) the

[xiii] Principal Investigator (PI): Dr Betina Durovni (former Superintendent of SMSDC-Rio).
[xiv] Prof Kenneth R. Camargo.
[xv] Dr Marcia M. Pinto.
[xvi] Dr Maria Alice Telles.
[xvii] CONEP's opinion no. 494, page 7, August 3, 2011.
[xviii] Since the technique was already being privately used in the country and the study being prepared had a roll-out concept, the validation study was obsolete, as acknowledged by the partners on that occasion.
[xix] Publication of approval by the regulating body in Brazil (ANVISA) appeared on p. 79 of DOU no. 196, October 14, 2009, (Cf. reference 14), although the BRATS Bulletin no. 16 (Sep. 2011) states that it took place in December, 2009.

political agenda to perform the pilot study for Xpert's introduction was a priority.

On World TB Day (March 24), 2012, the Minister of Health[xx] issued a press statement saying that Brazil would introduce the molecular method across the whole country. On that occasion, the government's decision to adopt the method was sealed. The political decision to adopt the new molecular diagnostic for pulmonary tuberculosis across the SUS network was not based on national scientific evidence, but was supported by international recommendations – the WHO indicated the method for high burden countries in November, 2011[16] – and on scientific evidence generated in studies outside Brazil.

A meta-analysis was already under way during this period, which would be published in mid-2013,[17] reviewing 15 studies involving Xpert around the world, including over 7500 participants. A combined reading of sensitivity and specificity was calculated to detect MTB through Xpert, when this method was used as a replacement to SSM, reaching 88 per cent and 98 per cent, respectively.

The discrepancy in the different tempos prevailing in politics and in science caused the latter to be overrun by the former. The expectations of researchers to produce local evidence, which would ultimately lend support to the political decision, were frustrated by this decision being brought forward.[xxi] On the other hand, there was an opportunity then for the public administration to reaffirm its commitment to TB policies through the decision to adopt a method which was already recommended by WHO (albeit for MDR diagnosis) and which had been producing evidence internationally, especially the decision to adopt the method to detect pulmonary tuberculosis in South Africa.

The pilot study was thus started with the aim of generating the necessary technical evidence – the performance in the service routine – to provide technical backup for the State in the political decision which had already been made: Xpert's adoption by SUS in Brazil.

[xx] Minister Alexandre Padilha.

[xxi] This decision brought about heated debates during the Fifth National Tuberculosis Meeting/Second Forum for the Brazilian Stop TB Partnership, which took place between May 30 and June 2, 2012 in Brasília.

1.3. Distinctive Factors of the Pilot Project

Some factors should be highlighted in the preparation of the pilot project. These factors represented unique features which made viable a project of this scale and nature.

The five factors which determined the viability of a project of this scale were: (i) intense consultation and key managers' engagement in the process; (ii) the ability to wield political leadership by those responsible for executing and backing the project, both politically and technically; (iii) the possibility to flexibly manage the due funds; (iv) the definition of a cautious and attainable plan, which would include training of the professionals who would become involved; and, lastly, (v) professional management for the project, wholly independent from the public administration, but capable of interacting closely and clearly with the program and health units managers, ensuring the study was on course and that its targets were within reach.

1.3.1. Consultation and engagement of managers

The decision-making process around the pilot study and the complementary studies directly involved local managers, as well as various people who were closely acquainted with the operation of the primary care level and the laboratories where research sites had been established.

In the case of a federal country, such as Brazil, engaging local management to execute national proposals and guidelines is an indispensable political requirement. The autonomy of the federation units should be observed, considered and respected. The pilot study and the complementary analyses involved institutions in the State of Amazonas, the health care system in the municipality of Rio de Janeiro and some health care units in the municipality of Manaus. This complex picture demanded a careful, ongoing negotiation among the various participating actors.

In the technical scope, the viability of a study to introduce a new technology in the service routine also depends on political, administrative and managerial decisions. It was only possible to satisfactorily engage the health care professionals performing core roles through the engagement of the local TB program managers and health unit managers.

1.3.2. Political leadership

Process execution: It was vital that the NTP-SVS-MoH led the process of the pilot study proposal. This has ensured the legitimacy of the study, in tune with national interests, which is a critical parameter for the regulatory bodies, especially to the National Committee for the Incorporation of Technologies on the SUS (CONITEC) and the surveillance bodies (ANVISA) and those concerned with ethics in research (CONEP and local research ethics councils – CEPs).

Managing bureaucracy: the NTP-SVS political leadership was also key to ensure prompt action over internal procedures required by the federal level state bureaucracy. An example is the prompt approval of internal documents,

which aimed to secure covenants and agreements for the study, regular tracking of proceedings at the regulatory agencies (eg. CONEP) and at the federal councils (eg. CONITEC). The same took place in the state and municipal levels, for the procedures required to perform the study: management's commitment to the study has ensured the compliance of the necessary conditions to its completion, on schedule.

Local level management: as previously mentioned, the implementation of the pilot study by the manager itself, as was the case in Rio de Janeiro, or by researchers dealing with the management aspect in the State of Amazonas,[xxii] as was the case of Manaus, has ensured the necessary political and technical backing for the good field execution of the project, securing not only its integration with the local health system, but also its harmonization with the priorities set forth by public policies.

This leadership has enabled not only easy access to internal bureaucratic proceedings, based on management's political decisionmaking, but mainly adequate levels of technical support to attain early training of professionals to perform core roles, as well as rigorous tracking of data flows, data collection and data recording over the course of the intervention.

In the case of the municipality of Rio de Janeiro, SMSDC-Rio's harmony with the national policies was already noteworthy, especially as regards the expansion of the Basic Attention network and of the Family Health Programs (PSF), besides its commitment to improving its TB indicators. Mobilizing the huge health care structure available in the municipality of Rio de Janeiro in such a short period of time required this institutional commitment.

In the case of Amazonas, a notable example of the positive federal influence on State level happened when key managers at relevant local institutions, including at the FMT, were replaced, following changes at the new state administration. The direct dialog between the NTP Coordinator and the new State government office ensured an adequate continuity in the implementation of the study in Manaus.

1.3.3. Flexible funding

Another vital element to ensure the study's viability was the decision to allocate its resources to an independent institution, which was able to manage them flexibly.

In most countries, the public administration of resources requires the compliance of certain steps for its approval and release of funds. This was a lesson that the international community had agreed upon more than a decade earlier. The best example is the disbursement concept of GFATM's monies, which requires assignment of a Principal Recipient (PR), preferably from outside the governmental structure, to manage its donations. This recipient should be assigned by the Country Coordinating Mechanism (CCM), an institutional council formed by political, social and technical stakeholders.

Flexible resource management has enabled the hiring of adequate personnel to carry out numerous tasks for the study. Flexible hiring of personnel for development actions by the public financing bodies in the

[xxii] Prof Reynaldo Dietze, from UFES, and Dr Marcelo Cordeiro dos Santos, from the Tropical Medicine Foundation (FMT-AM).

country is hardly ever attained, as these bodies impose numerous restrictions and require compliance with a series of bureaucratic conditions.

In the case of Brazil, the Ataulpho de Paiva Foundation was one of the institutions which have acted as Principal Recipients of GFATM's resources for the DOTS expansion project. Based on its long experience managing national and international resources, this institution has been assigned by the NTP-SVS-MoH to manage the funds for the pilot study to implement Xpert, for the complementary studies and for the 4:1 FDC study.

1.3.4. Planning and training

As shown above, since the pilot study was carried out by the local administration, the appropriate training conditions were ensured, both for the use of the data processing on the new laboratory environment management system (GAL), and for the adequate clinical management with the new 4:1 FDC scheme.

1.3.5. Professional and independent management

While in some countries it is commonplace to expect that the health management be professional, and able to prove and ensure administrative competence, this is not the expectation in other countries. Brazil's case belongs with the majority of countries. Management of health services and businesses is eventually done by health care professionals who do not hold the right qualifications in administration, let alone in performing commercial business.

In order to ensure that the studies for the InCo.TB project worked satisfactorily, it was necessary to ensure an adequate management was in place. This should be able to permanently orchestrate the various actors involved in the studies: researchers, health care professionals, managers, and suppliers.

As well as the ability to orchestrate and manage, especially as regards meeting deadlines and the quality of information, the role also required remarkable academic knowledge, to ensure oversight of methodologies and the adequate reporting of studies.

An especially capable staff was necessary to deal with the supplies provider who, as discussed below, was linked to various problems over the course of the project execution.

The project was also supported by an Advisory Committee which comprised managers, technicians, researchers and academics, who have been helpful from the study planning stages through to the analysis and offshoots after its completion.

2. Undertaking the Pilot Study and Correlated Studies

The main aim of this axis is to discuss some criteria of the pilot study, as well as some procedural issues, such as:

- choice of model and scenario for the pilot study;
- the algorithm set for the pilot study; the expected outcome;
- its focus on primary care;
- earlier implementation of the laboratory information system (GAL);
- correlated studies to the pilot study;
- some intermediate evidence;
- difficulties and obstacles: interface with the manufacturer;
- reflections on the political decision;
- other issues.

2.1. Model and Scenario for the Pilot Study

The pilot study to introduce Xpert attempted to show the effectiveness of the molecular method to replace SSM within the existing work conditions at SUS's health care services, giving support to the decision-making process by CONITEC on whether or not to prescribe the method.[xxiii]

The pilot project, performed at Rio de Janeiro and Manaus, has adopted the design of a pragmatic clinical trial. This study model does not propose changing the routine service conditions. Nothing should be changed on patient intake, from the suspicion of pulmonary TB through the initiation of treatment, to the work flows and methods.

The pragmatic study model seemed to be the most appropriate to the proposed pilot study as it attempted to generate evidence based on situations which are closer to the reality of services where the new technology is to be introduced. It was therefore attempted to convey the best evidence to managers and to technical health areas.

The study has prescribed changing work methods only where it was being performed: within the laboratory routine, but not across other services.

The introduction took place in 11 laboratories in Rio de Janeiro and three in Manaus. The comparison units, which were randomly chosen in the intervention stage, were the laboratories used by the primary care units of both cities.[xxiv] [18]

The study consisted of a random comparison among groups, with Xpert being introduced in a staggered fashion, so that the design was set up

[xxiii] CONITEC has replaced the Committee for the Incorporation of Technologies (CITEC), at the same Science, Technology and Strategic Supplies Secretariat (SCTIE), Ministry of Health, in assessing the relevance of new technologies for SUS.

[xxiv] 'Randomization and data analysis will not be individual for each patient, but according to laboratories/health units'. Pilot study protocol, page 6.

according to a stepped-wedge, or stage implementation, within a short period. After eight months of intervention, all 14 units had replaced SSM with the molecular test to diagnose pulmonary TB.

2.2. Algorithm for the Pilot Study

The study algorithm was based on the epidemiological characteristics and the priorities of the public TB policies in Brazil, which include (i) the need to increase detection and bacteriological confirmation of tuberculosis, especially at the primary care network, and (ii) the low prevalence of multidrug resistance.

> 'There was no point in performing SSM followed by Xpert for the negative cases because 90 per cent would be negative. This would delay diagnosis and increase costs. The NTP aimed at studying Xpert as a replacement for microscopy, not as an add-on, or an extra test. On the other hand, it has been decided to perform SSM later, for those results which proved positive on Xpert. This was only done because of the study, and it does not make any sense in clinical terms or as a program in the service routine. It was important for the study because, if we were not able to show the effect on every sample, at least the effect could be seen in the negative microscopies. However, some people working on core roles suggest that the first SSM should have been done, so that a control parameter would be available. That has been done in South Africa.[xxv]

As a result, the pilot study focused on primary diagnosis of sensitive TB, not on follow-up exams, which carried on being done through SSM. The challenge involved the possibility to carry out quick diagnosis of the disease, and not keeping the method for secondary use along the diagnostic flow or for the indication of multidrug resistance.

2.3. Expected Outcomes

The key outcome was the notification rate for pulmonary TB, confirmed at the laboratory. The secondary outcomes included the notification rates which were not followed by any tests that confirmed the presence of MTB in the patient's respiratory samples; samples which were associated with negative results, as well as the effect on the notification rates of all pulmonary TB cases, regardless of the test results. The number of tests performed by the laboratory was also analyzed, as was the interval between test application and initiation of treatment (inferred by the notification date), and the proportion of patients with indication of resistance to rifampicin, who had undergone drug sensitivity tests (DST) and resistance profile on the DST.

Each laboratory underwent an observation period, during which the outcomes were analyzed over the course of its normal routine (SSM). The intervention stage took place after that, with the introduction of Xpert as a replacement to SSM. The laboratory entry order on the intervention stage was random.

[xxv] Observations by Anete Trajman, Senior Consultant at InCo.TB, September 30, 2013.

Data was collected at the official information systems, including SINAN and GAL. A series of separate considerations will be given to the latter system, as it is a key factor in the development of the pilot study.

2.4. Choice of Primary Care Services

Though 22 per cent of the TB cases in the city of Rio de Janeiro (in 2008) were diagnosed at public hospitals, [xxvi] [17] the choice to focus on primary care services was due to the expansion policy undertaken across the SUS.

Dismissing the tertiary units meant nearly one-fourth of the TB cases diagnosed in Rio de Janeiro were not included. Though this may hamper generalization of the study results, as regards the most serious cases, diagnosed at hospitals, this choice meant it was possible to conduct a broad, robust and precise study, with a view to applying it to the primary care level. In actual fact, the preference for the units which support the primary care services has resulted in a significant benefit to the execution of the study. It should be emphasized that the laboratories where the study was performed are units (mostly secondary) that carry out diagnostic tests for samples collected on the primary care unit network.

It has been crucially important that the study's participating units pay due attention to the quality of data. Hence the need for close and effective surveillance by the managerial level.

2.5. Earlier Introduction of GAL

Perhaps the most significant feature of the pilot study has been acknowledging and bridging a considerable gap in the health system before its own implementation: information.

Brazil has a complex system of information networks or, to be more accurate, a series of health information platforms which live side by side without any connections. Various abbreviations and acronyms (for case reporting, mortality data, etc) describe vertical information systems which extend over the three levels of the health system, but which, as a rule, neither communicate among themselves nor are fully computerized. It is safe to say that a great proportion of the Brazilian information system still depends on written records, often incomplete and non-traceable. Fairly often, this situation leads to the loss of laboratory results, to failure of cases to be adequately notified; it hampers information from meeting its principal aim, which is to provide quick, accurate diagnostics to allow appropriate clinical case management.

The existing information systems in Brazil include the Laboratory Environment Management System (GAL), devised by the General Coordination of Public Health Laboratories (CGLAB) and the Health Surveillance Secretariat (SVS), Ministry of Health (MoH). GAL was developed with a view to 'computerizing the National System of Epidemiological Surveillance and Environmental Health Surveillance Laboratories, enabling

[xxvi] Pilot study protocol, page 16.

management of routines, tracking of stages involved in fulfilling epidemiological and production exams and reports across the public laboratory networks'. This system also aims to 'send to the Case Reporting Information System (SINAN) the results pertaining to suspected or confirmed cases for compulsory notification of disease', that is, to create links between the systems. Finally, GAL has been designed as an auxiliary instrument for health care laboratories to 'make epidemiological and managerial decisions'.[19]

Although practically all Central Public Health Laboratories (LACENs), which are State level units, are already 'capable' of using GAL, the system is actually far from being effectively in place across the country's networks of public laboratories and health care services.

This system, which was being underused, has a crucial role, making available, in real time, the laboratory results for the adequate management of cases at the health care units. With that in mind, there was a concentrated effort to train the whole municipal network of laboratories and health units to introduce GAL before the adoption of Xpert.

> 'We had three months to prepare the whole network [of primary care services and laboratories in the municipality of Rio de Janeiro], the [TB] program and the units, so that they could grasp the meaning of GAL and of Xpert. The foremost concern was to implement GAL and make sure the [primary care] network would be able to interpret the material it was going to start to receive from March [2012] onward.'[20]

2.6. Correlated Studies to Introduce Xpert

As well as the pilot study, studies which concerned acceptability, economic assessment and evaluation of the laboratory infrastructure were commissioned to provide a broad context analysis for the incorporation of technology, which will be described in detail in item 3.

The first study, which was carried out still in 2011, involved the evaluation of the laboratory infrastructure requirements, in order to introduce a new diagnostic technology. A detailed, thorough survey of conditions and bottlenecks was made across the system, generating some recommendations.

The approach used in the acceptability study was qualitative and attempted to establish the aspects pertaining to understanding, perceptions and meanings to the people involved in the process of introduction of health technology – health care professionals, health managers and patients (SUS users). It should be emphasized that, in this case, it would be hardly possible to analyze the object of the study through a quantitative approach.

As for the economic assessment studies, there are two reasons that justify their contribution: (i) the need to show evidence in terms of costs, efficacy and budgetary impact of a new diagnostic technology and (ii) the establishment of new rules[21] to incorporate health technologies across SUS.[2]

The economic studies comprise the following components:

- analysis of (direct) unit costs for Xpert and SSM;
- analysis of Xpert's cost-effectiveness;
- budgetary impact;
- analysis of Xpert's costs from the patient's perspective.

2.7. Intermediate Evidence

During the study's intervention stage, it became evident from various accounts gleaned from interviews conducted by the authors, as well as those dealt with in the report, 'Qualitative assessment of Xpert MTB/Rif acceptability among health care professionals, health managers and patients',[1] prompt acceptance of the method by health care professionals and the marked 'learning curve', after express resistance or incredulity at the study introduction. The laboratory personnel displayed the most zealous acceptance, as reported by Prof Kenneth, having 'nearly unrestrainedly' welcomed the new method, still over the course of the study execution.[xxvii] [1]

During training to implement the study, managers of the basic and secondary units displayed good acceptance levels of the method and a perception of the benefits of the new information system.

Over the course of the introductory stages, a significant increase was noted in the detection of new cases. This accomplishment encouraged those involved in the study, who started to observe the results even more closely.

> 'Intrigued by the difference, after noticing so many new cases detected by Xpert, some laboratory professionals sought confirmation through the slides, through smear microscopy.'[22]

2.8. Difficulties and Obstacles

After overcoming the initial fears of professionals about the new method, reported problems concerned administrative and technical issues. These are in no way related to health care practitioners, but mainly to equipment (servicing) and supplies (purchase of cartridges) and to communication with the supplier.

Some difficulties were highlighted on the qualitative report which pertained to health care professionals' interaction with the GAL system, which was justified by their being not familiar with – or having no access to – the use of computer systems in their work routine.[1]

This factor should be taken into account when introducing the method across SUS; however, in principle this did not represent an insurmountable obstacle, as the general trend is to boost access to different means of electronic communication and the expectations are that local professional staffs increase their ability to use and handle new techniques, supplies and gadgets.

Approximately 7 per cent of samples were insufficient for processing by the machine, indicating the need to ensure close supervision as regards the compliance with guidelines for the collection of samples. This also points to a limitation in the technique.[xxviii] [23]

[xxvii] Report by Prof Kenneth, page 44.

[xxviii] Durovni *et al.* 'Operational lessons drawn from pilot implementation of Xpert MTB/Rif in Brazil' of the pilot study, awaiting publication. Under examination by PLoS Medicine.

2.8.1. The Interface with the manufacturer

Over the course of the study, six modules were defective,[xxix] or 10 per cent of the total number of modules (each equipment had four modules and one laboratory in Manaus had two pieces of equipment). The modules had to be replaced, a slow, difficult process, during the short intervention period. According to the manufacturer, the modules do not usually undergo problems.

Since the study was staggered, replacement of the faulty modules was possible before they became operational at the sites (laboratory units). However, this problem persisted until the end of the intervention period.

This study has indicated the need, in a national rollout, to anticipate a safety stock, which would not only address the average 10 per cent of modules which failed or presented inconclusive results, but also ensure uninterrupted provision of supplies. The supplier's limitations were evident during the study's interventions.

Besides the ongoing communication difficulties between the project's management and the supplier, the responses by the latter were persistently unsatisfactory. This included the lack of clarity in the division of responsibilities between the European and the American branches as regards the difficulties in replacing the modules, for which some technical assistance was expected, as well as the time to complete this request, which completely contradicted the supplier's express interest to endeavor meeting the client's requirements in Brazil.

It should be emphasized that over the course of the study the manufacturer changed the equipment model ('generation'), which started requiring the use of more recent cartridges; because an earlier contract was in place, these cartridges were replaced by the supplier. Also over the course of the study the machine calibration stopped being done manually. The manufacturer/supplier defined an electronic calibration, whose software could only be installed on the system's desktop computers, which made it more difficult to perform setup and calibration. ANVISA had to validate the new electronic calibration, which also required a much longer period than the execution of the study, eventually being approved only in mid-2013.[xxx] [24]

Even after the personal intervention by the supplier company's Vice-President, there were no significant improvements during the project's execution. It should be stressed that, after the study was over, a branch office was opened in São Paulo, which may lead to improved supply conditions when rolling out the method in Brazil.

2.9. Reflections on the Political Decision

As previously mentioned, on item 1.2.2., when the Minister of Health announced the introduction of the diagnostic method in Brazil, in March, 2012, he brought forward what should have taken place as a result of the evidence brought on by the study.

[xxix] Ibid.

[xxx] Certification for the electronic calibration, by ANVISA, took place in July, 2013, according to publication by the DOU.

The overriding effect of the political decision on the scientific output has generated some discomfort among some researchers as regards their institutional commitment.

Furthermore, when the Minister made the announcement, he created an inconsistency between the introduction of the method by SUS – still without any evidence produced within the country nor without the requisite technical backing by way of recommendations by CONITEC – and the implementation of the pilot study which had just started. This implementation has grown indistinct from the introduction of the method, generating expectations for continuity and frustration about the interruption in the use of the method following the pilot study, as will be explained below.

In spite of the best political intention by the Ministry of Health to reassert its commitment to improve TB indicators, and of the intention to secure the country's participation among those that adopt promising technological innovations in unison with international trends, the announcement of the implementation has laid bare the lack of a plan for this introduction that took into account the different epidemiological realities of Brazil.

The political decision has certainly created a demand for advance technical definitions, which were devised and put in place along the pilot study and after its completion.

2.10. Other Issues

Since patients were not involved in the pilot study, this has somewhat distanced users from the debate concerning the introduction of this technology across SUS. The Xpert pilot study did not raise substantial discussions in the TB social movement in Brazil, as compared with the heated debates among member of the AIDS social movement when technologies were introduced in the 1990's, such as the exams to count T cells (CD4), determination of viral load through polymerase chain reaction (PCR) and HIV genotyping.

However, it should be stressed that the study was presented in meetings of SMSDC-Rio's Community Advisory Board (CAB), before, during and after the intervention,[xxxi] and some community activists in Manaus were also acquainted with the execution of the study.[25] It should also be noted that both at the NGO Forum to Fight Tuberculosis in the State of Rio de Janeiro and at the Metropolitan Committee Against Tuberculosis in Manaus, the study was announced and reported in 2011 and in 2012.

Before the study, a significant step to engage the social representatives in the incorporation of technologies for TB took place during a debate on the topic at the National Health Council, which culminated in the

[xxxi] According to the records by the CCAP SMSDC-Rio coordinator, Giselle Israel, meetings to present the project were held from August, 2011 onward, until the last update, held in October, 2012. Email disclosure. October 20, 2013.

specific 2011 resolution regarding TB, recommending 'introducing the quick TB diagnostic across the whole of Brazil.'[xxxii] [26]

Item 3.5, below, will deal with the Xpert adoption plan across the SUS network.

[xxxii] Item no. 3, CNS Resolution no. 444, July 6, 2011.

3. Results Obtained in Studies of Adoption of Xpert in the Public Health Network in Brazil

A synthetic approach will be outlined to the results of each study which correlated with the implementation of the pilot study to introduce Xpert in Brazil.

3.1. Evaluation and Recommendations on Laboratory Infrastructure Needs

The report, issued in July, 2011, therefore before the pilot study was released, discusses the new TB diagnostic technologies, and how the laboratory network should prepare itself for their onset and incorporation. One of the bottlenecks which were spotted across the network was the information system. At the time the report was published, GAL's development was described as the solution offered by the Ministry of Health for the issue of information shared by laboratories. As well as the topic of infrastructure, another relevant point is the lack of a unique patient identification number to enable tracking from the moment they are taken into the health unit, diagnosed, through to treatment completion. The report suggests that the creation of a unique identification number would largely contribute to getting rid of double records across the information system and to reducing lost cases. This report had already recommended an interface between GAL and SINAN, so that all relevant information to track the treatment could become more comprehensive.

The report addressing the laboratory infrastructure study points to the key requirements to attain an effective introduction of new technologies, including Xpert:

- algorithm adaptation to the epidemiological reality of each region;
- well established reference mechanisms;
- funding to ensure sustainable, continuous provision of supplies;
- training of personnel;
- guarantees for equipment servicing and calibration;
- well planned procurement logistics;
- adequate quality control.

3.2. Pilot Study for the Introduction[27]

In the pilot project that was performed in Rio de Janeiro and Manaus, more than 34 thousand samples were analyzed at 14 laboratories, with a final approximate figure of 12 thousand samples in each arm (SSM and Xpert), after exclusions have been factored in. Among SSM, the positive cases amounted to 9.7 per cent, compared to 14.2 per cent by the new test, a

4.5 percentage point difference, representing a statistically significant increase of 46 per cent. [xxxiii]

Over the pre-intervention period, the TB notification rate with bacteriological confirmation was 30.5 per 100 thousand people/year in the group employing SSM, whereas, during intervention, the rate was 48.7 per 100 thousand people/year. Therefore, the proportion between the non-adjusted notification rates[xxxiv] in the two methods was 1.59, indicating a 59 per cent increase in the confirmed TB notifications.

As regards the interval between processing sputum and the onset of treatment, there has been a statistically significant reduction, from 11.4 days, in the SSM arm, to 8.1 days, in the Xpert arm.[xxxv]

An important point revealed by the project was the number of patients who have taken up treatment without receiving bacteriological confirmation: 44 per cent in the SSM arm, and 39 per cent in the Xpert arm. In spite of the decrease, the proportion between the notification rates did not constitute a significant statistical change.

Several physicians have advised starting treatment either without performing SSM or Xpert, or without the laboratory results, or despite a negative result, indicating the maintenance of this practice in the services. This group may also indicate those patients who have had bacteriological confirmation outside the study environment to which no access was granted; alternatively, they may have been patients who have had bacteriological confirmation in the study environment, but who had not been identified by GAL.

In practice, the indication to take up treatment is still largely done based on symptoms, chest radiographs and lack of response to non-specific antibiotics.

The pilot study team hypothesized that the limited time in the intervention stage was responsible for the failure to reduce this group's rate after Xpert had been introduced. If more time had been allowed for exposure to the test, given its high sensitivity, it would have been possible to boost confidence in a negative Xpert result, therefore avoiding starting treatment – obviously if a pulmonary TB suspected case had been involved. In this case, patients without tuberculosis could have avoided taking up an unnecessary course of treatment.

Results pertaining to resistance also deserve their own discussion, as they were not the main focus of this project. As far as the attitude to be taken is concerned, this is a controversial point, since the genetic signal for rifampicin resistance is detected on MTB.

[xxxiii] These rates were calculated firstly by gathering inputs recorded over the eight months of pilot study; the corresponding preliminary data was presented along 2012 and 2013. In early 2014, after collection of the final data, corrections were made, and the reviewed figures are presented herewith.

[xxxiv] Non-adjusted notification rate.

[xxxv] Preliminary data have recorded a 19.4 day decrease in the SSM arm, to 11.4 days, in the Xpert arm; the aforementioned data review undertaken in early 2014 has corrected these calculations.

The median time between sample processing and onset of second line therapy, should rifampicin resistance be suggested, was 127 days. This result has important consequences, which are detailed below.

A sign of rifampicin resistance does not mean, according to the evidence currently available in Brazil, that this case is an MDR case. Over the course of the study, the cases which displayed this sign were referred to culture and DST.

Some caution should therefore be exercised when stating that the MDR treatment could have been put forward four months by using this result as a parameter. Onset of MDR treatment should be supported by strong epidemiological evidence about the correlation, in the present introduction setting, between rifampicin and isoniazid resistance and the other first line drugs.

This point should be more thoroughly discussed, with the definition of priorities for the collection of new data in the country, so that these new algorithms may be adopted with the required safety.

Currently, the NTP recommends that, should the resistance sign be revealed, a culture and DST[xxxvi] [28] should be requested, the basic scheme should be started and the patient should be referred to the reference unit for MDR, partly justifying the long period between detecting resistance and initiation of MDR treatment.

In situations where MDR prevalence is low, even with high specificity, Xpert's positive predictive value (VPP) towards rifampicin resistance may be low. NTP's Technical Advisory Committee should conduct this discussion within the next few months, in order to define the most adequate algorithm for the epidemiological reality of each Brazilian region, as recommended by the study report addressing laboratory infrastructures.

One of the gaps of this pilot study is assessing Xpert in HIV-infected populations.

It was not possible to evaluate this aspect as a secondary objective because the sample had not been calculated with that in mind. Since the test for this population displays an estimated sensitivity of 80 per cent, the HIV+ population may be an important niche to optimize the use of the new tool.

Another relevant finding refers to Xpert's ability to influence most decisively those services which have been experiencing problems in fulfilling laboratory exams. This fact may be due to differences observed in notification rates, which were higher in the laboratories where the rates were already low for SSM. Since Xpert depends little on the laboratory professional, or at least to a lesser extent than SSM, these differences could be due to the operational difficulties prevailing before the intervention. Briefly, the new technology had a higher impact on laboratories associated with poor performance levels.

The report dealing with the pilot project also indicates several other knowledge areas which may suggest, from conscientiously produced evidence, the best way to accomplish a broader use of Xpert in Brazil. In

[xxxvi] Page 36 of the Manual de Recomendações para o Controle da Tuberculose (Recommendation Manual for TB Control).

future studies, it will be possible to generate the necessary bases to refine the test's target population, with the best allocation of machines, so that their use is effective.

3.3. Xpert Acceptability Study

This component of the project was a qualitative study to evaluate the method's acceptability by patients, health care professionals and managers. Two services (clinics) were chosen among those used on the project in Rio de Janeiro, as well as another service in Manaus. Eleven patients were interviewed who had been diagnosed through SSM in Rio de Janeiro and nine through the new technology. In Manaus, ten interviews were carried out with patients whose diagnosis had been made through Xpert. The group interviewing technique was used to assess perceptions among health care practitioners. Some key sources were interviewed in the two municipalities after the new method had been introduced in order to assess the managers' perspective. Among these sources note was taken of what had changed, what were the advantages and disadvantages of Xpert, as well as their views on broadening Xpert's use across SUS.

The major concerns among patients related to treatment (its long duration) and the stigma related to the disease. The type of diagnostic technology was secondary. Access to the services was not a major problem. Neither was limited time availability, since most of the patients were on leave from their jobs because of tuberculosis.

As for health care practitioners, in comparisons drawn between the two sites – Rio de Janeiro and Manaus – findings varied, probably due to the different introduction time schemes of the new test in these two cities. In Rio de Janeiro, the two major issues raised were the changes to the laboratory workflow and the onset of using the GAL information system, which took place at the same time as the project. In Manaus, on the other hand, only the first issue was highlighted as being key during the process. In general, professionals have not been resistant to the new method nor have they had any difficulties using it. Researchers hypothesize that this finding may be explained by the fact that the laboratory professionals did not feel that the introduction of the new technology would challenge their roles.

The interviewed health care professionals did not attach any importance to the time required to complete the exam. However, the time it takes for results to be forwarded and the way these are handed were highlighted in the interviews. Again, this is related to GAL's introduction. It should be noted that the extent of computer use and the ability to use GAL in all its potential, especially as regards its prompt responses, varied across the sites, depending on the available infrastructure.

Among laboratory professionals, test acceptance was very good, because it avoided contact with fire, as well as unpleasant reagent and

dyestuff smells, and did away with the need to stoop over microscopes for long periods.

The test's ability to provide a sign for rifampicin resistance was pointed by all managers as being very important. Another point to be stressed was the reliability associated with the machine. Other advantages which were noted included the ability to monitor the laboratory output more efficiently, the professionals' satisfaction, the issue of biosafety and workers' protection, training ease, higher efficiency to deploy supplies and the reduced diagnostic time. Few difficulties were noted, and they included lack of clarity in result interpretation to professionals performing core roles, financial resources to keep up the new technology.

Lastly, nearly every manager interviewed has said GAL was an opportunity, but also a challenge. The main reason for this viewpoint was the absence of an infrastructure to operate the system under ideal conditions.

As regards wider use of Xpert across SUS, accounts were unanimous in stating that it would be welcome and would bring benefits to diagnostics and to TB treatment, even if the factors mentioned above were taken into account.

3.4. Economic Studies

The results pertaining to the components of these studies are shown below:
(i) direct costs analyses for Xpert and SSM;
(ii) analysis of Xpert's cost-effectiveness for TB diagnostics;
(iii) analysis of the budget impact and
(iv) analysis of the costs to the patient.

3.4.1. Direct costs analyses for Xpert and SSM

The first component aimed to evaluate the unit costs of the tests under scrutiny, by using cost methods based on activities. The setting corresponded to a pragmatic trial; that is, the actual Xpert implementation setting at three of the 14 laboratories taking part in the project to evaluate the new methodology. The analysis was undertaken from SUS's perspective.

Following figures in Brazilian Reais (BRL) were exchanged into United States Dollars at the rate of USD1=BRL2.05, values which were in effect at the time of the study.

Results of the first study have indicated that the factors most affecting the costs of the two tests are different: supplies and reagents, in the case of Xpert, and human resources, in the case of SSM. Estimated average costs for the Xpert test were BRL35.57, and for SSM (one sample), BRL14.16.

3.4.2. Analysis of Xpert's cost-effectiveness for TB diagnostics

The key outcomes used in the second component, the cost-effectiveness, were detected TB cases, cured TB cases with treatment and their total cost; the component above generated the cost data for the test. To assess Xpert's cost-effectiveness the chosen parameter was the country's GDP per capita, proposed by WHO, which also incorporates DALY (Disability Adjusted Life Years), although this one has not been used in the present study.

In the cost-effectiveness analysis, when considering direct cost assessments, both strategies are cost-effective. However, when the measures used for this analysis are compared, Xpert was the most cost-effective strategy.

The results of this component have shown that, even if the reference value used on SUS (BRL4.20) is maintained, instead of BRL14.16 – which was the value gauged over the course of the project – Xpert was still cost-effective.

It should always be emphasized that an extra BRL9.96 is added on top of the reference value of BRL4.20 paid at the federal level on SUS, at those sites where this cost had been gauged by economic studies. Depending on their operational costs, other government levels will increase this value, according to the health unit's affiliation.

3.4.3. Analysis of the budget impact

Lastly, analysis of the budget impact has measured the impact of Xpert's introduction across SUS, as a replacement to SSM. NTP's perspective has been adopted, which was responsible for funding, diagnosing and treating pulmonary tuberculosis on SUS.

Calculation of the budget impact has indicated that the increase in total costs to SUS with Xpert diagnostics would amount to approximately 15.7 per cent, as compared with the costs involved in SSM. That would correspond to 6.3 per cent of the government NTP's budget, worth approximately BRL131.5 million.

The study emphasizes that over the second year of Xpert use as a replacement to SSM, there would not be any costs associated with machine purchases. Taking into account depreciation, servicing and calibration, the increase in total costs associated with Xpert diagnostics would be 15.3 per cent, which would amount to 3.1 per cent of NTP's budget.

3.4.4. Patient cost evaluation study[29]

As part of the economic assessments, this component was carried out at six clinics in Rio de Janeiro and 14 clinics in Manaus. Data was collected through interviews with 218 patients, and focused on the costs related to the test (SSM versus Xpert). Direct and indirect costs were calculated accordingly.

Total median cost per patient diagnosed through SSM was USD25.24, which is 54 per cent higher than the value gauged for patients diagnosed through the new method. Both direct and indirect costs were higher for SSM, the latter being responsible for the greater difference. Patient transport was the component bearing most weight on direct costs, and it was higher in Manaus, where users are responsible themselves for taking their samples to

the laboratory, as opposed to what prevails in Rio, where an SMSDC car transports the samples.

These results indicate that Xpert has the potential to reduce the patients' financial burden, even if one considers that the public system they access is universal and free of charges. In the study environment, the new test has reduced patients' expenses, as well as time wasted with procedures and displacements related to the diagnostic process. This effect could have been even more significant if Xpert had replaced SSM completely, as during the study, regardless of the method being used, patients were required to supply two sputum samples. In the future, Xpert may require a single sample, which will reduce even more the costs contained by this component.

3.4.5. Outcome of the economic studies

The high costs gauged for SSM, as compared with SUS' reference value, led to an increase of costs to track extra cases which had been diagnosed through Xpert due to its high sensitivity, since the new technology would solely be used for diagnostic purposes, not control nor tracking. This finding does not invalidate the cost-effectiveness comparison, but should be taken into account when interpreting the results and monitoring Xpert's incorporation on SUS in the medium and long terms. Should the technology allow DNA quantification as a way to track treatment, this technology may become even more cost-effective per cured case.

The researcher considered the results to be robust, especially because the better ratio of Xpert's cost-effectiveness is maintained even when parameters such as costs, test sensitivity and incidence of the disease are varied.

Lastly, since the concept of efficiency is linked to the relationship between costs and benefits involved in delivering a service, it will be essential to ensure good operation of the network responsible for implementing the new method in the SUS. If this condition is met, then the efficient use of public funds should be assured.

3.5. Plan for the Adoption of Xpert across the SUS Network

As previously stated, the political decision to introduce Xpert, even though it was announced at the onset of the study, in March, 2012, lacked some planning to introduce the diagnostic method across the network. Partial results of the pilot study and of the correlated studies have helped devise the plan, which meets NTP's prioritization concept.

The plan for the adoption of Xpert across the SUS network has been described in the proposal submitted to CONITEC by NTP in 2012. [xxxvii] [30] During two consultations with an assessing technical group in the second half of 2012,[xxxviii] still over the course of introducing the pilot study, it was decided that priority should be given to municipalities with more than 200 new TB

[xxxvii] The description of the adoption plan is on pages 16-18 of CONITEC's Final Report no. 49.

[xxxviii] First and Second 'Meetings for the Adoption of Technologies', held at NTP's headquarters, in Brasília, on September 18, 2012 and October 3, 2012.

cases in 2011 and which had laboratories with adequate physical and biosafety structures to perform SSM. The 200 new cases per year cut-off took into account the operational capacity of the equipment (8 to 16 tests a day). As well as those municipalities, the plan included State capitals, as diagnostic and treatment benchmarks for the disease, and any municipalities housing prisons or with indigenous populations with at least 50 new notified cases in 2011.

A decision was made that the LACENs should receive the equipment, since they would be in charge of training and controlling quality for the laboratory network of each State. The plan establishes that receipt of the equipment should be prioritized by grouping clusters for number of MDR cases and TB-HIV co-infection, pursuant to a WHO recommendation.

Currently, the NTP has a strategy in place for purchasing equipment from the Global Drug Facility (GDF) in Geneva, through PAHO's office in Brasília, to meet requests that enable a wider coverage by the States already defined in the introduction of the Quick Tuberculosis Testing Network (RTR-TB) by the NTP, as well as allowing for more flexibility to make some equipment more widely available in strategic places, both in terms of program reach and in generating more evidence through other research initiatives. [xxxix]

By 2014, RTR-TB[xl] should benefit 92 municipalities, identified and agreed upon by different government levels, as well as 145 differently sized public laboratories. These places account for more than 55 per cent of new TB cases notified in the country.[31]

Over the course of the first year of network introduction, the plan aims to purchase 160 pieces of equipment (each comprising four modules) and 464 thousand cartridges. São Paulo, Rio de Janeiro, Rio Grande do Sul, Pernambuco and Amazonas would be the first States to undertake the first stage, corresponding to 50 per cent of the country's network.

Information, education and communication (IEC) strategies have been initiated and the qualification of coaching-agents (trainers) is being planned in the selected States and localities where health care professionals are going to be trained to perform the test. It is estimated that approximately 300 laboratory technicians should be trained, who should perform the exams in laboratories.

[xxxix] Information obtained from Josué Nazareno de Lima by Mauro Sanchez, NTP-SVS-MoH, in 2013, and confirmed by Ezio Távora on May 20, 2014 by Skype call.

[xl] Initially, RTR-TB should have been introduced in 2013. However, only on March 24, 2014 was delivery of the first 50 machines and supplies announced, with initial operation scheduled for the following month.

4. Conclusions, Challenges and Recommendations

4.1. Conclusions

This report attempted to interpret the experience with the pilot study and the results from different studies pertaining to Xpert's introduction in Brazil. The findings from the pilot study and its correlated studies have met their targets, as required by CONITEC, to support the previously announced government decision to adopt the method in most municipalities associated with high TB burdens.

As shown above, this government decision was announced by the Minister of Health in March, 2012, when the pilot study was started, and was published on the Federal Official Gazette (DOU) on September 11, 2013,[32] after being approved by CONITEC on March 7, 2013. [xli]

It should be stressed that the pilot study did not aim to obtain the method's validation. It attempted to show how the Xpert method works routinely across SUS' Basic Attention network, to diagnose pulmonary tuberculosis, and whether or not it brings benefits to the system and the user.

In short, it has been concluded that the series of results shown here indicate that when Xpert is applied routinely, it (i) increases by 59 per cent the bacteriological confirmation of cases, (ii) reduces from 11 to 8 days the onset of treatment, (iii) is well accepted by health care professionals and (iv) appears to be more cost-effective than SSM to detect TB cases and to attain complete treatment outcome.

However, the study also indicates several deficiencies in the health care system. Solving these problems and deficiencies is vital, so that this technology – or any other – may properly contribute to the performance of the health care system, especially to improve the quality of assistance to the user.

These deficiencies pose various considerations and questions, listed below as 'challenges', followed by some recommendations.

[xli] On December 7, 2012 CONITEC members unanimously recommended Xpert MTB/RIF for TB diagnostics and for the indication of rifampicin resistance. Public consultation followed, between January 15, 2013 and February 04, 2013, with two contributions; the final resolution recommending introduction of Xpert MTB/RIF took place by simple majority on March 7, 2013. SCTIE's Directive no. 48 with the resolution, dated September 10, 2013, was finally published on September 11, 2013.

4.2. Challenges and Recommendations

First Challenge: Adjusting the health information systems

The first point to be raised concerns the deficient health information network. As previously stated along the report, a key point for the pilot study's success was the earlier implementation of GAL.

The pressing, indispensable need for earlier implementation of GAL was emphasized at the debates around introducing Xpert[xlii] nationally, during the final stage of execution of the pilot study. According to CGLAB, 'nearly all LACEN's were already qualified to use that instrument. However, no assumption should be made that priority states and municipalities for tuberculosis had already been qualified or had incorporated and made full use of that system. The need for the earlier introduction of GAL in relation to Xpert at the units in Rio de Janeiro and Manaus confirms that the laboratory environment management system had not been introduced across the networks in the priority states and municipalities.

The studies point out the deficiencies in the system, as a molecular diagnostic method which processes the result of a sample in less than two hours takes on average eight days to reach the patient. The local administration should therefore be prompted to recognize and solve its bottlenecks. It should be stressed that the failure to diagnose and adequately treat is a system-wide problem, as it feeds the transmission chain that perpetuates the problems of public health.

As previously stated, in the implementation study, committed and competent administrators were careful in fulfilling their roles, in a political and administrative scenario which was conducive to a redoubled attention when collecting information. Though it was a pragmatic study, because a routine had been adopted, it was still a study; in this case, results were constantly and carefully monitored, which does not correspond to the routine put in practice by health care services. Several questions remain: how could favorable conditions be ensured in the routine, so that similar results to the pilot study could be obtained? How could laboratory personnel be encouraged to input data to the system with the desired speed, as has happened in the study, along with the conditions provided by the new method? How could one ensure that the health professionals are going to constantly access the data contained in the system and are going to quickly take the necessary actions to adequately track the patient?

A question should also be posed as to when SINAN will incorporate the new methods and when the system will have adequate interfaces with other health information systems.

These are some of the challenges faced by management and administration of the public health care services which the diagnostic method is not able to solve by itself.

[xlii] Question raised at the First Meeting for Technology Introduction, convened by the NTP-SVS-MoH to debate the national implementation of the method, on September 18, 2012, at the NTP headquarters, Brasília.

Recommendations: To promote and ensure the earlier introduction of GAL and the interfaces between it and SINAN and other information systems are in place, as well as to engage local administrations to plan ahead of the introduction and expansion of the method.

Second Challenge: Ensuring adequate training and support for professionals and technicians

Often, qualification does not result in the adoption of a new proposed method. Full access to computerized services is not a consistent reality in health units across the country, as is widely acknowledged.

We are aware that, to ensure an effective introduction of the new diagnostic method it is indispensable that the information system be used fully by laboratory personnel who are dealing with the sample results, by the professional clinicians who are going to treat the patient, and by the managers, who are going to monitor the data.

Some questions should be posed: who should be responsible for training, monitoring, tracking and supporting the professionals performing core roles? The Federal Government or the local administration levels? How could the administrators of state and municipal health units which are presented with the method become committed to ensuring the necessary support to laboratory technicians and health care professionals who are going to access the system, correctly interpret the results and follow up on the correct treatment of the patient?

Recommendation: To provide adequate support, both technical and financial, so that the local managers may ensure the necessary training and support efforts of professionals and technicians on the use of the new method. It should be emphasized that in order to extend the reach of the method, some joint planning and execution is necessary among different administration levels, going beyond mere recommendations by central management.

Third Challenge: Ensuring procurement of supplies

Purchase of machines and supplies has already been defined by the Federal Government, which will provide the method to the priority States and municipalities that contain more than 55 per cent of new TB cases in Brazil. How could the continuous provision of supplies be ensured during the roll out and scale up stages? The successful experience of the pilot study was followed by a discontinuous provision of supplies (cartridges and modules) to the municipalities of Rio de Janeiro and Manaus.[xliii] The interruption in the use of Xpert and resumption of SSM have led to a certain disappointment about politics, losses in training investment, disillusion about technology among

[xliii] Cartridges were used which had been 'saved' by the study after its completion, in October, 2012, until they had run out in both cities, in February, 2013. As of March, 2014 these supplies had not been made available.

personnel,[xliv] [33] but mainly a loss to the SUS user who, ultimately, is the main beneficiary of the method and a tax-paying citizen.

Stock reserves are necessary, as well as setting up emergency provision mechanisms, in case of worst case scenarios, which would thus avoid supply shortages and suspensions.

Even if one considers the suspension as an atypical situation in terms of program, as it happened in the transition from the pilot study to the implementation of the RTR-TB, any disruption suggests that difficulties may come up along the routine service. A clear definition of roles and a system of accountability are necessary for the regular purchase of essential supplies, as well as a frequent dialog with the manufacturer/supplier.

Recommendation: To ensure that emergency stocks of supplies and parts are kept, to meet demands if and when regular supply levels are disrupted for any reason.

Fourth Challenge: Establishing technical assistance to be provided by the manufacturer

The point above highlights the inadequate provision of supplies and delivery of technical assistance. Even more importantly than the purchase of supplies (mentioned above), any technical problem should be promptly solved so that the user is not faced with interruptions in the service supply. The presence of a manufacturer representative in the country is a positive aspect, but it does not represent any guarantee for an adequate supply or assistance. Since the implementation of the method was an initiative by the federal level, it is vital to secure quick responses to the states and municipalities' requests.

Since late 2012, purchase of machines and cartridges (as well as other correlated supplies) has been underway in Brazil, to roll out and scale up the method nationally. It is important to make the partners in this stage aware of the guarantees offered by the manufacturer to provide supplies and assistance.

In the case of large scale national clients, such as SUS, the extent of the problems expands geometrically. It is vital that the problems observed during the pilot study are avoided, such as the case of delayed replacement of faulty modules and machines, as well as the supply of cartridges and replacements.

It should also be noted that the purchase prices that prevailed for SUS at the time of the international agreements, should vary with time. Calculations done in 2011 by FIND, which fixed cartridge prices used during the pilot study, have considered a production of at least 3 million cartridges, which would ensure financial returns to the manufacturer/supplier. However, this mark was already overtaken in early 2013, having exceeded, by December of the same year, the 4.5 million cartridge mark produced for the whole international market. Therefore, it is not justifiable that Brazil (and other countries) refrains from negotiating more favorable conditions and lower prices with the supplier or through middlemen being resorted to (PAHO, GDF).

[xliv] Accounts during a visit to the health units in Manaus and collective interview with local managers, May 9, 2013. Transcript of interviews. Word document.

The likely scenarios for employing the method in the medium and long terms should also be anticipated, ensuring some conditions for the country are safeguarded when new generations are launched and replacements are on offer for the models purchased previously.

Recommendation: To ensure the manufacturer meets every condition which safeguards SUS' interests toward the adequate provision of machines and adequate supplies, and the prompt delivery of technical assistance.

Fifth Challenge: Managing dependence on a monopolized technology

The new methodology at hand is owned by a single manufacturer. The features that have led it to be recommended by WHO are obviously acknowledged. The endorsement given by this organization is in itself a strong influence on the decision to perform studies and assessments, which lead to the method's adoption by the country.

What are the necessary conditions to avoid turning Brazil into a hostage to an exclusive method, from a single supplier, given the aforementioned limitations? How are the options being evaluated to reduce dependence from exclusive manufacturers/suppliers? Is due attention being paid to other technological options in Brazil and overseas?

It is also important that the federal government, in tune with other government spheres, ensures that capable and firm negotiations are in place for purchasing, distribution, replacement and servicing of equipment and supplies purchased from the manufacturer, who holds exclusive production rights.

Recommendations: To create ongoing mechanisms for operational assessment, at SUS, of other molecular tests which may become available at the domestic and international markets so as to promote ways to reduce the dependence on exclusive technologies which may weaken the national ability to negotiate; to create purchasing mechanisms which may enable the renegotiation of prices and flexible conditions.

Sixth Challenge: Ensuring reliable culture data

In the pilot study, of approximately 60 cases for indication of resistance which were referred to culture, only around 40 results had been obtained by the end of 2013. One third of the results remained unknown up to that period. In the national expansion scale, how could one ensure that this situation will not repeat itself?

It is crucial to ensure disclosure of information on the culture and DST results for those patients with signs of rifampicin resistance. As previously reported, during the course of the study, many results for cultures were not accessed by the health team. Some did not show any growth, which brings to mind the discussion on the exam's accuracy, others were not found, which brings to mind the deficiencies in the organization of the health care system. If Xpert is able to detect this marker for resistance, this information should not be lost, especially in those cases in which treatment had been started on the basic scheme. There are already some proposals to introduce, at least among

a selected group of patients (to be defined by NTP), liquid cultures (MGIT)[xlv] – quicker than solid cultures, albeit more expensive. Economic assessments may suggest the best target population selection, in order to maximize the investment benefits which should be necessary, helping to build the adequate algorithms to manage the indication of resistance for each setting.

> **Recommendations:** To expand laboratory capacity to carry out culture and sensitivity tests; to help states and municipalities to set up realistic information flows which ensure the quick availability of data about culture and sensitivity tests to the health care practitioners seeking adequate management of cases that point to resistance.

Seventh Challenge: Establishing the algorithm(s) in the country: to improve management of symptomatic and suspected drug-resistant patient

Taking into account not only the epidemiological scenario but also the country's reality (precarious information flow, deficient patients' referencing and counter-referencing), we should still discuss the algorithm(s) to be adopted in Brazil when Xpert is introduced.

As previously mentioned, on item 3, the currently recommended algorithm for patients displaying a positive sign for resistance to rifampicin should follow local epidemiological conditions, since the study's data still appear insufficient to define it. Xpert's expansion across Brazil will be useful to collect more data to support the review of the adequate algorithm for patients with sensitive tuberculosis and drug-resistant tuberculosis. Other studies, which involve adoption of Xpert under different circumstances in Brazil, also commissioned by NTP, should also be considered. In 2013, some studies presented assessments of the molecular and bacteriological methods which are employed to detect drug resistance.[xlvi]

With the expected increase in indication of rifampicin resistance, it will be necessary to adjust the health care system so that it can adequately take in, refer, treat and monitor those patients suspected of harboring MDR. The obstacles observed during implementation should be taken into account, where, even with careful surveillance of laboratory data, a considerable number of culture results remained unknown, indicating gaps in the management of patients and in the laboratory routines for cultures.

> **Recommendations:** To define the algorithm(s) to introduce the new method, which optimize the benefits of managing patients, taking into account regional differences, evidence produced by different studies presented herein (among which are bottlenecks in the laboratory structure), as well as evidence produced by other studies commissioned by the NTP.

[xlv] According to Draurio Barreira, in 2012 NTP's Technical Advisory Committee recommended, as part of the debate on GeneXpert, implementing liquid growth media; however, the inclusion of the quick test and liquid growth media on SUS' table was discussed by CONITEC but no action was recommended on the issue. (Email disclosure. November 26, 2013).

[xlvi] IN BRAZIL, THE PROVE IT study by REDE TB/UNION, which includes Xpert as a diagnostic method for MDR, has communicated its results on November 2, 2013, during the 44th World Union Conference, in Paris.

Eighth Challenge: Reviewing the use of 'quick testing' terminology

Over the course of visits to health units and laboratories in Manaus and in Rio de Janeiro, health care professionals complained about the use of the term 'quick test' in association with Xpert. According to these professionals, this leads patients and system users to expect that they will leave the health unit with the result for their TB exams ready. However, on average the result takes eight days to be disclosed after sputum collection.

Again, it is important to stress that if there has been a significant decrease in the average period of result delivery – from 11.4 to 8.1 days – this period is still unacceptable for a test which is processed in a couple of hours; this situation can be significantly improved.

Even if the CNS has recommended 'the introduction of quick TB tests across the whole country' in 2010, the molecular methods available should not be construed as being speedy. The use of the term should be reviewed, in order to avoid any liability by the primary care services.

> **Recommendation:** Bearing in mind that the term has generated some frustration by patients and professionals in some units, it is advised reviewing and changing the use of the term 'quick testing' in association with the method, since it usually does not produce as immediate or speedy a response to the patient as HIV or pregnancy tests.

Ninth Challenge: Broadening the discussion with society players about the adoption of the method

Widening the debate with activists and members of health councils about adopting the technology to detect sensitive TB, as well as the algorithms for MDR, may help its introduction to the system. This may especially be the case if there is public demand by users, who may also help to sanction its use in the system by monitoring access to services and complying with policies already in force.

Again, it is important to remind that mobilization around the adoption, by SUS, of diagnostic methods for AIDS in the 1990's has favored the introduction and social control of these methods, triggering political and even judicial mechanisms to safeguard the benefits across the network, a factor which remains important to this day.

> **Recommendation:** To foster discussion with civil society, especially with users, about incorporating new health technologies, and including representatives of these users in the planning and surveillance stages of introduction.

Tenth Challenge: To broaden and share benefits gleaned from the study, in order to introduce the method nationally across other countries and contexts

The Seminar for the Introduction of New Technologies to Control Tuberculosis, which was held in Maputo,[xlvii] has shown the need to implement pilot projects prior to the adoption of new technologies such as Xpert.

Considerably diverse circumstances prevail across countries such as South Africa, Mozambique, Angola, Cape Verde, and Guinea-Bissau, each country being faced with their own limitations, but all have to deal with similar bottlenecks to the ones that prevail in Brazil, as regards the information system, sample and patient flows, references, etc.

Each country is responsible for the discussion and definition of algorithms, according to their epidemiological data and the context of their health care systems.

As soon as the results for the Fourth Generation Xpert are published, more data will be added to set up new expansion scenarios for this and other technologies.

The experience from the studies performed for introducing Xpert in Brazil helped establish cooperation to introduce and expand the method across different countries.

Recommendation: To broaden international collaboration, especially with African Countries of Portuguese Official Language (PALOP), about the introduction of health technologies in the treatment of TB.

[xlvii] The Seminar was organized by the Brazilian and Mozambican Ministries of Health, between May 14 and 16, 2013, backed by the National Health Institute of Mozambique (INS) and InCo.TB, as part of the cooperation agreement between the Brazilian Ministry of Health and The Bill & Melinda Gates Foundation, through FAP.

Final Remarks

As anticipated at the beginning of this document, the experience of implementing the pilot study to introduce Xpert was a great success. However, the discontinuity of the technique in the pilot sites after the study ended and the long delay to resume the implementation nationally represented partial loss of the investments made on the study implementation, especially regarding the mobilization around this initiative.

In spite of all difficulties and obstacles, the adequate planning, choice of principal investigators and the engagement of a wide network of partners have encouraged the positive result for the implementation of the pilot study, and generated considerable expectations among health managers and workers around the adoption of the method in the country.

Xpert represents the closest diagnostic alternative to the ideal: it is simple to handle and set up, has no high level biosafety demands; is nearly point-of-care and nearly a quick test. It is the method which enables freeing the laboratory technician – partly, at least – from antiquated microscopy techniques, launching them into the 21st Century. Under adequate processing circumstances and correct information management, it may in fact revolutionize diagnostics and help attain adequate treatment, leading to improved TB indicators.

The method represents more than a new diagnostic technique. It imparts the feeling to the collective imagination (among managers, health care practitioners, laboratory personnel and users) that progress is being made. It is therefore essential not to thwart the expectations associated with its introduction and satisfactory use, if Brazil is indeed committed to substantially improving its TB indicators.

In short, the method has a huge potential. However, that depends on a complex health system working satisfactorily. Taken individually and without the due contextual improvements, no new diagnostic will have the expected impact.

The implementation study has shown to what extent the fluctuations of public policy, public administration, bureaucratic negotiations, academia and negotiations with commercial bodies have variable tempos, paces and patterns. To reconcile them is a herculean task, often not viable when decisions, findings or interests overlap each other. What remains is to manage their effects and factor in the benefits and lessons learned; they are the prizes for this long process.

The MoH's decision to commission a pilot study over 2010 and 2011 to introduce a method already indicated a perspective or interest to adopt it. The pilot study was devised to provide national evidence firstly to support the technical decision-making process and, secondly, the political decision to introduce the method.

The study started where it should have ended: at the (political) decision, by the Minister of Health (in March, 2012) to introduce the molecular diagnostic to detect pulmonary tuberculosis as a replacement to SSM. The

technical recommendation, by CONITEC, which should have supported this decision, only took place in March, 2013 and was published on the following September, after presentation of partial evidence which had been generated until October, 2012.

Has this invalidated the economic studies and other complementary approaches to the pilot study? Certainly not. Different studies have shown the true conditions of the health system. They may favor the best evaluation of management to make the most sensible decisions over the course of introducing the method nation-wide.

However, it is important to seek agreement and mutual recognition of the genuine interests that inspire the different actors. It should be emphasized that lining up the different tempos prevailing in politics and in science may benefit all, encouraging decision-making processes which are based on data produced in the context where one hopes to introduce the new technology. This agreement certainly strengthens the national institutions and ensures the safeguarding of the best public interests.

Other operational pilot studies should also be recommended, in the same mould as those which are managed by the InCo.TB project, which enable the evaluation of new technologies under circumstances similar to SUS's routine. More than a new bureaucratic requisite, this is the only means of producing valid evidence to adopt new techniques and technologies. The country could only benefit from this kind of political-scientific initiative.

It is hoped that this experience favors new initiatives to incorporate technologies and that these recommendations help attain successful adoption of Xpert in Brazil and other countries.

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