

Razi Institute, A Hundred Years of Honor in Iranian Health

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Article Info:

Received: 24 December 2024

Accepted: 26 DDecember 2024

Keywords:

Razi Institute, Vaccine,
Disease, Centenary, Research.

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ABSTRACT

Razi Vaccine and Serum Research Institute was established in 1925 in response to the Rinderpest outbreak in Iran. This institute, which is currently located in Karaj, comprises various departments for the production of biological products for humans, livestock, and poultry, research departments in the field of developmental, basic and applied veterinary research, diagnostic departments for diseases diagnosis and pathogens isolation, educational departments for holding domestic, national and international courses and also holding various postgraduate education levels. Currently, the Razi Vaccine and Serum Research Institute is on the verge of its centenary, and during a century of activity and service to the community's health, the institute's researchers have provided valuable services in line with its organizational duties. The mission of the Razi Institute is to contribute to the public health of humans and livestock in the country by the eradication and control of livestock, poultry and human diseases through producing biological products, conducting veterinary and human research, diagnosis and isolation of pathogenic agents in specialized laboratories and national and international reference laboratories, publishing reputable international journals, expanding production and research throughout the country through its branches, controlling the quality of all domestic and imported biological products at the institute and national levels, holding training courses, seminars, and training students at educational levels, conducting scientific research on biological products and related topics, and producing technical knowledge at the institute, national and regional levels, which has served well in these matters over these many years.

How to cite this article: Soleimani S, Motamed N, Hajizadeh A, Tadayon K. Razi Institute, A Hundred Years of Honor in Iranian Health. *Archives of Razi Institute*. 2025;80(Special Issue):1-9. DOI: 10.32592/ARI.2025.80.Special Issue.1

1. Introduction

Vaccination campaigns conducted by British army doctors in Tabriz gained popularity in Iran during the time of Fath Ali Shah Qajar. Dr. John Cormick brought the smallpox vaccine from London to Tabriz in 1812 and vaccinated the court and all courtiers. Amir Kabir publicized the vaccination against smallpox. In recent years, Rinderpest disease has emerged as one of the most deadly livestock diseases that spread worldwide, causing the loss of millions of cattle. The emergence of this disease, which caused heavy economic losses, led countries to make important decisions and measures in animal health, including the establishment of the world's first veterinary school in Lyon, France, in 1761 by Claude Bourgelat (Figure 1).



Figure 1. Mustafa Gholibayat, the founder of Razi Institute.

One of those panzootics also affected Iran, due to severe livestock losses and the Health Committee of the Assembly of Allied Governments' call to establish a veterinary department, with efforts by the late Mustafa Gholibayat (Deputy Minister of Agriculture, Trade and Public Benefits) (Figure 1). On October 1924, the bill for the establishment of "Institute of Animal Pests Control and Serum Production" was drafted and submitted to the Fifth Parliament by the mentioned Ministry. That year, the Animal Pest Control Institute was established under the

supervision of the Pasteur Institute of Iran. A few months after the institute began operations, due to the lack of a suitable place to house large animals in the Pasteur Institute, Mustafa Gholibayat ordered that some lands of Kamal Abad near the village of Hesarek Karaj be allocated to the Pasteur Institute for use as a workplace, residence employees and for construction of animal stables (to prepare serum). Therefore, in May 1925, the institute moved to Karaj. The Institute of Animal Pest Control and Serum Production was the premier laboratory for diagnosing livestock diseases and preparing related sera and vaccines established in Iran.

The missions of this institute were to prevent animal diseases using scientifically proven methods that are common worldwide, to prepare vaccines and serums against all diseases in which serums and vaccines have been discovered to study plant diseases, to identify beneficial and harmful insects, to obtain a scientific and practical way to get rid of harmful insects such as locusts, centipedes, etc., to try to increase domestic animal populations and useful plants based on scientific principles, expand the institute's branches in all states and provinces, and to expand its operations throughout the country (Figure 2).

The continuous efforts of researchers at the institute have led to eradicate the outbreak of Rinderpest in 1927. In 1928, as Rinderpest subsided and locusts invaded the country, agricultural supervisors shifted their focus toward the production of arsenic poisoning and the fight against locusts, and serum production was stopped for three years. However, the spread of many infectious diseases threatening the lives of humans, animals, and birds prompted officials to revive this institute to fight against animal and human infectious diseases. Therefore, with the parliament's resolution on June 16, 1929, it was decided that the Falahat Department should hire a veterinarian specializing in bacteriology and serum production from the Animal Pest Control Institute (Figure 3).

Initially, the institute produced anti-cattle plague sera. After some time, this institute started the production of animal vaccines, and in 1938, research and study for the production of human therapeutic products and sera started in this institute, which was completed in 1941. In 1946, its name was changed to Razi Serum Institute in honor of Muhammad ibn Zachariah Razi (famous Iranian physician) (Figure 4).



Figure 2. One of the old buildings of the Razi Vaccine and Serum Research Institute.



Figure 3. The Razi Vaccine and Serum Research Institute's headquarters building years ago.



Figure 4. Some researchers at the Razi Institute in the past years.

Currently, Razi Vaccine and Serum Research Institute is located in the city of Karaj, occupying more than 94 hectares, with a century of service in the field of animal and public health, and over the past hundred years, valuable services have been provided by the researchers of this institute in line with its organizational duties (Figure 5).

Other missions of the Razi Institute, besides protecting the human and livestock population health through prevention and production of biological products are supporting the country's economy by creating economic prosperity, reducing dependence on the import of similar products, preserving the country's livestock capital, and lowering costs. This institute is an excellent treatment and helps promote the scientific and research activities through applied research and holding specialized courses.

2. The performance of the Razi Institute in Iran during the last century

During the past century, Razi Institute has played a vital role in various aspects of improving the health of society. On the eve of the 100th anniversary of the Razi Institute, we reviewed a century of experience, dedication, and pride. Therefore, this article identifies and introduces the valuable services offered by this institute during these years. The institute's 100-year performance is remarkable in various aspects, some of which are as follows:

2.1. Eradication and control of livestock, poultry, and human diseases

Since the inception of the Razi Institute, it has been working to control and eradicate diseases. Beginning with the eradication of Rinderpest in Iran, this institute has

been able to control or eradicate many human, livestock, and poultry diseases by producing various biological products and conducting extensive research on diseases and pathogens, as well as development research on manufactured products. Therefore, the eradication or control of many endemic diseases in the country, such as polio, cholera, measles, rubella, mumps, diphtheria, tetanus, pertussis, Rinderpest, and horse plague (African Horse Disease), can be attributed to Razi Institute's products.

2.2. Production of biological products

Since its establishment, Razi Institute has manufactured and marketed dozens of products, however, due to eradication or control of some diseases, the production of some items has stopped (Table 1). Razi Institute supplies six out of ten mandatory human vaccines, more than 90% of livestock vaccines, and 30% of the common poultry vaccines required by the country.

In addition to vaccines, Razi Institute also plays a key role in the production of many biological products, including therapeutic serums (anti-snake serum, anti-scorpion serum, and anti-diphtheria serum), various solvents and physiological serum, various antigens including Mallein, Johnin, Avian Influenza antigen, Milk Ring antigen, Rose Bengal antigen, Wright antigen, and salmonella pleurom antigen, various tuberculin antigens (human, avian, and bovine), complete and incomplete Freund's adjuvant, brucellosis and Johne's diagnostic kits, blood products including complements, plasma, and hemolysin, and normal horse and calf sera.



Figure 5. Razi vaccine and serum research institute.

Table 1. Name and date of production of products at Razi Institute.

Product name	Production date	Product name	Production date
Anti-Rinderpest	1925	S19 Brucellosis	1953
Rinderpest vaccine	1932	DTP	1953
Anthrax	1933	Mallein	1956
Sheep pox	1935	PPD	1956
Black Leg vaccine & Anti Serum	1936	Ionin	1956
Anti-Anthrax Serum	1936	Ring Test	1956
Bovine Pasteurellosis	1937	Sheep -Anthrax-Pox	1956
Anti-Diphtheria & Tetanus Serum	1938	Goat Pox	1957
Anti-Tetanus Serum	1398	Newcastle B1	1957
Anti-cholera Serum	1942	Avian Spirochetosis	1957
Tetanus vaccine	1942	Swine Pasteurellosis	1957
Enterotoxaemia vaccine	1944	Tet RAZI	1957
Diphtheria vaccine	1946	Contagious Ectyma	1958
Anthrax-Horse Tetanus	1946	Anti-Rabies Serum	1958
Swine Salmonellosis	1946	Agalactia	1958
Contagious goat pneumonia	1946	Anti-Human Serum	1959
Typhoid Ag	1946	FMD	1960
Fowl pox	1949	Equine Plague	1960
DT	1948	Anti-Snake Serum	1961
Avian Salmonellosis Ag	1949	Teni RAZI	1962
Brucella Ag	1953	Rev.1	1963
Pertussis	1953	Disto RAZI	1966
Injectable Newcastle	1953	Piro RAZI	1966
S19 Brucellosis	1953	NMRI Mouse	1966
Injectable Newcastle	1953	Wistar Rate	1966
Sprague Dawlry Rat	1966	MMR	1988
NMRI Rat	1966	Rabbit Serum	1993
Syrian Hamster	1966	Rabbit Plasma	1993
Pirbright Guinea pig	1966	Leptospirosis	1994
Dutch Rabbit	1966	Rabbit Complement	1993
Melioidosis	1967	Guinea pig Complement	1993
Bovine Theileriosis	1968	Hemolysin	1993
Gangrene	1969	Mutant Hairless Guinea pig	1995
Measles	1969	Inactive Newcastle	1998
Newcastle Lasota	1971	Inactive Avian Influenza	1999
Rozbangal	1971	Inactive Newcastle Influenza	2003
Polio	1972	IRIBA	2007
Anti-Scorpion serum	1972	B1-H120	2008
Lab Animal Pellet	1973	Fish Lactococosis	2011
Bronchitis H120	1974	H120 Lasota	2013
Bronchitis H52	1975	Rev.1 eye Vaccine	2013
Pasteurellosis - Black Leg	1975	PPR	2013
Laryngotracheitis	1977	Ion diagnostic kit	2014
BALB/C Mouse	1977	SPF Egg	2014
C57BL/6 Mouse	1977	MR	2015
NIH Mouse	1977	Heat Resistance Newcastle	2015
Anti-Tetanus Serum	1981	Clone Newcastle	2015
Avian Pasteurellosis	1982	Brucellosis diagnostic kit	2018
Gumbro	1982-1995	H1 Newcastle - Avian Influenza Kit	2018
Marek	1982	Canary Pox vaccine	2019
Sheep Theileriosis	1984	Bronchitis IBIR	2019
Rubella	1986	Fish vibrio's auto vaccine	2019
Mumps	1987	DBA2 SPF MOUSE	2020
Razi/A Mouse	1987	Covid-19 diagnostic kit	2020
Razi/A Rat	1987	Covid-19	2021

3. Research and diagnosis of livestock and common diseases and isolation of pathogenic agents

In addition to producing biological products, Razi Institute has conducted a critical research on many infectious diseases in livestock and poultry, and prevalent diseases. Over the years, researchers have controlled the desired diseases by studying diseases and pathogens, and by developing appropriate and effective vaccines. Studying diseases and identifying pathogenic agents have been one of the valuable activities of this institute over the years. Among the diseases that were first identified by researchers at Razi Institute are encephalomyelitis, laryngotracheitis, myeloblastosis, psittacosis, newcastle disease of turkeys, paratyphoid, infectious bronchitis, Gumboro and blackhead disease of turkeys in birds, infectious diarrhea diseases, viral abortion, Q fever, infectious lung cancer, foot and mouth disease strains A and SAT1, copper deficiency, pseudomembranous colitis and infectious diarrhea in goats and sheep and IBR diseases, mucosal disease (MD), malignant catarrhal fever (MCF), three-day fever, malignant tuberculous edema, symptomatic anthrax, gangrene and bacillary hemoglobinuria in cattle and buffaloes, and diseases of Sura by Carapatiea, horse plague, pseudomembranous colitis, and cutaneous gangrene in equines. In addition, diseases such as hog trichinosis, rodent pseudomembranous colitis, and bee lice have been identified by Razi Institute.

Among the pathogens isolated by Razi Institute researchers are *brucella melitensis* from goat milk by Dr. Entesar and Dr. Kaveh, the cause of infectious diarrhea in newborn lambs, *clostridium novei* from Hyderabad sheep, *actinomyces necrophorus*, the cause of umbilical necrobacillosis in lambs from Baghestan, contagious ecthyma virus from Kurdan sheep, three-day fever, *leptospira grypotifoza*, *trichomoniasis* in turkeys, due to contact with pigeons, turkey hexamitosis, bovine tuberculosis, *spirocheta persica*, the cause of relapsing fever caused by tick bites by Dr. Rafiei, *Ornithodoros latyshevi* ticks, *babesia crassa* and *theileria orintanis* by Dr. Fesharki, IBR from imported cattle, bluetongue, *listeria monocytogenes* from sheep, and bacillary hemoglobinuria.

The latest case study on diseases and the identification of pathogens and the necessary measures to control them relates to the development of a recombinant protein vaccine against the coronavirus in the COVID-19

pandemic, demonstrating the institute's capability to respond to contemporary health challenges with modern technologies.

4. Establishment of National and International Reference Laboratories

Due to the extensive production and research activities of Razi Institute, there is extensive international communication between this institute and various scientific and research associations inside and outside the country, including the WHO, FAO, and WOAH. The Office of Combating Communicable Animal Diseases introduced this institute as an international reference laboratory for diagnosing goat and sheep pox. In addition, the National Avian Influenza Laboratories, Toxicology Reference Laboratory, Venomous Animal Reference Laboratory, Regional Scorpion Research Laboratory in the southwest of the country, Newcastle Regional Reference Laboratory in the northwest of the country, Regional Bursal Disease Reference Laboratory in the northeast of the country, National Bovine Tuberculosis Laboratory, National Theileriosis Research Laboratory, National Foot and Mouth Disease Laboratory, National Pasteurella Laboratory, National Tick Laboratory, *Leptospira* Reference Laboratory, Regional Neospora Reference Laboratory, and Reference Laboratory for Camel Diseases and the Production of Camel Biological Products in the Northeast Branch of the country are also located in this institute and its branches. They are engaged in various fundamental and applied research.

5. Publication of prestigious international journals

Since January 1939, with the efforts of Dr. Delpi, the Razi Archive journal has been published in French, and its publication continues. It can be said confidently that the Razi Archive is the oldest scientific journal in Iran that has survived. Of course, there was a break in its regular publication at two historical points (during World War II and the revolution in Iran). However, the annual volume of the Razi Archive has reached 80 in English so far. Since 1984, this journal has had an international standard and shorthand number (Razi.Inst.Arch -0365-3439, ISSN), and is currently printed and published bimonthly. Since 2017, it has been indexed in PubMed, and since 2012 in Scopus.

The most prioritized subjects in the journal are vaccine and biological product studies. The second scientific

journal at this institute is the Journal of Veterinary Research and Biological Products. This journal was published in the autumn of 1988 under "Livestock Affairs Journal" in the Livestock and Aquatic Affairs Committee of the Ministry of Construction- Jahad.

The scope of articles published in this journal has changed over time, and with the relocations made, its name has also changed: "Journal of Agriculture and Livestock," "Journal of Research and Construction" until, starting from issue 116 (autumn 2017), it was published under the new title "Journal of Veterinary Research and Biological Products" in two orientations: "Veterinary Medicine" and "Animal Sciences." Since December 2020 Razi Institute has obtained the privilege of another journal called Vaccines and Disease Prevention in Veterinary Medicine, which is dedicated to promotional articles. In addition, the presence of more than 18,000 books, scientific journals, and reference books in the Razi Institute's library has made it one of the wealthiest scientific resources in the country.

6. Expanding production and research throughout the country by establishing several branches in several parts of Iran

The Institute began establishing branches throughout Iran in 1949 to expand its activities nationwide . The first branch of the institute was established in 1949 in the northeast of the country in the city of Mashhad. This branch currently produces livestock clostridial and poultry Gumboro vaccines. After Mashhad branch, other branches of the institute were established in the following order: The southwestern branch of the country in Ahvaz in 1959, which is active in the production of livestock clostridial vaccines and anti-scorpion sera, the northwest branch of the country in Marand in 1993, which is active in the production of killed poultry vaccines including Newcastle, Influenza and bivalent vaccines for these two diseases, the southern branch of the country in Shiraz in 1995, which is active in the production of anaerobic livestock vaccines and poultry vaccines, the southeastern branch of the country in Kerman in 1997, which is active in the production of anaerobic livestock vaccines, and the Markazi branch of the country in Arak in 2007, which is active in the production of diagnostic kits. Thus, these branches in different parts of Iran, besides producing biological products, play an important role in veterinary research in the local geography.

7. Quality Control of All Domestic and Imported Biological Products at The Institute and Country Level

To comply with global requirements, the independence of the quality control unit from the production departments was one of Dr. Delpi's goals. This was achieved in 1941 by assigning the responsibility for quality control of the institute's products to Dr. Fathollah Entesar. After Dr. Delpi's departure, the quality control of the products was once again assigned to the production departments. In 1966, two separate departments were formed to control the quality of veterinary and medical vaccines.

With the rise of GMP issues and increasing national and global attention and requirements for the quality of biological products, in the second half of 1995, the Central Laboratory for Quality Control of Veterinary Products began operating. In 1992, an independent quality control department was established for all biological products of Razi Institute, and in 2005, this department was promoted to management. Currently, Razi Vaccine and Serum Research Institute has a very advanced and up-to-date quality control system in which all products are examined and evaluated, if they pass the relevant tests, the products are released. Also, in this complex, all imported biological products are controlled in a laboratory approved by the Ministry of Health and the Veterinary Organization.

Quality control at the Razi Vaccine and Serum Research Institute consists of 6 departments as follows:

7.1. Viral Biological Products Quality Control Department

In this department, all human, livestock, and poultry viral biological products are examined and tested in the Human Viral Vaccines Quality Control Laboratory, the Animal Viral Vaccines Quality Control Laboratory, the Poultry Viral Vaccines Quality Control Laboratory, and the Cell Culture Laboratory.

7.2. Bacterial Biological Products Quality Control Department

In this department, all human, animal, and poultry bacterial biological products are examined and tested in the Human Bacterial Vaccines Quality Control Laboratory, the Animal Aerobic Bacterial Vaccines Quality Control Laboratory, the Animal Anaerobic Bacterial Vaccines Quality Control Laboratory, the Parasitic Vaccines Quality Control Laboratory, and the Bacterial Antigens Quality Control Laboratory.

7.3. Microbial Quality Control Department

In this department, all microbial tests of biological products, including sterility tests, mycoplasma tests, as well as quality control tests of anti-snake and anti-scorpion therapeutic serums are performed in the sterility, mycoplasma, Therapeutic serum quality control laboratory and the raw materials and environmental monitoring Quality Control Laboratory.

7.4. Physicochemical Department

In this department, all physicochemical tests required for controlling biological products are performed in the Physics and Chemistry laboratories.

7.5. Experimental Animals Department

In this department, all animal tests required for controlling the quality of biological products are performed in the Pathology Laboratory and the Livestock, Poultry, and Rodent Laboratories.

7.6. Biobank Department

One of the achievements of Razi Institute, especially in recent years, is the establishment of a biobank complex to preserve the valuable genetic reserves of the institute. This department is responsible for storing, maintaining, and documenting vaccine seeds and cells, as well as determining the characteristics of these seeds and cells in virus, bacteria, and cell laboratories. In this department, vaccinal seeds are stored under fully controlled conditions in a building resistant to natural disasters with continuous monitoring to be used when necessary to produce biological products.

8. Holding Training Courses, Seminars, and Student Education at Educational Levels

Over the years, Razi Institute has held various training courses to expand and exchange scientific information, including national and international training courses under the supervision of WHO, such as the international course on vaccine production for developing countries and the training course on the production and quality control of biological products for African countries and Asian (Malian, Somalian, Uzbeks internships on veterinary vaccines production and quality controls). The institute has also held various national and international congresses in the country, including the congresses on virology, microbiology, and parasitology. On the other hand, the institute's researchers actively participate in various international courses and seminars.

In addition to the abovementioned scientific activities, Razi Institute has involved in training students at

postgraduate levels in virology and bacteriology. Given that this institute has a valuable treasure trove of educated human resources and is a clear example of direct communication between universities and industry, many students have graduated from this institute in the past century.

9. Scientific Research and Development on Biological Products and Related Topics and Production of Technical Knowledge at the Level of The Institute, the Country, and the Region

One of the most important concerns of Razi Institute is to conduct research and development (R&D) to improve existing products and produce new products. The comprehensive developments carried out in the institute's product portfolio over the years, as well as the new products repeatedly produced at Razi Institute in various stages and finally reaching mass production, are evidence of this. Looking at the new products that were developed by relying on institute's production of technical knowledge, we find that new products were produced in this institute in relatively short periods.

For example, in the 1990s, 5 new products were produced at Razi Institute over 10 years, including the Gumboro vaccine in 2011, the PPR vaccine in 2013, SPF eggs in 2014, the heat-resistant Newcastle vaccine and the bivalent Newcastle Lasota and H120 bronchitis vaccine in 2015, the Newcastle clone vaccine in 2015, the Brucellosis, Newcastle and influenza diagnostic kits in 2018, and the Covid-19 recombinant protein vaccine in 2019. This approach to product development is still fundamental at this institute, as in recent years the institute has introduced new products to the country, including the ORT vaccine.

10. Conducting Veterinary Research at the National Level

Razi Institute also plays a very prominent role in conducting veterinary research in the country. Due to the comprehensive scientific support in this institute, it is known as the custodian of veterinary research at the national level. In this regard, the prominent achievements of Iranian veterinary science have been achieved by this institute.

In this article, on the eve of the 100th anniversary of the Razi Institute, we attempted to describe some of the valuable services that its researchers have provided to the health and hygiene of the community over the years, so

that this institute can be better known to the scientific community around the world. We hope that this institute will be sustainable and continue to pursue its mission in the future.

Acknowledgment

We would to thank all of our colleagues at Razi vaccine & serum research institute for their kind cooperation.

Authors' Contribution

Study concept and design: S. S.

Acquisition of data: S. S, A. H.

Analysis and interpretation of data: S. S, N. M.

Drafting of the manuscript: S. S.

Critical revision of the manuscript for important intellectual content: S. S, K. T.

Statistical analysis: Not applicable.

Administrative, technical, and material support: S. S, N. M.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Grant Support

The authors confirm that they did not receive any financial assistance for the research, authorship, and/or publication of this article

Data Availability

The data that support the findings of this study are available upon request from the corresponding author.

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