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Pasteur Institute of Iran: A Leading Institute in The Production and Development of Vaccines in Iran

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ABSTRACT

The 100-year-old Pasteur Institute of Iran is a research, manufacturing, and educational institute providing services in terms of public health. It has taken great steps towards producing required vaccines in Iran. The institute has played a key role in controlling infectious diseases in Iran by producing many vaccines such as smallpox, cholera, Bacillus Calmette–Guérin (BCG) and recombinant hepatitis B as well as introducing infectious disease control programs and making use of diagnostic laboratories. The institute is currently pursuing a program to develop its production lines for human polysaccharide-conjugate vaccines and viral vaccines for the health system of Iran. This paper reviews manufacturing activities of this institute over the past 100 years.

INTRODUCTION

Vaccines prevent deaths of millions of children in the world. Growing efforts are being made to produce new vaccines and prevent other diseases. Given the usefulness of the vaccines, it has been argued that the life expectancy has been increased up to 30 years on average in the twentieth century (1). Vaccines consist of substances that are introduced into the body and provide immunization, and thus microbes cannot cause diseases in the body for a specified period. Vaccines are often used to prevent illnesses, and sometimes to treat and protect against microbes entering into the body. Sera are also injectable components containing a microbial substance derived from the inoculation of a microbial pathogen to animals; they are often used to treat diseases and sometimes to protect body against diseases (2).

Before the Constitutional Revolution (1906 AD), the Iranian government was not taking the responsibility for the national health. After this period, the National Consultative Assembly passed laws to improve the national health and involved the government in this field. The Pasteur Institute of Iran was established to promote the public health of Iranians during the late Qajar period. During the first Pahlavi period, the provision of health was practically state-owned. In the second Pahlavi period and at the onset of the World War II, famine and infectious diseases became widespread in Iran and the role of prevention programs became more important in controlling infectious diseases (3). In 1953, the general vaccination law was passed by the National Consultative Assembly, followed by the immunization of target groups. Seemingly, this new preventive approach, along with Iranians gradual independence on domestic production of vaccines, was a symbol of the emergence of a dominant medical model in Iran and reduced dependence on foreign products. In the past 100 years, the productions of high-quality vaccines in accordance with the national and international standards and regulations against vaccine-preventable diseases in the Pasteur Institute of Iran and Razi Vaccine and Serum Research Institute have been successful activities to protect target groups, provide immunization and reduce the burden of related diseases in Iran. The production of vaccines and injectable sera have been the main services of the Pasteur Institute of Iran since its establishment (4).

The Establishment of Pasteur Institute of Iran

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The history of the Pasteur Institute of Iran dates backs to the year 1919, when Iran had newly survived from blights of the World War I and faced the spread of some infectious diseases. At that time, the Iran's Higher School of Medicine was the only center that was active in the field of medical education in Iran; however, it had no qualification to study and control infectious diseases. Therefore, there was an unmet need for establishing a scientific institution that could work on infectious diseases and produce some biological products, including vaccines in some cases. In the morning of October 23, 1919, a group including Dr. Mohammad-Hossein Loghman Adham, Dr. Hakim Al-Doleh, Dr. Mahmoud Khan Motamed, Mohammad-Ali Zoka Al-Molk Foroughi, and Nosrat Al-Doleh Firouz went to the Pasteur Institute of Paris on behalf of the Iranian government, and talked to Dr. Pierre Paul Émile Roux, the discoverer of anti-diphtheria serum and the successor to Dr. Louis Pasteur, about the establishment of the Pasteur Institute in Iran. Following the agreements, the Dr. Joseph Mésnard from France travelled to Tehran to set up and manage the Pasteur Institute of Iran on July 1920. In cooperation with some of the Iranian researchers, Dr. Mésnard began his work in the first building of the Pasteur Institute of Iran in Modabber Al-Doleh Samiee Garden, located on the current Estakhr Street in Tehran; hence, formal activities of the Pasteur Institute of Iran began and expanded day by day while the quantity and quality of its services increased (4).(Fig. 1).

During the establishment period, the Pasteur Institute of Iran consisted of six sectors for producing various vaccines and production of smallpox inoculation (2). Due to their potential risks and high costs of the imported sera and vaccines from Europe, the Pasteur Institute of Iran sought to provide enough

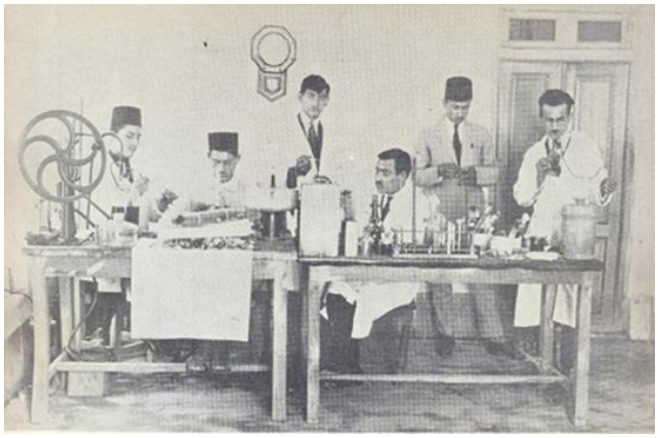

Fig. 1. Employees of the Pasteur Institute of Iran at the time of establishment; from right to left: Dr. Ahmad Najmabadi, Dr. Abdollah Hamedi, Dr. Seyed Hassan Mirdamadi, Teymour Mirza Dolatshahi, Dr. Seyed Reza (Lab expert), Mehdi Zorriasateyn.

and cost-effective amounts of sera and vaccines. There were initially many barriers to the production and use of vaccines. For instance, there was a need for the special glassware that were not produced in Tehran. Moreover, a permanent corral was required for the production of smallpox inoculum. It was also very difficult to establish and maintain the Institute due to delays in its budget payments while vaccinations were not widespread and using the produced vaccines was uncommon. Despite the above problems, the above-mentioned problems were gradually solved and large amounts of cholera, smallpox and individual vaccines were provided.

In the first two years of establishment of the Pasteur Institute in Iran, a large amount of inocula of cholera, smallpox and other sera and vaccines were imported from the Pasteur Institute of Paris (Fig. 2), and a backup was provided at the Pasteur Institute of Iran until the launch of vaccine production line in Iran. Dr. Mésnard quickly produced a number of vaccines that were necessary in Iran. In the first 19 months of its establishment (during 1921 and 1922), 19 types of sera and vaccines were produced or injected at the Institute, and about 190,000 doses of smallpox inoculum were produced (Table 1).

Pasteur Institute of Iran provided a great service for Iran in the early years of its establishment by producing smallpox inoculum that was so necessary for Iran as well as the provision of typhoid and cholera vaccines that were two other important causes of death of the Iranian people at that time (5).

Dr. Mésnard started building new laboratories in the lands that Abdol-Hossein Mirza Farmanfarmaian donated to the Pasteur Institute of Iran in 1922. According to the endowment text of the late Farmanfarmaian, the intention of endower was “the provision of injectable materials and inoculated vaccines for diseases such as smallpox, plague, cholera, diphtheria, rabies, syphilis, and gonorrhea”(5). Abdol-Hossein Mirza Farmanfarma said about his intention for endowment to the Pasteur Institute of Iran: "I built an institute where smallpox inoculum could be produced, and rabid animal bitten ones could be treated, and sexually transmitted diseases were treated, and finally inocula were prepared for all human and animal diseases (6)”. By 1924, the control and vaccination of important

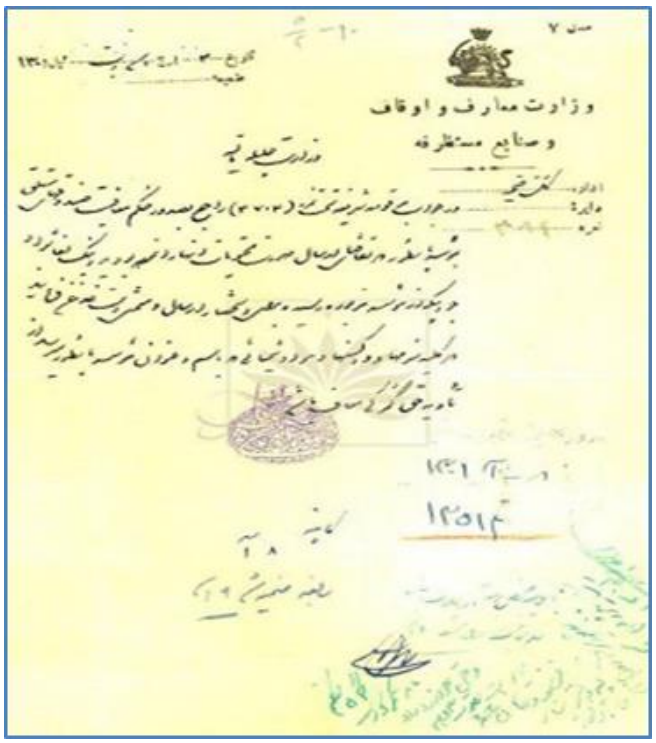

Fig. 2. Request from the Ministry of Finance for the exemption of serum, vaccine and chemical funds of Pasteur Institute of Iran from payment of customs duties; Document Date: 27/7/1922. Content of the letter: Dear Official in the Ministry of Finance, in response to the letter No. 3704 regarding the issuance of a decree for exempting funds belonging to the Pasteur Institute requesting the submission of their content, and according to the reply from the Institute, please exempt all sera, vaccines and chemicals received by the Pasteur Institute from paying customs duties.

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animal diseases such as Anthrax and Rinderpest were also the main tasks of the Pasteur Institute of Iran (Fig. 3). At that time, it was argued that the government should make the use of some vaccines such as Anthrax for animals obligatory because of the public unawareness and the lack of attention to the prevention of infectious zoonotic diseases (2). For the first time, Dr. Joseph Mésnard, the first Director of the Pasteur Institute of Iran brought a Smallpox inoculum from Paris to Iran in April 1922 and produced the Smallpox inoculum by a scientific method (5).

Table 1. List of produced sera and vaccines in the first 19 months of establishment of the Pasteur Institute of Iran (during 1921 and 1922) available for use at the Pasteur Institute of Iran (2).

Quantities	Size of the vials	Serum/Vaccine
646 glass tubes	10-cm^3 glass tubes	Diphtheria serum
130 glass tubes	10-cm^3 glass tubes	Tetanus vaccine
119 glass tubes	10-cm^3 glass tubes	Anti-Streptococcus
194 glass tubes	10-cm^3 glass tubes	Meningitis vaccine
177 glass tubes	10-cm^3 glass tubes	Human anthrax vaccine
90 glass tubes	10-cm3 glass tubes	Snake Serum
29 glass tubes	10-cm3 glass tubes	Anti-dysentery
144 glass tubes	20-cm3 glass tubes	Anti- pneumonia
76 glass tubes	20-cm3 glass tubes	Anti- Plague
138 glass tubes	Six-ampoule box	Gonorrhea vaccine
172 glass tubes	10-cm3 glass tubes	Cholera vaccine
n=200	2-cm3 glass tubes	Typhoid vaccine
Individual vaccines		
336 ampoules	1-cm3 ampoules	Body pimple vaccine
672 ampoules	1-cm3 ampoules	Anti-infection

Services and products of the Pasteur Institute of Iran increased in quantitative and qualitative terms in the following years. In 1961, smallpox, BCG, rabies, and microbial vaccines (typhoid, paratyphoid, cholera, etc.), tuberculin, antigens, synthetic sera, blood transfusion instruments, blood serum injection instruments, and human plasma were produced by this institute. Meanwhile, the institute provided training on methods of inoculating smallpox, testing tuberculin, and injecting BCG, cholera, typhoid and parathyroid vaccines(7).

On the 50th anniversary of the establishment of the Institute (1970), 23 million doses of smallpox vaccine were produced and exported to Turkey, Pakistan, Saudi Arabia and Ethiopia. The income of Pasteur Institute of Iran from its produced vaccines in this year was three times higher than its annual budget (Table 2).

Fig. 3. Letter from the Prime Minister, Commander Reza Khan, to Tehran Municipality regarding the purchase of Rinderpest vaccine and serum from health institutes of Mesopotamia due to the inadequate serum supplies in the Pasteur Institute of Iran. Document date: 14/9/1924.
Content of the letter: After receiving the letter (No. 5257) about the outbreak of rinderpest, the Ministry of Education and Endowments wrote in response as follows: "As reported by Dr. Ehya Al-Doleh, the incidence of rinderpest and its diagnosis was presented in the health council, and since the Pasteur Institute currently did not have any supply of the vaccine and serum, it was decided to prepare them from other health institutions. After ensuring its effect, the sufficient amount would be imported gradually. Dr. Mésnard also suggested producing this type of serum and also other types of sera to the Ministry of Education, and estimated the costs at one hundred and thirteen thousand Tomans. The proposal should be presented in the health council; and the municipality office will be re-notified of the results of secondary measures".

In addition to the production program, the Pasteur Institute of Iran sought to boost its knowledge on the production of vaccines and to receive the technical knowledge on the production of new vaccines by dispatching its researchers to vaccine manufacturing centers in other regions of the world. For instance, in 1972, Dr. Sabbar Mirza Farmanfarmaian, the director of the Pasteur Institute of Iran, dispatched Dr. Rasoul Pouranki, the head of Department of Virology, to France, Switzerland and the United Kingdom to study viral vaccines (Fig. 4).

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Table 2. The production program of the Pasteur Institute of Iran in 1970

Quantities	Products
20000000 L (5.1)	Smallpox inoculum
3000000 L (0.75)	BCG vaccine
200000 L (2.5)	Rabies vaccine
2000000 L (2.5)	Microbial vaccines (Typhoid, paratyphoid, cholera, etc.)
6000000 L (0.5)	Tuberculin
200000 L (50)	Antigens
200000 L (50)	Synthetic sera
20000 glass tubes (50)	Blood transfusion instruments
30000 devices (30)	Blood serum injection instruments
500000 ml	Human plasma

Fig. 4. Mission for Dr. Rasoul Pouranaki to consider the feasibility of producing viral vaccines, 1972

Content of the letter: Mr. Prime Minister, 17/7/1972

We would like to inform you respectfully that Dr. Rasoul Pournaki, the head of the Department of Virology at the Pasteur Institute, has a mission for six weeks from the beginning of August to travel to France, Switzerland, and the United Kingdom to consider the feasibility of producing viral vaccines and preparations for relevant vaccines. The travel cost and departure tax and daily extra expenses of the mission will be paid from the Pasteur Institute budget according to the regulations. Please allow issuing a service passport for him and we appreciate your confirmation.

Director of the Pasteur Institute of Iran,
Dr. Sabbar Mirza Farmanfarmaian

PRODUCTION & RESEARCH COMPLEX OF THE PASTEUR INSTITUTE OF IRAN

Due to the increased population in Iran and the superiority of preventive medicine over the therapeutic medicine, and the expansion of manufacturing activities of the Pasteur Institute of Iran in Tehran, the authorities of the Ministry of Health and the institute considered a land with an area of roughly 19 hectares for establishing a research and production complex, located at 25 kilometer west of Tehran, along Tehran-Karaj highway. After completing four units of the buildings and facilities, the Institute Director, Dr. Ahad Milani Nia, ordered to open the complex by the Iranian president on March 18, 1989 and it started working with a total area of 18 hectares. Presently, over 10 production sites of this complex are utilized to manufacture over 50 products for Iranian health system. This complex aims to improve the public health, to prevent the import of above-mentioned products and to develop the export of the biological products (4). Approximately, 400 personnel are working in this complex. Next to the Pasteur Institute in Tehran, this complex (in Karaj) is the largest branch of Pasteur Institute of Iran. This complex is also one of the largest and most advanced vaccine manufacturing sites in Iran and the Middle East that also provides consulting services in the field of production and quality management of pharmaceutical products, vaccines, diagnostic products and laboratory animals breeding.

Produced Vaccines at the Pasteur Institute of Iran

The Pasteur Institute of Iran as well as Razi Vaccine and Serum Research Institute are the pillars of manufacturing human vaccines in Iran. The vaccines produced in the Pasteur Institute have played major roles in improving the public health and immunization in Iran. Pasteur Institute of Iran has been very influential for the state of health of Iran over its hundred years of activities. In particular, controlling diseases such as cholera, smallpox, typhoid, tuberculosis, rabies, and hepatitis B were made possible due to the efforts of researchers and manufacturers of this institute. An overview of the produced vaccine by this institute is presented as follows:

Smallpox vaccine: The inoculation emerged in Iran sixteen years after the discovery by Edward Jenner (1704-1882). In 1855, Mohammad Ali Mirza Dowlatshah (1824-1858), the governor of Kermanshah and the eldest son of Fath-Ali Shah Qajar, the second king of Qajar, inoculated 25 princes in Kermanshah, and then in Tehran, Hamedan, Kashan, Isfahan, and Jolfa following Jenner method in both arms. The inoculation became obligatory for all people by the Chief Minister, Amir Kabir (1807-1852) in early 1888. The preparation of the inoculum from calf became common in line with the establishment of the Pasteur Institute in Iran in 1920 (8). Before establishment of the Pasteur Institute of Iran, the physicians took the inoculum from those with smallpox and

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injected it into children. Approximately, 80% of these children were immune against smallpox for their entire life (5).

Dr. Joseph Mésnard, the first Director of the Pasteur Institute of Iran, imported the smallpox inoculation from Paris to Iran due to the insistence of the Health Assembly (the Ministry of Health) in April 1922, and sought to produce inoculation by a scientific method and make it available for all. In June 1929, an obligatory vaccination bill was introduced to the parliament and the abandonment of inoculation was punishable after its approval. The Health Assembly established places for free inoculation in Tehran and it was carried out at schools and many cities of Iran until the end of the Qajar period. After the establishment of the Pasteur Institute of Iran, the inocula were made through modern methods and inoculation was done by new procedures in Tehran (5). Dr. Mésnard's first work with his Iranian counterparts in Iran was the provision of modern calf inoculum that was very effective and useful. The smallpox vaccine was the same as old inoculum applied on skin, and it was injected by a pen-like instrument with a wooden handle and metal point (5, 9) .

In 1936, the Pasteur Institute of Iran produced 4-5 million doses of the inoculum; however, after the end of World War II in 1947, it annually produced 50 million dried smallpox inocula that were more expensive and resistant (10). In June 1941, a program was approved for the prevention of communicable diseases by mandatory inoculations at 2 months and 7, 13 and 21 years of age. In 1953, the Iranian parliament passed the Vaccination Act and the Ministry of Health managed the public vaccination program (11). With the launch of the National Committee of the Rapid Response for the eradication of smallpox in 1953, 120 healthcare groups traveled to every region of Iran by Jeeps. Two years later, this model was also implemented in neighboring countries by the World Health Organization (WHO) (12). With produced vaccines by the Pasteur Institute of Iran, smallpox was controlled throughout Iran (10). Besides, tourists from around the globe were vaccinated against the disease at the Institute. In 1956, Dr. Biuk Seyyedian, the head of the Smallpox Department, went to England and learned the method of improving the production of the inoculum from Lister Institute of Preventive Medicine (5).

In 1970, more than 35 million doses of the inoculum were produced at the Pasteur Institute of Iran. The basic plan for fighting against smallpox in Iran began from 1955 and continued until 1964. The number of people with smallpox and its resulting deaths decreased almost every year (13). In November 1978, the Ministry of Health reported smallpox eradication in Iran to the Smallpox Eradication Unit of WHO in Geneva (11). By eradication of smallpox from Iran, the production of its vaccine was stopped at the Pasteur Institute of Iran (10).

Cholera Vaccine: In the first 50 years of the establishment of the Pasteur Institute of Iran, the cholera epidemic occurred in Iran at least five times; hence, the Pasteur Institute provided a large amount of anti-cholera inoculum (5). According to the conducted experiments by the Pasteur Institute of Iran, it was found that water in some aqueducts of Tehran was infected with cholera microbe. For the prevention of cholera epidemic in Tehran, the Institute provided the mineral water of Tehran's springs in closed containers and also disinfected drinking water in Tehran (10, 14).

During the cholera outbreaks in Iran and the eastern neighboring countries, approximately 400,000 doses of cholera vaccine were prepared in the Pasteur Institute of Iran every day, and about 24 million doses of cholera vaccine were produced during a limited time (14). After the establishment of the Pasteur Institute in Iran, the cholera outbreaks occurred in Iran in 1922-1923 and 1927. During the cholera epidemic in 1927 and due to the high demand of the country for cholera vaccine and the lack of sufficient production by the Pasteur Institute of Iran, a part of the necessary vaccine was purchased from Germany and transferred by plane to Iran, and then the vaccination was done at the Iran-Iraq border. The cholera epidemic reappeared in 1938-1939. At this time, the Office of Health (Ministry of Health) developed a list of vaccination instruments for the development of vaccine production of the Pasteur Institute of Iran to meet its needs in facing communicable diseases, and purchased the listed equipment from Germany. On the other hand, it increased the number of employees at Pasteur Institute of Iran, so that the staff would work day and night and produce vaccines as much as possible. The Pasteur Institute managed to produce about seven to ten thousand doses of vaccine per day and delivered them to the Health Office.

The Pasteur Institute of Iran produced 5.9 million doses of cholera vaccine for Afghanistan and Pakistan in 1960 during the outbreak of cholera. During this year, countries like India, Iraq, Georgia, and Azerbaijan also demanded the cholera vaccine from Iran. In 1955, when Cholera O1 El Tor became widespread in Iran, the Pasteur Institute of Iran and Razi Vaccine and Serum Research Institute provided millions of anti-cholera inoculum units for the Ministry of Health (8). In 1970, the amount of produced cholera vaccine was 23 million doses in the Pasteur Institute of Iran; among them, 15 million doses were provided for the Ministry of Health, and 28 million doses of anti-cholera inoculum was sent to Eastern Pakistan, Turkey, Saudi Arabia and Ethiopia. Therefore, the Pasteur Institute played a key role in controlling cholera epidemics in the region (Fig. 5).

Fig. 5. The Pasteur Institute of Iran, September 1965; Members of the Consultative Assembly on cholera;
Top- row from right to left: Dr. Marcel Baltazard, Dr. Ali Mashhoon (microbiologist), Dr. Azizollah Sabeti (Head of Cholera Vaccine Department), Dr. Rasoul Pouranki (Virologist), Prof. Lapi sonny, Dr. Biuk Seyyedian; Bottom-row from right to left: Dr. Manouchehr Shahgoli (Minister of Health), Dr. Marcolino Gomes Candau (Director-General of the WHO), Dr. Mehdi Ghodssi (Head of the BCG Vaccine Department), Dr. Abdul Hussein Taba (The Iranian Regional Director of the Eastern Mediterranean Office of WHO (5)

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The Pasteur Institute of Iran under the supervision of Dr. Mansour Shamsa as an epidemiologist consultant, participated in the smallpox eradication program in Pakistan in 1971, and the eradication of smallpox in Syria in 1976. Dr. Shamsa was a member of the project team led by the WHO with experts from various countries to eradicate smallpox. Due to ongoing efforts of this team and management of WHO, the smallpox was finally eradicated in the world; and it was undoubtedly a great scientific and health achievement of mankind (15).

BCG vaccine: The letters "C and G" are the abbreviations of the surnames of two French physicians and veterinarians, Alber Calmette (1863-1933) and Camille Guérin (1872-1961) among the Pasteur Institute of Paris researchers who invented the human tuberculosis vaccine, known as Bacillus Calmette–Guérin or BCG. This inoculum consists of a live attenuated bacillus of bovine tuberculosis. It was done during the World War I when the Pasteur Institute of Paris stored the main and reliable strain of BCG in its tuberculosis department and granted it to all vaccine-making institutes, especially the members of Pasteur Institutes international network (8). After the end of the World War II in 1946, during Dr. Marcel Baltazard directorship of the Pasteur Institute of Iran, and after the visit of several scientists from the Pasteur Institute of Paris for technical and scientific cooperation with Iran, it was decided to establish the BCG vaccine-manufacturing department in Iran. The first strain of BCG was delivered to Iran in the spring of 1947 by Dr. Georges Blanc, the director and founder of the Pasteur Institute of Casablanca (Morocco) who was also the discoverer of anti-typhus vaccine. Dr Mehdi Ghodssi, the director of the Department of Rabies in Pasteur Institute of Iran at that time, managed to produce a high quality vaccine in a small laboratory with minimum facilities (16). The first anti-tuberculosis vaccine was prepared in October, 1947, and was first used as a lyophilized ampoule by experts of the Pasteur Institute of Iran for the vaccination of a number of infants in the municipality of Tehran. The use of this vaccine, which was unique for the Pasteur Institute in the early years, gradually expanded to health centers of Tehran and other health centers in Iran (9). BCG inoculum had been carefully prepared according to all scientific and technical principles by Dr. Mehdi Ghodssi and Dr. Mahdokht Pourmansour for many years (8). The first produced BCG vaccine was as 2-ml lyophilized vials and was provided to health centers by a cold chain. It was inoculated by an intradermal method on infants' arms after dissolving it in a solvent made by the Pasteur Institute of Iran. After their vaccination, the children were immunized two more times (7) (Fig. 6). This vaccine production project was supported by WHO (9).

The Pasteur Institute of Paris was re-visited in 1950 to reconsider the production of this vaccine and the vaccination was done by venous scratch until 1952 and then by intravenous injection from 1953. The BCG Department of Pasteur Institute of Iran was inaugurated with an area of 4800 square meters in Karaj Research-Manufacturing Complex in 1988. The average annual production of BCG vaccine was 3 million units in the past and the liquid vaccine was used until 1976. Then, the lyophilized vaccine was prepared with the provision of appropriate equipment and location. The durability of lyophilized vaccine is much higher and it is more resistant compared to the liquid vaccine under undesired thermal and environmental conditions. In the late 2012, a new building was opened for BCG vaccine production at the Pasteur Institute research-manufacturing complex according to the new standards and equipment, and it received a GMP certificate from the Ministry of Health in 2014. The current annual production rate of the vaccine is about 5 million doses of lyophilized doses and 50,000 vials of inter-vascular products per year. From 2006 to 2018, approximately more than fifty-five million vaccine doses were delivered to the health system.

Fig. 6. Implementation of the public BCG vaccination program based on the produced vaccine by the Pasteur Institute of Iran since 1947

Rabies vaccine: Rabies has been considered as a serious public health problem in Iran and in the world for centuries. During the lifetime of Louis Pasteur, rabid animal bitten patients from different countries were treated in Paris with the classic Pasteur vaccine for consecutive 21 days. The Pasteur vaccine was not a portable vaccine, and the patients had to go to the treatment center from wherever they were; however, a few years later, a vaccine was provided that could be transported in cold chain.

Dr. Abolghasem Bahrami, the vice-president of the Pasteur Institute of Iran, learned several methods of preparing a rabies vaccine at the Pasteur Institute of Paris for several months from Dr. Rene Legroux, the head of higher courses in the Pasteur Institute of Paris and the scientific manager of the Pasteur Institute of Iran. Afterwards, he returned to Iran and established the anti-rabies department in 1922 in collaboration with Dr Mésnard (5). Dr. Abolghasem Bahrami produced the rabies vaccine using Pasteur method and the vaccine was used for 14 years with certain restrictions. There are no documented figures and statistics about the treatment of rabid animal bitten patients during this period. Preparing the vaccine following this method had many problems and the vaccine did not play a key role in preventing rabies. The preparations for producing vaccine including the inoculation of rabies virus into rabbit brain and extraction of inoculated spinal cord of rabbits after several days and placing spinal cord pieces in sterilized glycerin were carried out by the Iranian scientists. Dr. Joseph Kerandel, the director of the Pasteur Institute of Iran, rubbed parts of the spinal cord at the bottom of the crystalline glass with a crystalline rod and then added physiological salt water and inoculated it under the skin of rabid animal bitten individuals and the procedure continued for up to 21 days.

Finally, the Italian scientist, Dr. Fermi presented his famous phenol vaccine in 1908. The most important work of Dr. Rene Legroux for the Pasteur Institute of Iran was substituting the classic Pasteur treatment (Neural tissue rabies

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vaccine) by Fermi's cell vaccine method. In 1936, Prof. Pierre Lépine, the head of the Department of Virology at the Pasteur Institute of Paris and a consultant in the Pasteur Institute of Iran, chose the anti-rabies vaccine, which was produced by Fermi's method, for Iran to develop a rabies vaccine. The necessary instruments for this vaccine were imported from Paris to Iran by Prof. Legroux in 1936 in collaboration with the late Dr. Sadegh Moghaddam, the head of Department of Chemistry of the Pasteur Institute of Iran, and Dr. Mehdi Ghodssi. Eventually, they produced the Fermi's vaccine with the help of Dr. Moghaddam and Dr. Ghodssi, and kept it in a refrigerator at 4°C. The expiration date of the produced vaccines was two months (5). The new vaccine was also used in Iran for ten years. In 1946, due to the risks of the Fermi's vaccine, Dr. Ghodssi produced a sample rabies vaccine free of live virus. Problems of the preparation and use of the Fermi's vaccine were described by Dr. Azizollah Sabeti, who had treated rabid animal bitten patients in Pasteur Institute of Iran for about thirty years (17). The patrons of the Pasteur Institute of Iran for injection of vaccine reached from 66 people in 1936 to 460 ones in 1946 (8).

The Pasteur institute of Iran research teams, who were observing the conditions of rabid animal bitten people for many years, explained shortcomings of their treatment through the existing methods in some papers. According to these articles, more than 25% of the patients with rabies treated by Fermi's method died, and if the bites were serious and deep on the head and the face, the mortality rate would be 40-50% (18, 19). By publishing these figures and referring to observations of the Iranian scientists at WHO, they sought to improve the treatment of rabies and requested the assistance of scientists from the Pasteur Institute of Iran. The WHO Committee of Experts sought to use anti-rabies immunization serum. To this end, a special anti-rabies serum was sent to the Pasteur Institute of Iran by Dr. Hilary Koprowski, a Polish-American scientist, in 1947 to be used for individuals bitten by rabid wolves. The serum, which was inadequate and expensive, was later substituted with a horse serum (7).

Iranian scientists at the Pasteur Institute of Iran were waiting for the opportunity to perform the combined treatment of the serum and the vaccine. This historic trial was another milestone in saving people bitten by rabid animals in the world. At a summer night in 1954, a rabid wolf shocked farmers of Sahneh Village in Kermanshah and wounded 29 people. They were transferred to Pasteur Institute of Iran in Tehran. Dr. Marcel Baltazard, along with Dr. Mirshamsi and other staff in the Department of Rabies, carried out the first aid and scheduled their special recommended treatments with the serum and vaccine. Among them, 9 had multiple and deep wounds on their faces and heads. Previous observations indicated that about 50% of the rabid animal bitten victims would suffer from rabies and die despite being treated with a single vaccine. A group consisted of 24 patients received either one or two anti-rabies serum injections along with the classic treatment with the vaccine alone. Only 1 out of 24 patients treated with the proposed method of combination of serum and vaccine but 3 out of 5 patients treated with vaccine alone got rabies and died. This promising treatment method was soon approved by WHO. Since then, the treatment of both vaccine and serum has been followed in Iran in all rabies treatment centers (8, 18).

The Pasteur Institute of Iran with the assistance of Razi Institute, led by Dr. Mahmoud Bahmanyar and Dr. Hossein Mirshamsi, provided anti-rabies serum from mules and horses, and treated rabid animal bitten patients while their product had better quality and less side-effects than the European and American sera (10, 20). Anti-rabies serum prepared with horse and mule plasma was used for prevention of rabies for many years till it was replaced with the human anti-rabies immunoglobulin. Under the agreement between the Pasteur Institute of Iran and the Iranian Blood Transfusion Organization, they both provided anti-rabies gamma globulin from volunteers for years (8). After the preparation of anti-rabies vaccine in human diploid cells, several tests of its immunization were performed on healthy volunteers. Dr. Bahmanyar from Iran accompanied by researchers from other countries reported good and harmless effects of the new vaccine in a conference at Mérieux Institute in Lyon in 1972 (8). The trials of anti-rabies vaccine, prepared in human diploid cells were performed in Iran and Germany, almost simultaneously and the immunization level of the produced vaccine by this method was reported satisfactory by the Pasteur Institute of Iran (21).The outstanding and interesting results of the new method of anti-rabies treatment were welcomed by WHO and all other countries. Most of the side-effects and complications of using the rabies vaccine have been eliminated or had reached to their lowest levels. For instance, the more or less severe paralysis effects, which were followed by the use of anti-rabies vaccines with bone marrow tissue, were not seen when the vaccine prepared by diploid cells were used. Unlike the neural tissue rabies vaccine, a small amount of cell vaccine was injected under the arm skin. The cell vaccine injection did not result in any local reaction, fever and pain (5). After studies at the Pasteur Institute of Paris, Dr. Mahmoud Bahmanyar produced a new rabies vaccine (BPL) that replaced the cellular vaccines (10).

From 1968, when the treatment centers were established in twelve regions of Iran and the serum and vaccine were distributed among the centers, the patients were treated as soon as possible by the rabies treatment centers. The production of rabies vaccine for animals was initiated by the Pasteur Institute of Iran since 1979. The vaccine was originally prepared using brain tissues by Pasteur method based on the international standards. Since the early 2011, the manufacturing method has focused on provision of rabies vaccine based on the cell culture in the bioreactor. The vaccine is produced based on the culturing a fixed cell-accustomed rabies virus on BHK cells (kidney of baby hamster). The rabies vaccine sector provides its necessary amount of rabies vaccine based on an inquiry from Iran Veterinary Organization. The production of necessary human rabies vaccine has been impressively started by researchers of Pasteur Institute of Iran since 2016 and it is expected to enter the market by 2021.

Gonorrhea vaccine: Dr. Hossein Mashouf, a leading researcher of the Pasteur Institute in Iran, produced a gonorrhea auto-vaccine in 1926, and his vaccine was useful for the treatment of gonorrhea and its complications.

Anti-Typhus Vaccine: In 1937, Dr. Mehdi Ghodssi went to the Pasteur Institute of Casablanca in Morocco (under the supervision of Dr. Georges Blanc) and conducted studies on anti-typhus vaccine and brought the required strain and then produced it in Iran.

Animal Anthrax Vaccine: The Pasteur Institute of Iran had human, animal, plant and industrial bacteriology sectors during its establishment. The animal bacteriology sector produced anthrax vaccine and provided it for the veterinarians throughout the country (5).

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Typhoid Vaccine: The Departments of Inactivated Vaccines and Microbiology of the Pasteur Institute of Iran started producing a classical typhoid vaccine since the first years of its establishment (5, 10). Research groups of the Pasteur Institute of Iran also participated in the general vaccination against typhoid in Iran. Native microbes were combined with anti-typhoid vaccine and provided the anti-typhoid vaccine for the health system of Iran (5). In the past, there was only one type of inactivated anti-typhoid vaccine. Despite the fact that inactivated anti-typhoid vaccines were widely used, they did not show adequate immunization (8). The inactivated vaccine was re-injected every three years, and often showed local reactions (8, 10, 22).

Recombinant Hepatitis B Vaccine: In the 1990s, the contract for the transfer of recombinant hepatitis vaccine technology was signed with Cuba, and thus the experts were sent to this country for trainings. The transfer of technology for the production of hepatitis B vaccine was completed in 2008. In 2009, the hepatitis B vaccine production unit was launched at the research–manufacturing complex of the Pasteur Institute where it is still being produced. The active matter of hepatitis B vaccine is produced using recombinant genetic engineering techniques. This department received a GMP certificate from the Ministry of Health in 2012. In 2013; Iran became independent in producing hepatitis B vaccine. The vaccine production capacity is now more than ten million doses per year and it is delivered to the health system according to the announced program of the Ministry of Health. From 2006 to 2018, approximately five million vials of ten-dose infant vials (equivalent to 50 million doses) of the vaccine were produced. The public vaccination against hepatitis B is the most effective way to prevent the infection and it has been routinely done for the infants and high-risk groups in Iran since 1992. The coverage of this vaccine reached from 62% in 1993 to 94% in 2005 in Iran (23). This coverage reached 99% in 2017.

Pneumococcal and Rotavirus Vaccines: In 2019, and after the allocation of 100 million US Dollars from the National Development Fund to Pasteur Institute of Iran for the production of these two strategic vaccines, the development of the necessary structure and infrastructures of these two important vaccines started in the complex. With this budget, conjugated pneumococcal vaccine and rotavirus vaccine will be produced at the Pasteur Institute of Iran to be introduced to the national immunization program. It is worth mentioning that pneumonia is a dangerous disease accounting for 7% of global mortality and about 20% of children death under the age of 5 in the world. A pneumococcal vaccine is applicable against Streptococcus pneumoniae. Normally, three or four doses of the vaccine create the body immunization of about 70-90%; hence, it is recommended by WHO as a child-immunization program in all countries. It is now a fixed part of the vaccination program for children in many developed countries, and is used in more than 70% of countries worldwide. In Iran, pneumonia is the most common cause of referral of patients with respiratory infections to the treatment centers. By transferring the conjugated pneumococcal vaccine technology, Iran will have the necessary infrastructure and will be able to produce other polysaccharide vaccines such as different types of the meningitis vaccine. In its first four years of rotavirus vaccination as a part of the United States vaccination program, it reduced 176,000 cases of hospitalization, 242,000 emergency visits, and 1.1 million outpatient visits to pediatricians for the

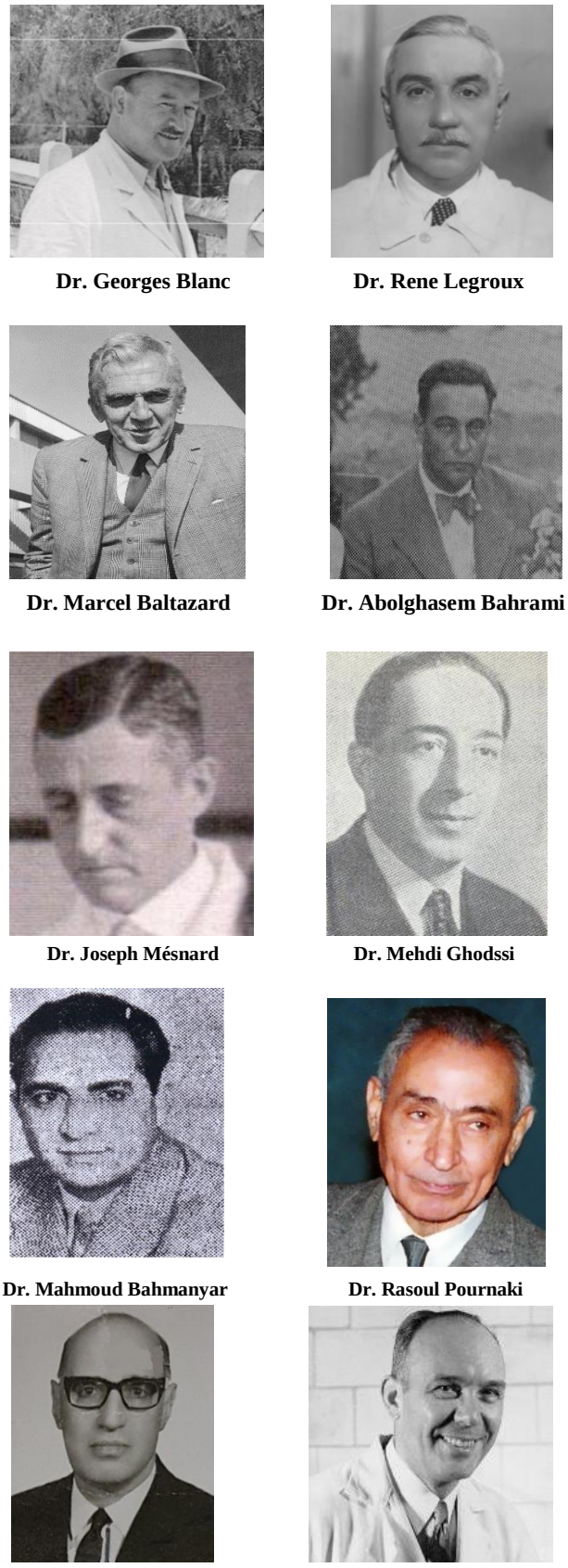

Fig. 7. Some of the researchers who played major roles in launching and developing vaccine production in the first 50 years of the establishment of Pasteur Institute of Iran

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children under the age of five, leading to one billion US Dollars saving of the health system (24).

For Iran, where the vaccination is considered a state-owned affair, investments to gain technical knowledge and vaccine production lines have value-added benefits. Therefore, the Pasteur Institute of Iran has developed its production lines for the production of these vaccines. Researchers at the Pasteur Institute of Iran now are delivering services in various fields of diagnostic, educational, research and production to accomplish their missions by producing necessary vaccines with the aim of achieving self-sufficiency in this field, regionally and internationally.

Vaccine Production After the Iranian Revolution

Great steps have been taken toward the development of a primary health care service network after the Iranian Revolution in 1979 when the maximum coverage of children immunization was 30%. Since 1984, efforts have been made to strengthen the children immunization despite the limited domestic production of vaccines. The immunization development program officially began as an essential component of a primary healthcare services since 1985. The immunization coverage of children under 1 year of age were more than 90% and 95% in 1990 and 1996, respectively (25). Due to achieving such coverage of over 95%, a significant reduction in the number of infectious diseases that cause high mortality rates among children in Iran has been obtained in the past decades.While the mortality rate of children under five years of age was 154 per thousand live-births in 1978; it has been dropped to approximately 20 per 1,000 live-births in 2010 and 16 per 1,000 live-births in 2016 (26, 27).

Razi Vaccine and Serum Research Institute is another important vaccination institute in Iran. The bill for the establishment of this institute was approved by the National Consultative Assembly in 1924. This institute produces about 40% of poultry vaccines, 90% of livestock vaccines and 80% of compulsory human vaccines in Iran. Human vaccines are being produced at the Razi Institute against diseases such as polio, diphtheria, tetanus, pertussis, measles, rubella, and mumps as well as various anti-scorpion and snake poison vaccines. In addition, bacterial livestock vaccines against brucellosis, black leg, horse tetanus, infectious gangrene, anthrax, foot-and-mouth disease, goat pox, sheep pox, bovine theileriosis, poultry pasteurellosis, infectious bursal disease (IBD), fowl pox, influenza (H9N2), infectious bronchitis of strains H-120 and H-52, Infectious laryngotracheitis, and virulent Newcastle disease are also produced by the Razi Institute.

The Pasteur Institute of Iran and Razi Vaccine and Serum Research Institute are significantly important health infrastructures in Iran and still function as two major research and manufacturing institutes with almost 100 years of experience. They have played important roles in self-sufficiency of Iran in terms of production of the most required vaccines and sera.

CONCLUSION

Vaccination can prevent the spread of infectious diseases. Vaccine-preventable diseases were controlled in Iran by the approval of the Public Vaccination Law in the National Consultative Assembly in 1953. Since the past 100 years, the Pasteur Institute of Iran has been able to control various infectious diseases including smallpox, cholera, rabies, hepatitis B and BCG by producing numerous vaccines and effective health interventions, and it has also produced other vaccines such as typhoid, anthrax, gonorrhea, and typhus. Moreover, it has planned to produce pneumococcal and rotavirus vaccines in the near future. It is hoped that this institute continue to play important roles in the field of infectious diseases as an effective research and production center at the national and international levels in the second century of its mission.

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CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

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