Bottlenecks and recommendations for the incorporation of new technologies in the tuberculosis laboratory network in Brazil*

Gargalos e recomendações para a incorporação de novas tecnologias na rede pública laboratorial de tuberculose no Brasil

Maria Alice da Silva Telles, Alexandre Menezes, Anete Trajman

Abstract

The World Health Organization (WHO) has recently recommended new technologies for the diagnosis of tuberculosis. The WHO recommendations include the development of a strategic plan for bringing the network up to grade; investment in supervision and quality control; and implementation of a system of laboratory environmental management. Without those measures having been taken, no new technology can be effectively incorporated. We surveyed the tuberculosis laboratory network in Brazil in order to identify possible bottlenecks for the incorporation of new technologies. We identified a lack of resources allocated to supervision and quality control; a low number of requests for cultures; a lack of effective laboratory information systems; and a lack of awareness regarding the future infrastructure needs of the laboratory network at the municipal level.

Keywords: Quality control; Tuberculosis; Laboratories; Clinical laboratory information systems; Technology.

Resumo

Novas tecnologias para o diagnóstico da tuberculose foram recentemente recomendadas pela Organização Mundial da Saúde (OMS). Algumas recomendações da OMS incluem a elaboração de um plano estratégico para a adequação da rede, investimentos em supervisão e controle de qualidade, implementação de um sistema de gerenciamento de ambiente laboratorial, sem o que nenhuma nova tecnologia poderá ser eficazmente incorporada. Realizamos um levantamento da rede laboratorial de tuberculose no Brasil para identificar possíveis gargalos para a incorporação dessas tecnologias. Identificamos escassez de recursos para supervisão e controle de qualidade, baixa solicitação de culturas, ausência de sistemas eficazes de informação laboratorial e o desconhecimento da rede periférica municipal quanto às necessidades futuras na infraestrutura.

Descritores: Controle de qualidade; Tuberculose/diagnóstico; Laboratórios; Sistemas de informação em laboratório clínico; Tecnologia.

The diagnosis of tuberculosis remains a challenge. After more than half a century using sputum smear microscopy as the principal diagnostic tool, new, molecular biology-based techniques have become commercially available. Some of these techniques, such as the Xpert® MTB/RIF assay, which allows rapid and simultaneous detection of *Mycobacterium tuberculosis* and rifampin resistance with great accuracy, are being recommended by the World Health Organization (WHO) and international partners.[1,2]

The Brazilian National Ministry of Health (NMH) has recently announced the incorporation of this technology in the laboratory network operated by the Brazilian Unified Health Care System.[3] In order to inform the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program) on the incorporation of the Cepheid Xpert® MTB/RIF assay, a study of the implementation, cost-effectiveness, and acceptability of the method is being conducted at two cities. The adoption of other new tests, the so-called line probe assays, which include

* Study carried out at the Adolfo Lutz Institute, São Paulo, and at the Gama Filho University, Rio de Janeiro, Brazil.
Correspondence to: Maria Alice da Silva Telles. Rua Cristiano Viana, 505, apto. 11, CEP 05411-001, São Paulo, SP, Brasil.
Tel. 55 11 3068-2895. E-mail: atelles.msh@gmail.com
Financial support: This study received financial support in the context of the project known as *Inovações para o Controle da Tuberculose* (InCo-TB, Innovations in Tuberculosis Control), which is the result of a partnership between the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program) and the *Fundação Ataulpho de Paiva* (FAP, Ataulpho de Paiva Foundation), with support from the Bill & Melinda Gates Foundation (#GH5254).
Submitted: 2 July 2012. Accepted, after review: 17 September 2012.

Hain Lifescience's DNA strip technology,[1,2] is also under study in the country.

We discuss here the potential that is currently available at the various hierarchical levels of the *Sistema Nacional de Laboratórios de Saúde Pública* (SISLAB, Brazilian National Public Health Laboratory System), as well as its major weaknesses in meeting the PNCT recommendations, in order to identify potential bottlenecks for the incorporation of new diagnostic technologies in the country and to propose measures to strengthen the laboratory network. Our opinions and conclusions are based on the annual self-assessment undertaken by the *Laboratórios Centrais de Saúde Pública* (LACENs, Central Public Health Laboratories), on technical visits performed by the *Laboratório Nacional de Referência* (LRN, National Referral Laboratory) between 2009 and 2010, on published interviews with actors in the field of tuberculosis, and on a review of official documents (directives, guidelines, norms, and recommendations by the PNCT and the WHO).[1,4-7]

In Brazil, diagnostic tests for tuberculosis are performed mostly in the SISLAB,[7] which is composed of the LRN, 27 LACENs, and another 3,000 local laboratories. The local laboratories perform sputum smear microscopy, and few of them also perform culture and drug susceptibility testing (DST).

Despite the major challenge of coordinating a network of continental proportions, the LRN adequately carries out many of its duties, which are defined in Directive no. 2,031[6]: standardization of techniques; human resource development; technical coordination of the laboratory network; and performance of highly complex laboratory procedures, such as genetic sequencing, genotyping, and second-line DST. However, the LRN needs to increase recent scientific partnerships and exchanges and improve the supervision of the LACENs, which is negatively affected by the inadequate information system and by the deficiencies in the team of supervisors. Between 2009 and 2010, the LRN directly supervised the 27 LACENs. However, with the current team, it will be impossible to perform this activity with the desired frequency. In 2011, the LRN joined the team that had been established by the PNCT and the *Coordenação Geral de Laboratórios de Saúde Pública* (CGLAB, General Coordination of Public Health Laboratories) to assess and monitor state and municipal tuberculosis control programs annually. This experience showed that the coordination of the different actors involved in this task can be a history of success.

Of all LACENs, only 8 consider themselves to meet 20 or more of the 25 quality criteria used in the self-assessment. The most frequently cited strengths are decentralization of sputum smear microscopy, use of standard operational procedures, computerized laboratories, organized teams of professionals, good work organization, quality control (QC) of reagents and media, qualified professionals, suitable size, and quality practices for sputum smear microscopy. The universally acknowledged weakness is the poor QC of the peripheral network. Re-reading of slides and technical visits are insufficient in nearly all of the Brazilian states, the average coverage being 22% (Chart 1). The LACENs with poorer performance in terms of QC are those with a greater number of laboratories in their network, which means that the most populous metropolitan areas receive less QC coverage. This difficulty is due to the excessive workload, since there is no team exclusively involved in performing this activity, and to the lack of resources for transportation and expenses. This weakness is a cause for specific concern, given that any other test that may replace or complement sputum smear microscopy will also require QC.

Sputum smear microscopy reaches 86% of the expected target, and bottlenecks occur only in more remote cities. Culture coverage, however, is insufficient (Chart 2): the number of tests does not reach that expected for situations in which culture and DST are recommended.[5,8] The laboratories do not establish quotas, and all cultures and DST requested by patient care professionals are performed. Therefore, for now, it is not a matter of supply but of reduced demand for tests by physicians and nurses, who do not believe in the ability and promptness of the laboratories. This credibility depends on the ability of the laboratories to meet the demand and report results promptly. Decentralization of culture to the network of municipal laboratories might be a solution that will make it possible to streamline the reporting of results and expand the installed capacity if there is an increase in the demand for culture in the country, which is in accordance with the recent recommendations by the PNCT.[5] There is a consensus among the various sectors of the Brazilian NMH that the

Chart 1 - Tests performed by the Central Public Health Laboratories, classified by state, 2009.

State	Sputum smear microscopy	Culture	Drug susceptibility testing	Identification of NTM	Identification of MTB	Incidence[a]
Acre	7,941	252	34	3	34	322
Amazonas	1,511	1,246	78	8	70	2,254
Amapá	342	300	5	1	21	218
Roraima	1,200	1,110	72	2	7	132
Rondônia	1,555	625	53	23	132	566
Pará	2,185	1,208	87	2	87	3,539
Tocantins	118	70	0	0	0	196
Maranhão	-	-	-	-	-	2,136
Ceará	6,604	6,805	978	58	606	3,837
Piauí	-	-	-	-	-	830
Bahia	1,225	1,673	629	129	1,090	5,740
Rio Grande do Norte	-	-	45	-	-	978
Paraíba	1,943	1,943	141	2	139	1,061
Pernambuco	2,014	1,306	289	17	292	4,167
Alagoas	3,285	445	50	34	411	1,176
Sergipe	757	445	42	5	37	565
Mato Grosso	780	780	39	49	66	972
Mato Grosso do Sul	6,119	6,097	181	94	480	883
Distrito Federal	2,367	2,922	131	5	124	286
Goiás	-	1,926	44	41	91	875
Minas Gerais	-	1,505	274	56	343	4,239
São Paulo	23,392	28,688	3,209	1,164	4,373	15,783
Espírito Santo	1,849	1,849	186	18	161	1,263
Rio de Janeiro	4,894	4,894	726	105	1,335	11,634
Paraná	1,270	1,517	289	7	289	2,409
Santa Catarina	3,344	3,344	690	23	667	1,641
Rio Grande do Sul	3,666	4,512	409	74	692	5,032
TOTAL	78,361	75,462	8,681	1,920	11,547	72,790

NTM: nontuberculous mycobacteria; and MTB: *Mycobacterium tuberculosis*. Source: General Coordination of Public Health Laboratories, 2009. [a]New cases per federal state of residence.

financial investment needed to meet any increase in demand for culture is low relative to the health care budget in the country.

Another serious weakness that might impact the incorporation of technologies is the staff of human resources. Although the professionals working at the LACENs are regularly trained and have a good technical level, the vast majority is close to retirement age, which requires training programs for urgent staff replacement. In order to overcome this and other weaknesses of the laboratory network, a technical group, composed of managers of the PCT and the LACENs, should develop a strategic plan on the basis of a careful analysis of the network, including assessment of needs in terms of infrastructure, biosafety, and human resources, as well as of the number of tests performed, definition of targets for each laboratory, and establishment of algorithms and needs in the case of the incorporation of new technologies. In the case of the adoption of the Xpert® MTB/RIF assay, for example, it is necessary that the electricity supply be stable, the materials be stored in refrigerated space, and the logistics involved in the purchase and distribution of the materials be refined, given that the cartridges are imported and have a 12-month expiry period.[9,10] Likewise, the PNCT could establish, at the federal level, a permanent group to foster links with the state network and develop a plan for network coordination, clearly establishing the duties of the CGLAB, the LRN, and the PNCT, which currently overlap.

One of the major bottlenecks in the SISLAB, however, is not found at the laboratory benches. The information system is weak. The various component sectors of the program have difficulty in obtaining information. Case reporting forms

Chart 2 - Composition of the laboratory network operating under the direction of the Central Public Health Laboratory of each state and proportion of laboratories for which the Central Public Health Laboratory conducted supervision and external quality control in 2009.

State	Laboratories performing sputum smear microscopy	Laboratories performing culture	Laboratories performing DST	Supervised laboratories	Laboratories with external QC of sputum smear microscopy
				n (%)	n (%)
Acre	38	3	1	12 (32)	26 (68)
Amazonas	58	7	2	0 (0)	58 (100)
Amapá	17	1	1	8 (47)	4 (23)
Roraima	51	2	1	26 (51)	48 (100)
Rondônia	27	2	0	1 (4)	4 (15)
Pará	261	7	2	77 (29)	146 (56)
Tocantins	89	1	0	29 (33)	59 (66)
Maranhão	197	1	1	18 (9)	32 (16)
Ceará	147	5	2	107 (73)	122 (83)
Piauí	-	1	1		
Bahia	345	20	2	56 (16)	94 (27)
Rio Grande do Norte	99	1	1	70 (87)	48 (61)
Paraíba	198	1	1	28 (14)	49 (25)
Pernambuco	126	2	1	25 (20)	66 (54)
Alagoas	80	1	1	9 (11)	15 (19)
Sergipe	92	1	1	16 (17	20 (22)
Mato Grosso	133	1	1	34 (26)	87 (65)
Mato Grosso do Sul	68	3	1	0 (0)	56 (82)
Distrito Federal	16	1	1	8 (50)	12 (75)
Goiás	66	1	1	23 (35)	42 (64)
Minas Gerais	597	15	1	49 (8)	51 (9)
São Paulo	214	70	5	92 (43)	50 (23)
Espírito Santo	80	6	2	68 (85)	59 (74)
Rio de Janeiro	220	26	6	60 (27)	60 (27)
Paraná	263	29	1	1 (0)	88 (33)
Santa Catarina	394	5	1	8 (2)	200 (51)
Rio Grande do Sul	290	14	1	51 (18)	113 (39)
TOTAL	3,969	221	35	876 (22)	1,609 (40)

DST: drug susceptibility testing; and QC: quality control. Source: General Coordination of Public Health Laboratories, 2009.

are completed and updated with a delay. More importantly, the information flow is inadequate at the bottom. Collection of samples from the health care facilities depends on a regular transportation service, which causes delays in the delivery of test results to the requesting facility and, consequently, in treatment. In order to overcome this bottleneck, the Brazilian NMH has developed a computerized system called *Gerenciamento de Ambiente Laboratorial* (GAL, Laboratory Environmental Management). For local managers, GAL represents the possibility of real-time identification of cases by health care facility's coverage region and the consequent referral control of such cases. For patient care professionals, GAL enables early case detection.

The major obstacles to the implementation of GAL have been the team responsible for its implementation, which is considered too small for the size of the country, and the lack of Internet access. Two years after GAL began to be implemented, it is still not used by 5 LACENs and it has been implemented in the whole network by only 5 LACENs. This system will only be universal if there is a significant investment in the recruitment of a team of multipliers to cover the entire Brazilian territory. Access of health care facilities to GAL will require, in addition to training, investment in Internet access. The

implementation of this computerized system should include the creation of a national identification number for health care purposes that would allow the correlation of all health-related information about a citizen.

In conclusion, organizing and strengthening the Brazilian national laboratory network is a key step for tuberculosis control. The incorporation of new technologies will be effective only if other technological advances, such as GAL and Internet access for health care facilities, are incorporated and the logistics of the laboratory network is reviewed. While there is not a firm political decision, on the part of the Brazilian NMH, for effective implementation of GAL, the problem of rapid diagnosis of tuberculosis will remain unresolved. This is a bottleneck that will jeopardize the success of any new technology that may be adopted. Soft technologies, such as the training of health professionals working in laboratories or in patient care, should be incorporated simultaneously. In addition, new technologies also required supervision and QC, which means investment in human and financial resources and strengthening of the LACENs. Finally, if the new technologies are proven to be accurate and feasible, the classic tests should be maintained, for the purpose of treatment control and confirmation of drug resistance. It should also be borne in mind that better and earlier detection of drug-resistant tuberculosis will result in an increased demand on referral centers, which should be prepared to accommodate the patient. The gearing should work as a whole, and, to that end, the integration between clinical practice and laboratories, as well as between managers and professionals, must improve at the federal, state, and municipal levels.

The present article was written as part of the activities of the project known as "Innovations in Tuberculosis Control". The authors alone are responsible for the views expressed in the present article.

References

1. World Health Organization. Policy Framework for Implementing New Tuberculosis Diagnostics. Geneva: WHO; 2010.
2. Migliori GB, Matteelli A, Cirillo D, Pai M. Diagnosis of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis: Current standards and challenges. Can J Infect Dis Med Microbiol. 2008;19(2):169-72. PMid:19352448. PMCid:2605858.
3. Portal da Saúde [homepage on the Internet]. Brasília: Ministério da Saúde. [cited 2012 Jul 2]. Clipping SVS-27 de março de 2012. [Adobe Acrobat document, 9p.] Available from: http://portal.saude.gov.br/portal/arquivos/pdf/27032012.pdf
4. Stop TB Partnership (World Health Organization), Global Fund to Fight AIDS, Tuberculosis, and Malaria, and World Health Organization. Priorities in Operational Research to Improve Tuberculosis Care and Control. Geneva: World Health Organization; 2011.
5. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de Controle da Tuberculose. Manual de Recomendações para o Controle da Tuberculose no Brasil. Brasília: Ministério da Saúde; 2010.
6. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48. PMid:19918635.
7. Fundação Oswaldo Cruz - Fiocruz [homepage on the Internet]. Rio de Janeiro: Fundação Oswaldo Cruz [cited 2012 Jul 2]. Portaria GM/MS no 2031, de 23 de setembro de 2004. [Adobe Acrobat document, 6p.]. Available from: http://www.castelo.fiocruz.br/vpplr/laboratorio_referencia/portarias/PORTARIA_2031.pdf
8. Portal da Saúde [homepage on the Internet]. Brasília: Ministério da Saúde. Brasília: Ministério da Saúde [cited 2012 May 10]. Situação da Tuberculose no Brasil. [Adobe Acrobat document, 34p.]. Available from: http://portal.saude.gov.br/portal/arquivos/pdf/apresentacao_dia_mundial_tb_26_03_12.pdf
9. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2012 Jul 2]. WHO policy statement: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF. [Adobe Acrobat document, 36p.]. Available from: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf
10. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2012 Jul 2]. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational "How-to"; practical considerations. [Adobe Acrobat document, 36p.]. Available from: http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf

About the authors

Maria Alice da Silva Telles
Senior Researcher. Adolfo Lutz Institute, São Paulo, Brazil.

Alexandre Menezes
Vice President. Global Health Strategies, Rio de Janeiro, Brazil.

Anete Trajman
Coordinator. Professional Master's Program in Health Education, Gama Filho University, Rio de Janeiro, Brazil.