The Significant Contribution of Pasteur Institute of Iran to COVID-19 Pandemic Control: A Successful Map over the Obstacles

Mona Sadat Larijani  
Pasteur Institute of Iran

Alireza Biglari  
Tehran University of Medical Sciences

Rahim Sorouri  
Pasteur Institute of Iran

Mostafa Salehi-Vaziri  
Pasteur Institute of Iran

Delaram Doroud  
Pasteur Institute of Iran

Keyhan Azadmanesh  
Pasteur Institute of Iran

Fatemeh Fotouhi  
Pasteur Institute of Iran

Ehsan Mostafavi  
Pasteur Institute of Iran

Amitis Ramezani (✉ amitisramezani@hotmail.com)  
Pasteur Institute of Iran

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Abstract

Background
The present study aims to show the comprehensive effort of Pasteur Institute of Iran and its scientists regarding COVID-19 chaos management, related studies, achievements and vaccine production though there were many imposed challenges.

Methods
The relevant literature review was done through the associated data from national and international databases, published and under review research articles and also through reports obtained from official meetings with the heads of the related departments.

Results
The taken strategy adopted by Pasteur Institute of Iran was based on six arms including COVID-19 laboratory network establishment, vaccine research and production, monitoring of SARS-CoV-2 variants, diagnostic tests production, conduction of applied and basic research, and community management and support which eventually utilized appropriate technology for facilitating vaccination as well as the pandemic control at the right time.

Conclusion
The COVID-19 pandemic which was going to be a real crisis, led to a precise and great performance of Pasteur Institute of Iran owing to the unity of the scientists and the staff. COVID-19 pandemic has been managed by COVID-19 laboratory network set up, approved vaccines in collaboration with Cuba, evaluation and validation system of diagnostic and immunological COVID-19 kits, community Support and careful SARS-CoV-2 Variants Screening.

COVID-19 is not over yet and the role of Pasteur Institute of Iran in dealing with this pandemic is still pivotal. There are some other challenges to overcome such as preparation for any COVID-19 probable trend, data management and update, long-term safety and efficacy of the vaccines and providing supplies.

Background
A Flash on the Glorious History and Activities. Pasteur Institute of Iran, as one of the oldest leading public health and research centers in the country and the Middle East, was established in 1920 after the agreement between the Iranian government and Pasteur Institute of Paris. This institute is one of the
worldwide Pasteur network members and also among the few ones which is capable to produce vaccines. Since its foundation, this Institute has played a crucial role in prevention and management of infectious diseases through holding numerous types of research, manufacturing vaccines and biological products as well as the public health surveillance (1, 2).

Research departments in Pasteur institute of Iran have been run to meet and suit the community health gaps during a-hundred-year of research work. Crucial steps have been taken to generate biopharmaceuticals through recombinant DNA technologies at the institute since the highlighted importance of medical biotechnology techniques in the 1970s. There is also a specified building for biotechnology research group with the name of Dr. Marcel Baltazard, the former French director of the institute, in honor of his great effort in Iran (3).

Pasteur Institute of Iran, currently operates projects through six research groups including twenty-one research departments with the pursued policy of basic and applied research conducting in the field of research and diagnosis, various disease management methods especially infectious diseases and also joint research projects with inside and outside centers (4, 5).

Due to the growing urgent need for vaccination, recombinant products and injectable solutions, Karaj Production Complex of Pasteur Institute of Iran started its associated mission in 1988, though these products had been generated since the early stage of foundation. This complex has made good strides to provide Pasteur Institute’s plan with infrastructure and expanding activities and is one of the human vaccine production pillars in Iran. During the past century, Pasteur Institute of Iran has been able to control many infectious diseases such as smallpox, plague, cholera, tuberculosis, rabies, hepatitis B and COVID-19 by vaccination and effective interventions (6–8).

It is also the national reference center for infectious diseases in the country which the diagnostic tests and research projects are conducted to improve the community health based on the public health priorities (9). There are other branches of the institute with the aim of diagnosis and control of infectious diseases. A research and diagnostic center in Akanlu, (Hamadan province) was founded in 1952 and Amol research branch in the city of Amol, northern Iran, was established in 1994 (10, 11).

**COVID-19 Era.** Iran with a population of about 84 million, a wide variety of cultures, socioeconomic conditions and different kinds of climates, has had many hardships regarding the equipment and facilities providing at the right time. Thus, the imposed challenges by the COVID-19 pandemic are different from many countries (12).

According to the WHO dashboard on 14th September 2022; there have been 7,539,698 COVID-19 confirmed cases and 144,199 death since the pandemic started. Moreover, the number of Iranian population who got two-dose of any COVID-19 vaccines is 58,423,668 (about 70% of the population) and also 30,986,468 got the booster dose of the third or the fourth round (13). There is no doubt that the people and the government have done their best to safely pass COVID-19 era in which Pasteur Institute of Iran has played a crucial role.
In the early episode of COVID-19 era (14), Pasteur institute of Iran provided the country with an effectively rapid response team which had been established before the pandemic started in Iran. This led to overcome the stressful situation which the new virus imposed on the society. The first COVID-19 diagnostic test was then produced by this team. Hence, Pasture Institute of Iran provided the first diagnostic laboratory for SARS-CoV-2 infection. All the collected COVID-19 suspected samples were sent to this institute and the educated staff and experts put all their effort day and night to handle the tests immediately and thus prevented from any probable crisis (15, 16).

Pasteur Institute of Iran is now the center of excellence regarding SARS-CoV-2 diagnosis, national COVID-19 reference laboratory, epidemiologic studies, emerging and re-emerging infectious diseases, clinical trials and notably vaccine manufacturing and research.

Hereby, we have presented the map of success over the recent pandemic hardships, planned and performed in Pasteur Institute of Iran which is currently in charge of the national COVID-19 laboratory committee.

**Methods**

Pasteur institute of Iran has contributed to the COVID-19 pandemic through six effective arms presented in Fig. 1

**COVID-19 Laboratory Network Establishment.** Although the COVID-19 pandemic imposed many hardships on Iran, considering the limitations of the supply, great approaches have been achieved among which was the Covid-19 laboratory network foundation.

As the Novel Coronavirus was identified, the forthcoming infection spread became a priority which was handled by experienced scientists from Pasteur Institute of Iran. The rapid response team of Pasteur institute of Iran, which is authorized for the outbreak investigation control and early diagnosis of infectious diseases, took the initial steps of the first diagnostic laboratory process to establish the molecular tests.

**Community Management and Support.** It was achieved through remote and on-site policies. In order to prevent any probable chaos among the community and to manage the outpatients, landlines and cell phone lines were dedicated in order to provide the people with sufficient information and support. In addition, a section was considered to visit the suspected people to COVID-19 for sampling and diagnosis.

**Monitoring of SARS-CoV-2 Variants.** This issue was investigated as the main priority of Pasteur Institute's agenda. Consequently, the main variants including SARS-CoV-2 alpha, beta, delta and omicron were identified prior to any severe trend incidences.

**Conduction of Applied and Basic Research.** In order to assess the contribution of Pasteur Institute of Iran and its scientists to COVID-19, the related keywords were searched in NCBI PubMed database
(https://pubmed.ncbi.nlm.nih.gov/) and also the unpublished data associated with the vaccine study, provided by the coauthors, were considered in the results.

**Vaccine Research.** During the COVID-19 pandemic, Pasteur Institute of Iran has manufactured PastoCovac (Soberana 02) and PastoCovac Plus (Soberana Plus) in collaboration with Finlay Institute of Cuba. The collaboration between the two countries started when Hepatitis B vaccine technology was transferred from Cuba and since then, this vaccine has been produced in Iran.

The conjugated COVID-19 vaccine successfully passed phase I and II trials in Cuba with significant results. Phase III clinical trial investigated in Iran and Cuba showed significant protection against the infection development and the vaccine was hugely effective against the severe form of COVID-19 and death in the heterologous three-dose schedule (17). Moreover, PastoCovac vaccine was then evaluated regarding safety and immunogenicity to be administrated as a booster dose in Iran.

**SARS-CoV-2 Diagnosis Tests Production.** Owing to the fact that Influenza and SARS-CoV-2 share some similarities in symptoms and the rate of infected people with flu increases in cold weather, a standard test to detect these viruses at the same time was investigated. Moreover, according to the spread of Omicron; a test which could detect this type of the virus was investigated based on a one-Step Real-Time RT-PCR.

**Results**

**COVID-19 Laboratory Network Formation.** In February 2020, the first COVID-19 laboratory was established at the Pasteur Institute of Iran when the commercial kits had not been imported to Iran yet. Thus, this institute was authorized to form the COVID-19 laboratory diagnostic committee and direct the national laboratory diagnostic network with the support of the Ministry of Health (15). Thousands of suspected COVID-19 samples were sent daily to the Pasteur Institute of Iran post the first case recognition in the country on 18th February 2020. Nevertheless, the widely spread of the virus throughout the country led to the formation of laboratories in each city later which resulted in a well-grown number of active labs to 500 with the capacity to test more than 100,000 cases per day (18).

The accreditation of Pasteur Institute of Iran regarding the new laboratories included providing the candidate labs with molecular kits besides the staff training, evaluation of the received PCR files and running the scheduled meetings with the lab team to check the quality of procedures in parallel with external quality control panels (19, 20). Moreover, a specified group was created on the social network application in order to provide an easy and quick cyberspace in which the questions, requests, complaints and experiences of the laboratories could be shared and responded.

**Launching the evaluation and validation system of diagnostic and immunological COVID-19 kits.** Pasteur Institute of Iran undertook the verification of the imported COVID-19 kits since the initiation of the pandemic. After the initial evaluation of the companies, Pasteur Institute of Iran investigated the quality assessment of the internal diagnostic and immunological kits and helped to improve their quality. The
protocols and responsibilities created for this system were handed over to the Food and Drug Reference Laboratory after about 6 months.

**Remote Protection and Support of Community.** Through the specified phone lines, people were able to ask their questions, get advice from specialists and be aware of the associated COVID-19 symptoms. They were advised to refer to a medical center or specific hospitals only in case of necessity. This action which might seem simple at the first glance, had a huge impact on the patient control by which healthcare workers could do their tasks in a less-stressful atmosphere. In other words, the remote guide of the people resulted in a managed hospital referral and avoided viral spread through the crowd in the medical centers.

Furthermore, educational and informative booklets and brochures were designed and published in the institute to provide people with different kinds of information in terms of SARS-CoV-2 symptoms, transmission, prevention and treatment.

**Visiting Patients and Sampling.** Pasteur Institute of Iran as a trustful center among the community, has also provided people with physicians and specialists. The suspected individuals who present COVID-19 symptoms could be visited in the referral department. The naso/oropharyngeal swab samples are taken to go through the molecular test according to the specialists’ recommendation. In case of a positive test, they could have the appropriate prescription and recommendation.

**SARS-CoV-2 Variants Screening.** The variants of SARS-CoV-2 alpha, beta, delta and omicron were identified by the molecular test (SANGER) by Pasteur Institute of Iran with the least missing time. The approved results were sent to the member laboratories of the network. Monitoring of SARS-CoV-2 genetic variation is currently done more effectively by applying NGS (next-generation sequencing) and new sequencing devices. This is owing to the sincere round-the-clock efforts of an eager massive group of colleagues across the country indicating the existence of admirable technical knowledge and a sense of responsibility across the country (21).

**Applied and Basic Research.** There has been a wide variety of SARS-CoV-2 studies conducted in the institute. More than 100 manuscripts are accessible in NCBI PubMed database (https://pubmed.ncbi.nlm.nih.gov/) in which Pasteur Institute has contributed to SARS-CoV-2 publications including basic, preclinical and clinical studies (22–24), COVID-19 mechanisms (25, 26), diagnosis and therapeutic targets (27–32), case reports (33, 34), long COVID (35, 36) reviews and meta-analysis (21, 37), bioinformatics and *In Silico* studies (38–40).

**Vaccine Research and Trials.** PastoCovac and PastoCovac Plus technology was successfully transferred to Iran. PastoCovac is composed of a highly immunogenic part of SARS-CoV-2 Spike (RBD) which is conjugated to the tetanus toxin (17). PastoCovac Plus as the booster dose is a dimer of RBD (50 µg] (17, 41, 42).
The clinical trial phase III in Iran was conducted in 8 cities and the immunization by a three-dose regimen was significantly effective against hospitalization in the Delta variant era. PastoCovac is approved to be administrated in children above 3 years old, and at the same time, it has approval as an effective and safe booster vaccine for all primary vaccines injected in Iran (43).

In the other studies carried out by Pasteur Institute of Iran (unpublished data), PastoCovac Plus immunogenicity was assessed among the individuals primarily immunized by two doses of COVAXIN (BBV152), ChAdOx1-S or BBIBP-CorV. PastoCovac Plus administration significantly led to anti-SARS-CoV-2 specific antibodies rise in the investigated group with no serious adverse event. According to the obtained data on a selected sample of health care workers who were primarily immunized by COVAXIN, neutralizing and anti-Spike antibodies reached 70 and 93-fold-rise after PastoCovac Plus booster shot, respectively (under review data).

The other study which compared the heterologous or homologous regimens among vaccinated individuals with ChAdOx1-S or BBIBP-CorV also showed that applying PastoCovac Plus as a booster dose is more effective than the homologous platform in which the highest rate of anti-Spike IgG rise was seen in ChAdOx1-S/PastoCovac Plus® followed by BBIBP-CorV/PastoCovac Plus which indicated that heterologous vaccine design against SARS-CoV-2 could bring excellent results (under review data).

In addition, the safety and immunogenicity of PastoCovac as a booster dose are currently investigated and the interim data has proved its safety and excellent immunogenicity as a booster vaccine.

Since the vaccine approval, about 15 million doses of COVID-19 vaccines have been produced and released to the health ministry of Iran. Moreover, a capacity of 3 million doses of vaccine production is currently provided monthly and Pasteur Institute has the potency to export PastoCovac vaccine to other countries in future.

In addition to the mentioned approved COVID-19 vaccines in Iran, another vaccine based on an Adenovirus-based platform was developed successfully and the preclinical studies conducted via highly regulated standards. PastoCoAd was evaluated as a novel heterologous of recombinant adenovirus. The results showed that this vaccine candidate can induce both humoral and cellular immune responses in animal models (44).

In addition to COVID-19 vaccine technology transfer, there has been another exchange agreement between Pasteur Institute of Iran and Bharat Biotech of India regarding rotavirus vaccine since 2021 in order to protect young children against infection (45). Moreover, the technical knowledge exchange of manufacturing pneumococcal vaccine was also agreed between Pasteur Institute of Iran and Cuba to prevent from infections such as pneumonia, sepsis and meningitis (46).

**Diagnosis Tests Production. Pasteur COVI/FLU A&B kit**

This kit was produced in the national COVID-19 center of Pasteur Institute of Iran to detect Influenza type A /B and SARS-CoV-2 simultaneously. The kit was firstly launched in November 2021 owing to the
probable increasing number of flu infections in fall and winter. This test is based on one-step Real-Time PCR which is capable to recognize two conserved regions of SARS-CoV-2 nucleocapsid, one from Influenza A matrix and one from Influenza B nucleocapsid on extracted viral RNA from nasopharyngeal swab samples with the basis of probe hydrolyzation.

**Pasteur Spike Gene Target Failure Real-Time PCR.** As the new variant of SARS-CoV-2, Omicron, started to spread globally, this test was investigated as a one-Step Real-Time RT-PCR to distinguish Omicron variant from other SARS-CoV-2 types based on the two deleted parts of Spike gene.

The significant contribution of the scientists of the institute to other research centers and laboratories has also been of a great value and had a significant impact on COVID-19 pandemic management in the country. Nevertheless, COVID-19 is not over yet and the role of Pasteur Institute of Iran in dealing with this pandemic is still notable.

**Conclusions**

Pasteur Institute of Iran stood tall and proud during the COVID-19 era. The recent pandemic resulted in an excellent performance and unity of the scientists in Iran. There is no doubt that Pasteur Institute of Iran has significantly contributed to COVID-19 management through the COVID-19 laboratory network set-up, two approved vaccines in collaboration with Cuba and one vaccine candidate on the go. Nevertheless, there are some obstacles to overcome including preparation for any COVID-19 new wave, data management, and long-term safety and efficacy of the vaccines and supplies which need to be considered.

**Declarations**

**Availability of Data and Materials:**

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

**Ethical Approval:**

Not required.

**Consent for publication:**

Not applicable.

**Funding:**

None.

**Competing Interests:**
None declared.

Authors’ contributions:


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Figures
Figure 1

The map of success by Pasteur Institute of Iran regarding COVID-19 pandemic management.

The six arms by which the institute has been able to manage the recent pandemic are simply illustrated. These actions have been taken in parallel though in order to get the best result.