

ORIGINAL ARTICLE



The National Center for Reference and Research on Rabies, Pasteur Institute of Iran: An Unforgettable Name in the Health History of Rabies Control in the World

Abstract

Rabies is a fatal zoonotic disease that usually occurs via infected animal saliva. Two years after establishing the Pasteur Institute of Iran, the National Center for Reference & Research on Rabies, chaired by Dr. Mahdi Ghodsi, was formed to control and treat this disease in Iran. In 1955, Dr. Ghodsi, Dr. Balthazar, and Dr. Bahmanyar made a global transition in the rabies vaccination process. The rabies department was established in 1923. In 1976, it was selected to cooperate with the World Health Organization (WHO). Since 2013, according to ISO 15189, it was established as the rabies reference laboratory for the Ministry of Health and Medical Training and Veterinary Organization. For the 100th year of establishing the National Center for Reference & Research on Rabies, this article reviews the history of the center and its activities, such as diagnostic tests of suspected samples of rabies, assessment of the effectiveness of rabies vaccine, and evaluation of rabies vaccine potency.

Key words: Rabies, Research, Diagnosis

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Nazanin Shaban Salmani¹ 
Maryam Fazeli²
Rouzbeh Bashar³ 

- 1- DVM, The National Center for Reference and Research on Rabies, Pasteur Institute of Iran, Tehran, Iran
- 2- PhD; Deputy of Research, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
- 3- PhD, The National Center for Reference and Research on Rabies, Pasteur Institute of Iran, Tehran, Iran

Correspondence:

Rouzbeh Bashar
PhD; The National Center for Reference and Research on Rabies, Pasteur Institute of Iran, Tehran, Iran

bashar@pasteur.ac.ir

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Introduction

Rabies and its history in Iran and the world

Rabies is an acute and fatal viral disease that can affect warm-blooded mammals (bats, carnivores, ruminants), even humans, and it usually occurs via infected animal bites, abrasion, or saliva between humans or other animals (Nadalian, et al, 2009, pp. 337-343). The main carriers are dogs, wolves, jackals, and foxes. It is one of the most critical public health problems globally, including in Iran (Nadalian, et al, 2009, pp. 337-343). The latency length depends on factors like the site of the injury, the number of the virus entering the body, the severity of the virus, the immunity system condition, and the injured age, which can range from a few days to a few months (Tajbakhsh, 2007, pp. 329-332). Twenty-eight countries from 35 Latin American countries have not reported any deaths due to rabies from the dog. Significant efforts have been made to reduce rabies in Bangladesh, the Philippines, Tanzania, Vietnam, and South Africa. Some developing countries, such as Sri Lanka and Indonesia, are currently implementing plans to eradicate rabies. Measures have been taken to reduce the number of deaths caused by rabies in these countries. These experiences have created an essential collective knowledge about the activity performed, improving the quality of data related to rabies. This contributed to developing preventive control plans.

The term rabies is derived from the Sanskrit term rabhas. The term “Lisa” has been translated in English as bitten by a dog. In Dehkhoda Dictionary (Persian), rabies has been described as a crazy animal, especially a crazy dog (Fazeli, Fayaz and Bashar, 2019, pp. 165-179). Rabies in the ancient world has also been known from about 2300 BC, commonly referred to as the main carrier of the disease (Nadalian, et al, 2009, pp. 337-343). In ancient Iran, the rabies disease was already known by farmers and shepherds, and well-known Iranian scientists, such as Ibn Sina (980–1037 AD) and Jorjani, also described the illness. Ibn Sina described the disease with a hydrophobia symbol and said that the location of the bite should not be covered up to 40 days (Nadalian, et al, 2009, pp. 337-343). In our country, more than 100,000 people annually are treated for bites by suspected rabid animals, especially dogs (Fazeli, Fayaz and Bashar, 2019, pp. 165-179). According to the studies, the dog is the leading and most crucial carrier, and reservoir of rabies in Iran and the world; 5-6 individuals die from rabies in Iran annually (Nadalian, et al, 2009, pp. 337-343).

Rabies is a fatal disease, and so far, no effective treatments have been presented; and the meaning of treatment and prevention of rabies is to make a responsible immunity after biting and during the latency of the disease (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

Louis Pasteur was the first person who discovered the rabies vaccine. In 1881, having divided the virus from the saliva of the kid who had died by rabies, Pasteur injected the rabies virus into the rabbit's brain. Then, he injected the infected rabbit brain into a healthy rabbit's brain and kept it on until the pathogenicity of the virus was reduced (Nadalian, et al, 2009, pp. 337-343). He kept the rabbit's spinal cord dry and could survive 50 dogs of rabies by injecting them with this suspension. In 1885, he treated a 9-year-old child, Joseph Mister, bitten by a dog. He saved the baby from certain death by subcutaneous injection of the spinal cord around the belly button and then by 13 more



injections. Thus, Louis Pasteur did the most outstanding service to humanity, and by his suggestion, the first Pasteur Institute was established in Paris (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

The History of the Research and Research Department of the Pasteur Institute of Iran

On November 14, 1888, the Pasteur Institute was officially established as an anti-rabies center in Paris. On October 14, 1919, the meeting of the Iranian political delegation with the professor of the Institute Pasteur of Paris was the start for establishing the Pasteur Institute of Iran in 1920, chaired by Joseph Menard.

At that time, rabies was a severe health problem in Iran. People used to resort to superstition when they were bitten by dogs and they sometimes lost their lives. In 1923, the son of one of the ambassadors of Tehran was bitten by a dog, and hence it became necessary to establish the rabies diagnosis and prevention department in Iran. This was accomplished by Dr. Mahdi Ghodsi at the Pasteur Institute of Iran. In 1925, in order to prepare the rabies vaccine, Dr. Abolghasem Bahrami brought the virus strain from Paris to Tehran, so the classic rabies vaccine was prepared in this center. To date, Iran has played a significant role in the new scientific advances in the rabies treatment field. (History of National centre for Reference & Research on Rabies, 2017). Dr. Ghodsi was the head of the rabies center in Pasteur Institute of Iran and conducted studies on the effects of the rabies vaccine for ten years. In 1946, he found the classic method of rabies treatment non-effective in people who had a severe injury and some of them lost their lives because of rabies (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

In 1950, the World Health Organization (WHO) rabies committee entrusted the evaluation of rabies vaccines and serum to the rabies department of the Pasteur Institute of Iran (Fazeli, Fayaz and Bashar, 2019, pp. 165-179). In 1955, researchers at the Pasteur Institute treated a rabid wolf attack in the Sahneh city of Kermanshah (Figure 1), in which 29 people were injured. The injured were referred to the Pasteur Institute, and Dr. Balthazar and Dr. Bahmanayr (Figure 2) used rabies serum and vaccine to cure the wounded. The injured were divided into two groups based on the depth and surface of the injury; one group was treated with rabies serum and vaccine together and the other received just the vaccine. The results were significant; one of the injured, belonging to the group who had taken the serum and vaccine died, but no one from among the people with a superficial and treated scar died (History of National centre for Reference & Research on Rabies, 2017). According to the results, this treatment method used rabies vaccine and serum were known by the World Health Organization (WHO) as the best way to treat rabies worldwide (Fazeli, Fayaz and Bashar, 2019, pp. 165-179). In addition, the findings of the studies carried out by Dr. Ghodsi from 1947 to 1955 confirmed that the rabies vaccine alone was ineffective for deep and multiple scars on the head and face (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

Currently, part of the rabies serum that Iran needs to prepare is imported from foreign countries by the Blood Transfusion Organization. In those years, rabies serum was produced by Dr. Hossein Mirshamsi and his colleagues at the Razi Institute in Iran, but the problem was that the use of horse and donkey blood to produce this serum would cause



allergic complications in humans. In addition, the use of vaccines prepared from the spinal cord was discovered by Louis Pasteur. However, until 1936, some complications, like paralysis, were reported from all countries around the world. Thus, in 1976, while using the anti-rabies serum on human cells was common, the evaluation of the first series of cell-culture vaccines developed over the human diploid cells by Dr.Kuperofski and Victor at the Vistar Institute of Philadelphia was entrusted to the Rabies department of Pasteur Institute of Iran. The results obtained from this test were excellent and were chosen as a therapeutic protocol for the vaccination of rabid animal-bitten people (History of National Centre for Reference & Research on Rabies, 2017). Iranian researchers injected the vaccine into five volunteer groups, following the assessment of antibodies in those people; this method, injected into the stomach skin on the days of 0, 3, 7, 14, and 30, and the booster on day 90, was known as the best method for preventing rabies. However, it was difficult and the Pasteur Institute decided to use a new method to inject the rabies vaccine (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

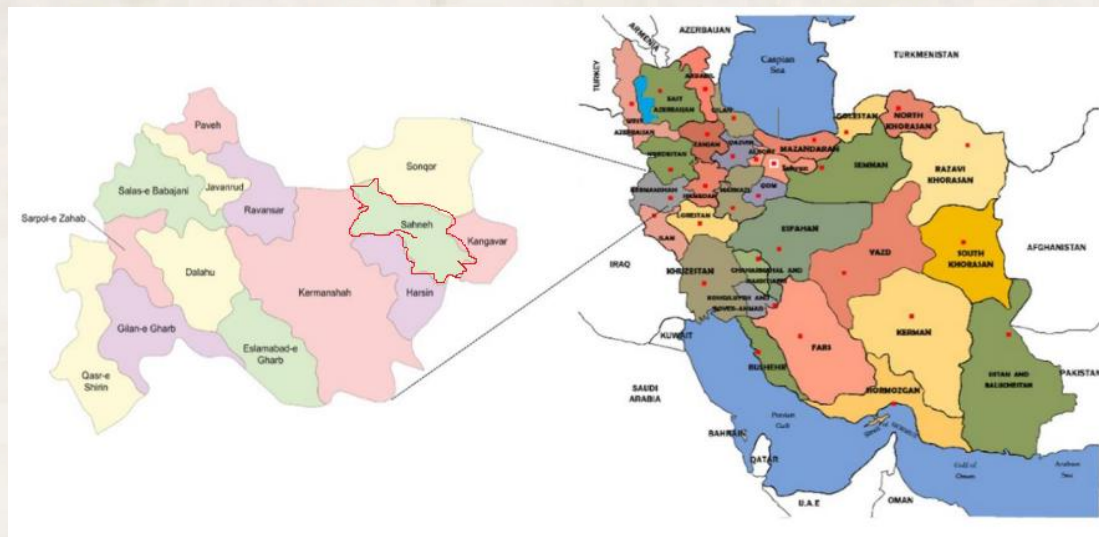


Figure 1. Sahneh city, Kermanshah (Mohammadi-Mehr, Bijani, and Abbasi, 2018, pp. 1353-1367)

Dr. Ahmed Fayaz (Figure 2), a graduate of veterinary medicine from the University of Tehran, is one of the famous scientists in the field of rabies treatment in Iran and one of the most important people in Iran’s rabies control process. After studying a virology course at the Pasteur Institute of Paris and an immunology course at the American University of Beirut, he returned to Iran to conduct some research on rabies at the Pasteur Institute of Iran. During epidemiological studies in 1975, Dr. Fayaz, in collaboration with Dr. Younus Karimi, introduced foxes as one of Iran’s most important reservoirs of rabies. Dr. Fayaz and Dr.Bahmanyar made efforts to find an effective treatment for the people exposed to rabies infection. One of the most important scientific achievements was developing the rabies vaccine in the human cell culture in 1976. The treatment method they introduced was the intradermal injection of the vaccine and anti-rabies serum in five



doses on days 0, 3,7,14, and 30. The World Health Organization approved the method, adding this to the international rabies treatment protocol. Since then, the injection is done through the same method. The advantage of this method is more immunogenicity of the rabies vaccine while using less dosage of that. Dr. Fayaz has chaired the National Center for Reference & Research on Rabies Activities since 1977. During these years, many activities have been directed to improve vaccinations, treatment, and control of rabies in Iran and other countries' training programs to control the disease. Another important activity that started in this center during Dr. Fayaz's directorship is the launch of a serological test to evaluate rabies antibodies in animal or human serum (RFFIT). This test has been set up by Dr. Susan Simani, a veterinarian and deputy of the Rabies department. Dr. Fayaz and Dr. Simani have written extensively about rabies, its treatment, and epidemiology. Dr. Fayaz was also selected as one of the best physicians for his 30 years of activities in health. Today, he is one of the most important advisors in the Pasteur Institute of Iran (Ghasemnejad and Mostafavi, 2018, pp. 268-272).

In 1976, thanks to the valuable services of the rabies department of the Pasteur Institute of Iran at the regional and international level in the promotion of the health, rabies department was appointed to cooperate with the World Health Organization, and since 2013, according to ISO 15189, it was established as the rabies reference laboratory for the Ministry of Health, and Medical Training and Veterinary Organization of the country. The rabies department of the Pasteur Institute of Iran has assumed responsibility for rabies diagnosis and participation in maintaining and promoting disease, prevention, and control processes. It has effectively collaborated with the World Health Organization for more than four decades to achieve the goals of the health system. The preservation of scientific and technical achievements is to improve the level of quality and programming to expand the activities in the country and the region from the fundamental missions of this sector. Expanding and improving educational, research, and technical cooperation with the government and international centers to better monitor rabies in the rabies control area are also the center's missions.

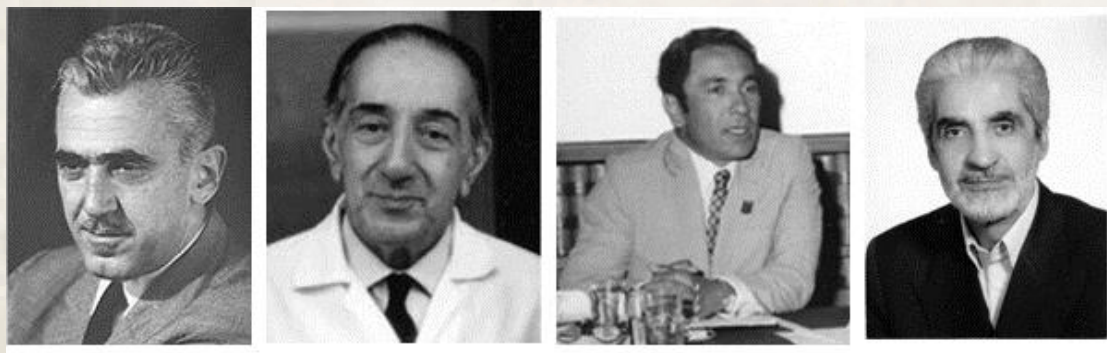


Figure 2. From left to right: Dr. Balthazar, Dr. Ghodsi, Dr. Bahmanyar and Dr. Fayaz

The National Center for Reference & Research on Rabies Activities

Currently, the National Center for Reference & Research on Rabies of the Pasteur In-



stitute of Iran is the only rabies reference laboratory. Some of the main activities of the center are as follows (Fazeli, Fayaz and Bashar, 2019, pp. 165-179).

1- The diagnosis test after the death by rabies; Fluorescent Antibody Test (FAT) and (Mouse Infectious Test / MIT)

In the laboratory, the rabies-suspected brain samples of animals or humans are investigated by accurate and sensitive laboratory methods, such as FAT and MIT. The results are sent to the center requesting the test. In this unit, the annual rabies statistics, including the total number of subjects bitten by rabid animals, rabies-related fatalities, and the prevalence of rabies in humans and animals in different parts of the country, are discussed and analyzed. This statistical information is determined on the GIS maps.

2- Serological Test (RFFIT / Fluorescent Inhibition Test)

This laboratory evaluates the amount of rabies virus antibody in the sample of human or animal serum or serums produced in Iran or imported from foreign countries. The evaluation of the rabies virus by ELISA method is also performed in this laboratory.

3- Tests for the assessment of the vaccine and biological products (National Health of Health / NIH)

The world health organization has approved the assessment of the potency of human and animal vaccines by the NIH method performed by the reference laboratory of rabies, According to standards prescribed by the Research Department and the Center for Medical Education of the Republic of Iran, the Ministry of Health, and Medical Education, and the Iran Veterinary Organization, the issue was granted to distribute these vaccines. In the center's research department, some projects are implemented on vaccines and their immunogenicity.

4- Molecular Test

In this laboratory, molecular studies and diagnoses are conducted on the genome of isolated strains obtained from all over the country, such as RTPCR, Real-Time PCR, and RT-LAMP. Other examinations performed in the department include the molecular analysis of infected brain, cerebrospinal fluid, skin, saliva, urine, and sera samples from antemortem and post-mortem rabies-suspected subjects.

5- Cell culture laboratory

In this laboratory, some activities are performed to produce rabies vaccine, diagnose, and carry out research methods about rabies virus that need animal cells.

The Design and implementation of rabies control plans

Until recently, the global response to rabies was fragmented and non-coordinated. Now, for the first time, WHO, the UN Food and Agriculture Organization (FAO), the World Health Organization of animal (WHOIE), and the Global Alliance for Control of rabies (GARC) collaborate to support countries to control rabies. They plan to eliminate rabies by 2030. After extensive consultations with the affected countries, WHO today has



prepared and published a global strategic plan to end human mortality due to rabies by 2030. There are a series of social changes to achieve these goals. These actions have been prioritized to target the condition of the disease in dogs and to improve health systems eventually.

The rabies committee, which consists of the representatives of the Ministry of Health and Medical Education, the National Center for Reference & Research on Rabies in Pasteur Institute of Iran, the Department of Environmental Protection, Municipality and Veterinary Organization with the target of eradicating rabies in wild and domestic animals in Iran, and the prevention of the bite, has developed a comprehensive rabies control program in the country (Mostafavi, et al, 2020, pp. 38-47). The proceedings of this program are:

- Recording and reporting all possible and decisive cases of rabies
- Reporting every animal-bitten to the health center
- Animal vaccinations, especially dogs and their population control
- Effective vaccine production
- Registering all rural dogs
- Increasing the number of health care centers to treat the injured and providing the existing centers with new equipment
- Strengthening public participation and education
- Co-operation among all departments

In the last few years, efforts, including increased health care, prevention, and public education, have been made to implement the control program and eliminate rabies. Nevertheless, the disease is still widespread in the country, and its control has faced some challenges, including lack of adequate treatment and prevention centers for rabies in the provinces, lack of reports of a bitten animal, especially in the provinces. Another measure that can help control and eliminate rabies in the country is to trace the transmission path of the virus. In the National Center for Reference & Research on Rabies of Pasteur Institute of Iran as epidemiological studies, the pathway of the virus movement inside the country, between domesticated animals and wildlife, as well as between Iran and neighboring countries, and the core of rabies in the country have been identified (Mostafavi, et al, 2020, pp. 38-47) (Table 1).

Table 1: Milestones of the National Center for Reference & Research on Rabies, Pasteur Institute of Iran in 100 years

Event	Year
Establishing rabies department of Pasteur Institute of Iran	1923
Entrusting the evaluation use of rabies vaccine and serum method from WHO to rabies department of Pasteur Institute of Iran	1950
Rabid wolf attack in Sahneh city (Kermanshah Province, the west of Iran) and use rabies vaccine and serum method to treat exposed people	1955
1. Producing and evaluating human rabies vaccine 2. Innovative treatment method with injecting five doses of rabies vaccine and serum and approved that by WHO 3. Selecting rabies department of Pasteur Institute of Iran as WHO collaborate	1976
Selecting rabies department of Pasteur Institute of Iran as reference rabies laboratory	2013



Discussion

The importance of rabies is due to its fatality after the appearance of clinical signs in humans or animals, huge economic costs resulting from the consumption of vaccines, and serum and financial and health losses due to livestock losses (History of Pasteur Institute of Iran, n.d.). Over the past few years, many countries have taken actions for controlling rabies through dog vaccinations, and easy access to pre - and post-training efforts. Because of these measures, rabies is eliminated from the dogs in Western Europe, Canada, the United States, and Japan. One of the effective measures to eradicate rabies from 1978 was oral vaccination in Europe, prompting the elimination of rabies in the wild, followed by a reduction in rabies in animals and humans. In many developed countries, in addition to effective measures described in removing rabies in wild animals, they have been able to eliminate rabies in stray dogs and fully implement the vaccination campaign in domestic dogs. The global strategic plan has set three goals for the involved countries, and the major stakeholders: (Tajbakhsh, 2007, pp. 329-332) effective use of vaccines, drugs, tools, and technologies that hinder the transmission of rabies from dogs to humans, reducing the risk of human mortality due to rabies; (Mostafavi, et al, 2020, pp. 38-47) increasing awareness and enactment of government and international laws to control and prevention of rabies (Nadalian, et al, 2009, pp. 337-343), and increasing cooperation among all departments.

The success of the elimination program is based on the existence of an accurate monitoring system based on reality, the data related to mortality, and the correct understanding of the epidemiological process. Unfortunately, the rabies of dogs and humans in many different countries is not taken seriously. An observation system is currently being implemented in Southeast Asia. Without a careful monitoring system, it is difficult to convince policymakers and decision-makers to give priority to rabies in the control scheme. To accomplish this, the National Center for Reference & Research on Rabies of Pasteur Institute of Iran, in cooperation with the ministry of health care and the veterinary organization, has launched a monitoring center for monitoring rabies and monitoring unknown encephalitis in the country. The center receives all the information about bites from health centers across the country with the help of the Health Ministry's zoonotic disease Management Center, the number of domestic or wild animals reported to the veterinary organization, and encephalitis cases with an unknown cause in hospitals across the country. In addition, the National Center for Reference & Research on Rabies carefully provides sampling protocol, needful tools, and the way to send samples for health centers around the country.

The necessary activities in this regard that can be undertaken by the National Center for Reference & Research on Rabies are as follows:

1. Equipping, promoting, and updating rabies detection laboratory for National Center for Reference & Research on Rabies.
2. Equipping and launching the molecular epidemiology laboratory for Lyssa viruses in the National Center for Reference & Research on Rabies.

Given the increasing trend of animal bites and animal and human rabies in our country, authorities are expected to collaborate with the National Center for Reference & Research on Rabies on animal vaccination. In addition, they are expected to train people and



staff to reduce rabies cases in Iran (Nadalian, et al, 2009, pp. 337-343).

Conclusion

Wild mammals play an essential role in the rabies cycle in nature. Conducting a detailed study to identify the rabies reservoirs in the country is one of the first steps taken by the National Center for Reference & Research on Rabies in cooperation with the veterinary organization and the environmental organization. Choosing a suitable oral vaccine compatible with Iran's nature, which is practical and cost-effective, would be the next step. Relevant organizations should also study the method of using the oral vaccine in the wild. Of course, suspected rabies samples should be diagnosed in the reference laboratory and provide accurate statistics by the Institute and the Environment organization to determine the image of rabies in the wild of Iran.

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Conflict of Interest

None.

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