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University participation in the production of molecular diagnostic tests for the novel coronavirus in Brazil: the response to health challenges

A participação da universidade na produção de testes diagnósticos moleculares do novo coronavírus no Brasil: resposta aos desafios sanitários

Participación universitaria en la producción de pruebas de diagnóstico molecular para el nuevo coronavirus en Brasil: respondiendo a los desafíos de salud

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"*Test, test, test!*"

The novel coronavirus epidemic declared in Wuhan, Hubei Province, China, on December 31, 2019, led to immediate and radical measures by public health agencies worldwide. By January 12, 2020, the viral genome sequences had been deposited in the Global Initiative for Sharing All Influenza Data (GISAID) [1] and became a priority for the development of diagnostic tests for the virus in networks of research centers and public laboratories. Community transmission was identified in various countries starting in February, with rapid and steady spread throughout Europe, the Americas, and Africa. The World Health Organization (WHO) declared COVID-19 a pandemic in early March. The first case in Brazil was reported on February 26.

Based on the accumulated collaborative experience in the diagnosis of respiratory viruses with real-time polymerase chain reaction (RT-qPCR) in previous epidemics such as SARS-CoV in 2003, the process was defined and validated for RT-qPCR use in screening and diagnostic confirmation of the novel coronavirus (SARS-CoV-2) in respiratory secretions, even before access to the viral isolates. The methodology developed in this process became the official WHO protocol [1]. Surveys were conducted to assess the presence of the necessary expertise for molecular diagnosis of SARS-CoV-2 in specialized laboratories in 30 European countries, and 24 countries were prepared to perform the diagnostic test by January 29. However, the countries reported difficulties in access to inputs, positive controls for validation of the test, and trained and available human resources [2].

There are currently various protocols available for COVID-19 diagnosis in the world, proposed by official public health agencies and private companies. The techniques differ according to the reagents and genes detected by the tests, but they are based on the same protocol, infrastructure, and inputs. Development in Molecular Biology and its application to molecular diagnostic tests allowed the rapid definition of protocols [3]. However, this knowledge alone cannot guarantee tests with adequate sensitivity and specificity, with the necessary speed and in the required amounts. That is, the recommendation by the director of WHO and echoed by national leaders at the start of the pandemic, for mass testing in populations, was unattainable.

This sparked concern among health professionals and especially among populations, due to the mass media focus on access to molecular tests as a tool for monitoring and controlling the pandemic. There was also enormous pressure on health authorities to perform large-scale molecular testing. Even

in developed countries and among manufacturers of inputs for tests, this goal proved unachievable. The research community in Molecular Biology in universities [4,5] called attention to the existence of available resources, but which could not be linked quickly to the public health agencies to perform the diagnostic testing. Such linkage is not simple or immediate.

To illustrate the size of the challenge faced by the Brazilian health system, the Ministry of Health announced on May 5 that there was a "waiting line" of approximately 93,000 suspected cases, with biological samples already collected, awaiting diagnostic processing [6]. In Brazil, as elsewhere in the world, universities could potentially play an important role in reducing this diagnostic backlog, since there had been important investment in Molecular Biology by research funding agencies in recent decades in equipment, infrastructure, and human resources trained and ready to take on responsibilities in COVID-19 diagnostic testing. Despite the enormous challenges, this had the potential to become an innovative experience with the scientific community's role as part of civil society's response to a public health crisis.

The current study proposes to identify and reflect briefly on the rapid implementation of an initiative by the Brazilian scientific community in Molecular Biology to perform COVID-19 molecular testing. Specifically, as an example, the article addresses the University Network for COVID-19 Diagnosis as a response to the emergency demand for the production and distribution of these tests in the state of São Paulo, the epidemic's epicenter in Brazil.

University Network for COVID-19 Diagnosis

News published in early April [6,7] announced the creation on March 19 of a collaborative network of universities and research centers in the state of São Paulo aimed at streamlining the development, production, and delivery of molecular diagnostic tests to the health system in that state. At the time, the "waiting line" was no less than 25,000 biological samples collected and awaiting diagnostic processing. The initiative mobilized 17 units at the University of São Paulo (USP) in the various campuses in the capital and other cities of the state, providing human resources, equipment, and inputs for testing.

The network was made official on April 2 [8], with six laboratories accredited to perform COVID-19 tests by the Adolfo Lutz Institute, the reference central laboratory (LACEN). The following institutions participated in the initial configuration: University Hospital of the School of Medicine, USP; University Hospital and Ribeirão Preto School of Medicine, USP; Clinical Pathology Laboratory of the University Hospital, State University of Campinas (UNICAMP); and Blood Center of the University Hospital, Botucatu School of Medicine, São Paulo University (UNESP). The platform was later joined by two more units from UNESP and three from USP.

The network has been coordinated since April 9 by the Butantan Institute, according to a decision by the Novel Coronavirus Crisis Committee of São Paulo State Government. One of the objectives of this new configuration was to deal with the testing problem resulting from Brazil's limited domestic production and intense competition for purchasing inputs on the international market. The network consists mainly of public laboratories but also includes private laboratories. Its mission is to optimize testing for COVID-19 diagnosis.

A major problem emerged at the start of the network's implementation: the inputs used to perform RT-qPCR in research laboratories do not meet the required criteria for performing clinical tests. This required specific certification of these laboratories to perform the tests, a process that requires resources, time, and expert knowledge. The reorganization, on extremely short notice, of a preexisting platform in Molecular Biology, now focused on solving an emergency problem, proved successful thanks to action by the researchers and the implementation of a strategic action tool to enable a public health policy to deal with the health crisis. The initiative's innovative feature was that it responded to an immediate problem (the processing backlog with collected samples), which required both simultaneous and after-the-fact implementation as opposed to the routine chronological order of testing capability.

The experience with the University Network in São Paulo showed clearly that the implementation of the following key stages is crucial for such a translational process to be successful:

(1) A university biomedical research platform based on integration between Biomedical and Health Sciences with Biochemistry, Immunology, Infectious Diseases, and Epidemiology: the science park

should be equipped to adequately receive, handle, and process biological material, meeting international quality and safety standards;
(2) Standardization and adequate conditions for collecting samples in the health services, with logistic support for transporting the material from the collection points to the laboratories: this process should guarantee rapid, sustained, and precise turnaround of the test results to the health services [9];
(3) Automation of the genetic material's extraction and amplification for RT-qPCR testing, as well as standardization of the tests' scientific and clinical validation processes [4]: these are fundamental tools for efficacy and efficiency in monitoring the infection's evolution;
(4) Material consolidation and human resources for maintaining a permanent national biotechnology park and/or improvement of conditions for access to the tests supplied by the international market: implementation of partnerships for production and purchasing processes for inputs with criteria according to the needs and proper use of public resources;
(5) Guaranteed economic sustainability of the design and implementation of legal measures to support public programs or policies for industrial development in heath, with clear regulatory definitions: this stage, downstream from an arrangement stemming from the research community and health services, should mobilize other actors in the Health Economic and Industrial Complex to ensure continuous access to the necessary inputs for this system's proper development.

These stages are important in every translational process with health technology research. However, in the COVID-19 pandemic, the complexity of the concurrent linkage of these processes, necessary to meet the demand for molecular tests and the intended clinical and epidemiological impact, is still a challenge debated globally, not only by the scientific community, but also in business and political circles.

The experience with the network in São Paulo shows that tentative governance agendas in science, technology, and public health are possible even in crisis periods and are currently experiencing full-blown development in Brazil and elsewhere in the world [10]. Such experiences represent ways to expand learning, gaining visibility and achieving results in the short term, with relevant impacts even if during a limited period. The network in São Paulo, as well as others in Brazil, should be monitored to learn whether the alliances established in this pandemic between universities, public health, and the private sector will be maintained, and what the implications will be for public policies in science, technology, and innovation (ST&I) in health.

Conclusions and recommendations

While the pandemic has shown that we were unprepared to meet a mass demand for molecular testing on extremely short notice, it has also taught us that diverse actors with the requisite technical training and expertise for delivering the necessary results already exist in Brazilian universities and hospitals, both public and private, ready for high-impact collaboration in health policy. The existing equipment parks in the universities demonstrated that they are sometimes better equipped than those available in the public health surveillance structure. The synergy allowed by organization in network format was evident, both in human resources and access to equipment. For groups with expertise in academic research, the experience was positive since it showed the critical importance of compliance with regulatory issues, focused on (i) quality control of inputs and (ii) safety, both for the laboratory test operator and the tested sample, and thus ultimately for the patient. Within just one month, the diagnostic network was prepared to reach the target of 8,000 RT-qPCR tests per day, which allows supporting proposals for expanding the tests beyond the hospitals.

A bottleneck for the network's operationalization was the shortage of inputs, swabs for collecting samples, plastic materials, and higher added-value inputs such as enzymes and probes for performing the molecular tests. Despite the development of the Molecular Biology field, Brazil is excessively dependent on the foreign market for acquiring basic inputs for molecular tests. This external dependence is not limited to Brazil, but extends to all countries of Latin America and the Caribbean.

The dependence on imports is not limited to the lack of domestic production of inputs. This challenge is debated at the national level by researchers interested in characterizing the Health Economic and Industrial Complex, in which one of the more obvious weaknesses is the disconnect between economic and social dimensions of development in health [11]. Historically, the arrangement has been marked by

the low technological intensity of Brazilian industry as a whole (and in the health sector specifically) and creates difficulties, in the case of molecular tests, for the maintenance of equipment parks that require skilled labor. Despite such shortcomings, solutions based on organizational innovations can rationalize the use of resources to support high-impact initiatives in ST&I in health, as illustrated in the current study.

Molecular tests are a key component for monitoring the current and future pandemics, and their incorporation by the Brazilian Unified National Health System (SUS) will come under heavy demand. The expansion of international production of molecular diagnostic tests, leveraged by the current COVID-19 pandemic, will drive this sector and promote its technical progress. This creates an interesting opportunity for systematically performing an analysis to monitor this trend and identify possible niches for the expansion of Brazil's own domestic capacity for molecular diagnostic tests, resulting in new scientific, technological, and innovative solutions.

Contributors

R. G. L. Silva and H. M. D. Novaes contributed to the article's conception, drafting, and revision. R. Chammas, G. A. Plonski, M. Goldbaum, and L. C. S. Ferreira contributed to drafting and revising the article.

Additional informations

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