J Med Microbiol Infec Dis, 2014, 2 (1): 1-10

Review Article

Rabies in Iran: Past, Present and Future

***Alireza Gholami[1], Ahmad Fayaz[2], Firouzeh Farahtaj[1]**

[1] WHO collaborating center for reference and research on rabies, Pasteur Institute of Iran, Tehran, Iran;
[2] WHO expert and consultant on rabies, Pasteur Institute of Iran, Tehran, Iran

Received Oct 08, 2013; accepted Dec 5, 2013

Rabies is a disease that has been known since antiquity. It is a highly fatal acute disease of the central nervous system caused by a lyssavirus. Prior to the discovery of the rabies vaccine, rabies-infected individuals fell victim to the delusions and superstitions associated with this disease. Though it has been neglected in many regions of the world, rabies remains one of the most feared diseases in many developing countries, where it takes the majority of its victims. The virus circulates mainly in domestic and wild carnivores, taking 60,000 human lives worldwide every year and inflicting significant financial damage. It can, however, be well controlled due to the availability of effective Post-Exposure Prophylaxis (PEP) protocols. Pasteur Institute of Iran has had a significant role in the establishment of current PEP protocols in the world. In spite of the availability of effective PEP protocols, preventive vaccination would be preferable in endemic regions. Annually, a considerable number of exposures to animal bites occur in Iran. The current situation in the country is well-controlled by virtue of a robust surveillance system and efficient PEP treatments, resulting in considerably low death incidences from rabies. High quality vaccines recommended by the World Health Organization (WHO) are expensive and unaffordable in developing countries, where the need for rabies vaccination is greatest. Therefore, there is an increasing need to develop new cost-effective and efficient vaccines requiring fewer injections and providing longer-lasting immunity. *J Med Microbiol Infec Dis, 2014, 2 (1): 1-10.*

Keywords: Rabies, Epidemiology, Vaccination, Prophylaxis.

RABIES HISTORICAL OVERVIEW

The recorded history of rabies goes back to 2300 BC, when a dog owner in ancient Babylon was charged for a death caused by a dog bite. Ancient Greek philosophers such as Democritus, Aristotle and Celsus as well as the prominent physician Galen, had warned people of the dangers associated with the bite of a mad dog, showing that the infectivity of the animal was suspected some 2000 years ago. However, a clear explanation for the mode of disease transmission was not provided until the first century AD, when the Roman writer Cardanus speculated saliva to be the carrier of the infectious agent. Most people during that era, blamed supernatural forces for the unexpected diseases afflicting both animals and men. Similar beliefs still exist in many regions of the world and create major public health obstacles in the way of providing adequate and prompt protection to exposed individuals [1].

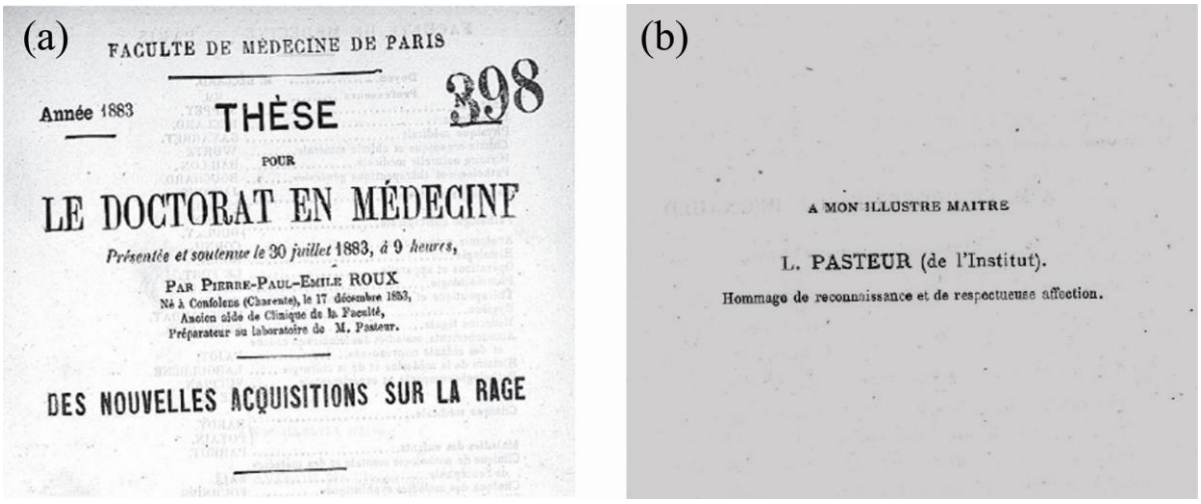
The first step towards a proper scientific understanding of rabies was taken in 1804 by Georg Gottfried Zinke, who experimentally demonstrated the infectivity of rabid dog saliva by inoculating a healthy dog with the suspected saliva [2]. A few decades later, the French scientist Viktor Galtier showed that rabbits could serve as suitable laboratory animals for both diagnosis and study of rabies [3]. At the same time in Paris, Pierre Paul Émile Roux, an apprentice of Louis Pasteur, demonstrated that the infective agent resides in the nervous tissue of the rabid animal. Those findings were followed by his outstanding breakthrough of intracerebral transmission of rabies from rabid to healthy animals.

He presented his results in his medicine thesis entitled "*New achievements on rabies*" (Figure 1) [4]. His works on rabies were principally based on Louis Pasteur's discoveries. Therefore, in 1884, his findings combined with those of Pasteur and his colleagues resulted in their first publication entitled "*New communication on rabies*" discussing different tissues during rabies infection [5]. The behaviour of the disease's specific agent was studied by Pasteur in more detail. He succeeded in maintaining the infective agent in the brain of laboratory rabbits by serial passages [6]. However, continuous efforts by Pasteur and colleagues to visualize the causative agent of rabies or to propagate it in artificial media remained unsuccessful. They came to the conclusion that the agent was not bacterial and called it 'Virus', meaning poison in Latin. The hypothesis was confirmed at the beginning of the twentieth century by Dr. Paul Ambroise Remlinger, a Pasteurian scientist working in Turkey, who demonstrated the ability of the infective agent to pass through a Berkfeld filter [7].

***Correspondence:** Alireza Gholami
WHO collaborating center for reference and research on rabies, Pasteur Institute of Iran, No. 69, Pasteur Ave, Tehran, Iran, 1316943551.
Email: agholami@pasteur.ac.ir

Tel: +9821 66403496 **Fax:** +9821 66480777

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]


(a)

FACULTE DE MÉDECINE DE PARIS

Année 1883

THÈSE

298

POUR

LE DOCTORAT EN MÉDECINE

Présentée et soutenue le 30 *juillet* 1883, *à* 9 *heures*,

PAR PIERRE-PAUL-EMILE ROUX

Né à Confolens (Charente), le 17 décembre 1853,
Ancien aide de Clinique de la Faculté,
Préparateur au laboratoire de M. Pasteur.

DES NOUVELLES ACQUISITIONS SUR LA RAGE

(b)

A MON ILLUSTRE MAITRE

L. PASTEUR (de l'Institut).

Hommage de reconnaissance et de respectueuse affection.

Fig. 1. (a) First pages of the thesis redacted and presented by Emile Roux in 1883, which was completed at Louis Pasteur's laboratory and under his supervision. In this thesis, he demonstrates great achievements on rabies research. (b) In the first page, he expresses his gratitude to his mentor Louis Pasteur: "TO MY ESTEEMED MASTER, L. PASTEUR (from the Institute). Tribute of gratitude and respectful affection"

COMMENCEMENT OF PASTEUR INSTITUTE OF IRAN AND RABIES RESEARCH

In November 14, 1888, Louis Pasteur inaugurated his institute in Paris, funded through international financial support. Thus, he was able to continue his work on developing a rabies vaccine as well as studying other infectious diseases and sharing his experiences. Since its inception, the Pasteur Institute of Paris declared an international mission. The Institute gathered a number of scientists to form five main research departments. One of those departments was headed by the physician and microbiologist Emile Roux. In 1900, Roux built the "Pasteur Hospital" to support investigations on rabies and other infectious diseases. A few years later, he was appointed as Louis Pasteur's successor. By that time, Pasteur Institutes had been established in a number of countries [8]. In October 1919, Roux received, at the Pasteur Institute of Paris, Iranian delegates seeking to establish medical and scientific collaborations with France. With the prospect of scientific support from the French counterpart, in January 1920 Roux appointed Joseph Mesnard as the first director of the Iranian Pasteur Institute in Tehran. Mesnard established a laboratory, on temporary premises, to perform the essential public health studies and developed Jennerian anthrax vaccine and serum. In 1924, Mesnard established Pasteur Institute of Iran in Tehran using land and funds donated by Prince Farman-Farma. However, constant difficulties due to political instability in Iran forced him to return to France and to give up the rest of his plans [9]. In 1946, the French physician and epidemiologist, Marcel Baltazard was appointed as the third director of Pasteur Institute of Iran, succeeding the late Joseph Kérandel, the second director of Pasteur Institute of Iran. Baltazard performed extensive remodelling of the architecture, as well as, the scientific structure of the institute. He also organized national vaccination campaigns against smallpox and tuberculosis and established collaborations with research institutes in France, America and Russia [10].

Through his close collaborations with Iranian scientists, especially Dr. Mehdi Ghodssi and Dr. Mahmoud Bahmanyar, remarkable achievements in Post-exposure Prophylaxis (PEP) of rabies were made. Ghodssi was a young scientist and a friend of Baltazard from George Blanc's laboratory in Casablanca (Figure 2). He had meticulously studied rabies and obtained valuable data on immunization protocols and PEP. Immunization protocols had not been significantly modified since Louis Pasteur's time.

Louis Pasteur had attenuated the virus, for vaccine application, using two methods: one was to transmit the disease from dogs to a series of rabbits by intramuscular transmission; the virus then remained attenuated when it was inoculated back into dogs, another method used air dry sections of rabid rabbit spinal cord, which resulted in a gradual diminution of the sample's virulence through time. Thus, Pasteur succeeded in developing a vaccine, which for the first time successfully immunized and protected 50 dogs against rabies [11]. The vaccine was also applied for rabies PEP. Two years after the establishment of the Iranian Pasteur Institute, an anti-rabies vaccination service was introduced by Mesnard to provide rabies vaccine derived from dried rabbit spinal cord. On his arrival, Baltazard noted that Ghodssi with the encouragement of Professor Legroux, was publishing the results of his studies on rabies PEP, and that research on rabies was a priority at Pasteur Institute of Iran; related facilities at the institute were being improved, stables and buildings dedicated to studying dog rabies were under construction, and nerve tissue vaccine against rabies was being produced. The rabbit nerve tissue vaccine (Pereira de Silva) was replaced by a sheep brain vaccine (Semple) in 1946. Throughout his research, Ghodssi had realised that current PEP was not very effective. In 1947, he published an article entitled "*Ten years of rabies treatment at Pasteur Institute of Iran*" in which he demonstrated the ineffectiveness of existing rabies PEP regimen.

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

Fig. 2. Baltazard (left) the director of Pasteur Institute of Iran (PII) and Ghodssi (right) head of rabies unit Year 1950 in Iran. They had significant contributions in development of the application of anti-serum therapy for rabies PEP. Ghodssi later became the director of PII. (Photo courtesy of Dr. Eskandar Omidinia, Public Relations and International Affairs, PII).

His studies indicated that rabid wolf attacks, a serious problem in a number of geographically distinct regions in Iran, resulted in the highest fatality rate [12]. Contemporarily, scientists were evaluating the application of anti-serum therapy for rabies PEP, as in this particular infection, the exact time and location of the infectious agent entry could be very important. Therefore, in the United States, where rabies would also remain a severe problem, researchers were optimising the production of anti-rabies serum [13]. Several other reports, beginning with that of Babès and lepp in 1889, also supported the advantages of anti-serum therapy of infectious diseases [14]. In 1950, the first meeting of the World Health Organization (WHO) Expert Committee on rabies was held in Geneva. Baltazard was a member of the committee and different aspects of serum therapy against rabies were thoroughly discussed during the meeting. Following extensive debates on the issue, given the level of expertise and the frequency of wolf attacks in Iran, Pasteur Institute of Iran was assigned to re-evaluate the serum therapy against rabies. The competent secretary of the committee, Dr. MM Kaplan, followed the trial's progress, collating the data and communicating it to the committee [15]. The awaited opportunity happened on August 22, 1954, when a large wolf entered Sahneh, a village in the West of Iran, 500 km from Tehran, and attacked 29 people. In that incident, 19 people sustained craniofacial injuries, some with serious skull fractures exposing brain tissue, whilst the 11 others had multiple bite wounds elsewhere in their bodies, including some deep lacerations. They were transferred to Pasteur Institute of Iran (figure 3) and divided into three groups.

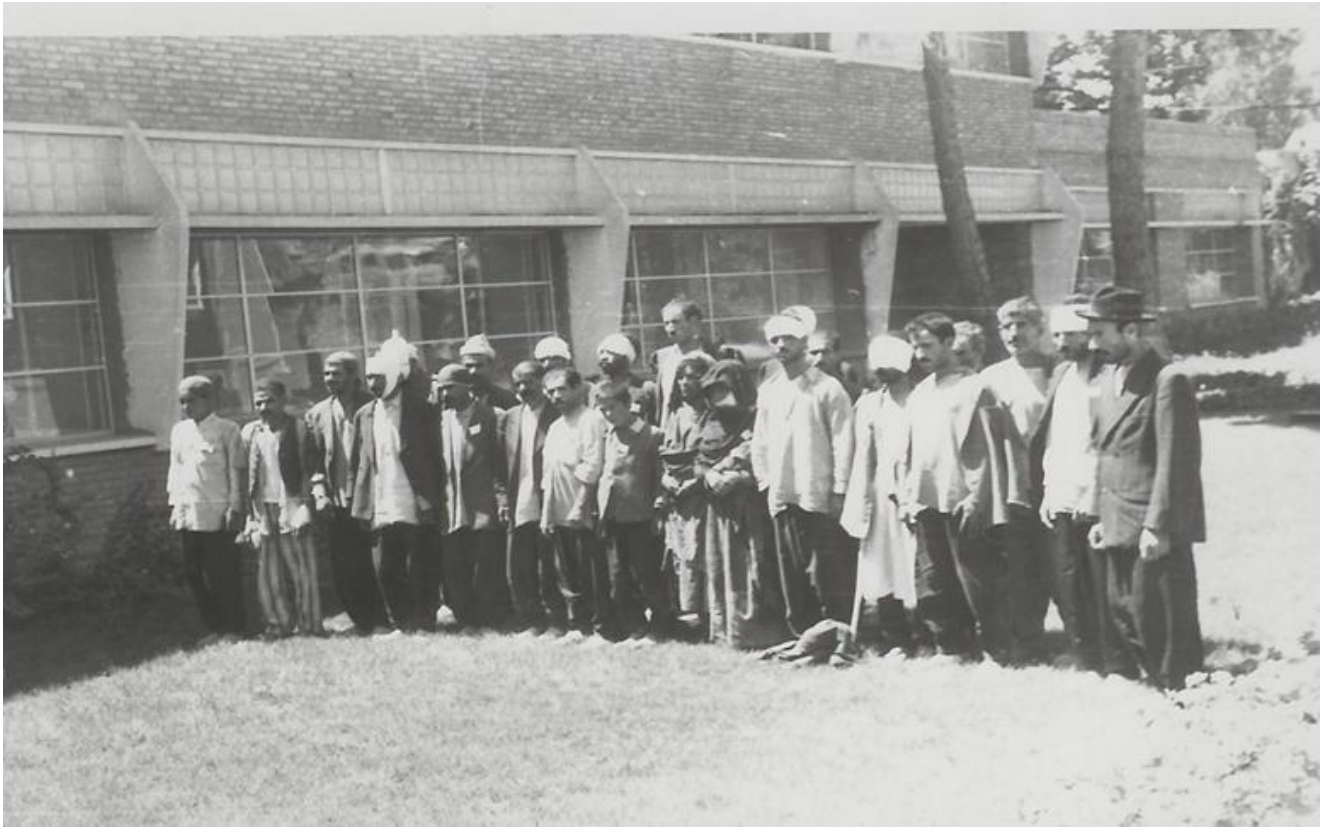


Fig. 3. Residents of Sahne County transferred to Pasteur Institute of Iran following attack by a rabid wolf.

The classic treatment with vaccine alone was applied to five patients with less serious bites. The other two groups received vaccine along with either one or two serum injections [16]. The treatment was conducted in strict accordance with the protocol, and blood samples were obtained from patients on the regular basis during the course of treatment and sent for laboratory analysis. Three out of five victims who had received classic treatment died

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

from rabies. Whereas, only one out of the 24 patients in the other two groups that had received vaccine plus serum developed rabies. These astonishing results clearly showed the impact of serum application on saving the lives of individuals exposed to rabies and were published in the next bulletin of the WHO [17]. In order to obtain a precise protocol for the application of anti-rabies serum and to determine the potency and schedule of the vaccine and serum to be applied, complementary studies were conducted in WHO collaborating laboratories [18, 19]. In conclusion, thanks to the significant contribution of the Pasteur Institute of Iran and the key role of Dr. Ghodssi in initiating this development, rabies PEP was globally revised [20].

For several decades, the rabies vaccine, developed by Louis Pasteur, did not change markedly. During 1950s, inoculation of the rabies virus into embryonated eggs, followed by virus adaptation in cell culture markedly improved the efficacy of the rabies vaccine. Later in that decade, the rabies vaccine was produced in a human diploid cell culture system. The vaccine was tested on volunteers at the Mérieux Institute in Lyon, France.

The results of that experiment were compelling enough for the Mérieux Institute to produce it in larger quantities. Impressed by the results obtained at the Mérieux Institute and discouraged by the classic vaccine, the Rabies department of the Pasteur Institute of Iran (designated as a WHO Collaborating Center in 1973 by virtue of its international services), agreed to design a PEP trial with the new vaccine. From June 1975 to January 1976, 45 individuals, severely bitten by rabid dogs and wolves, were successfully treated with the new vaccine [21]. The neutralizing antibodies, varying from 0.3 to 2.69 international units per millilitre of serum, were detected in 26 treated individuals even after 32 years [22].

THE IMPACT OF RABIES IN IRAN

The annual global number of human deaths resulting from rabies is estimated to be around 60,000, with more than four-fifths of deaths occurring in rural areas [23]. The most important factors affecting the cost of rabies control worldwide comprise human PEP and animal vaccination programs expenses. The majority of the disease burden is attributed to dog bites [24], and since the first meeting of the Rabies Expert Committee of the World Health Organization, the need for the prevention of rabies in humans and its control in dogs has been declared. The situation in Iran is somewhat different; human PEP following suspected bites has the major role in preventing fatalities and is the main direct annual cost for rabies control in the country. According to official reports, PEP application is increasing in Iran with an annual average of 125,000 exposed individuals receiving PEP between 2006 and 2011[25]. The absence of PEP application could prominently endanger the lives of at-risk individuals. On the other hand, the availability of PEP also depends on various associated factors such as vaccine and serum costs as well as the PEP regimen applied [26]. Rabies strikes many underprivileged regions of the world, where PEP–associated expenses are not covered.

Financial restraints in rural communities may force individuals to seek alternative inefficient treatments which may result in death in seclusion. Fortunately in Iran, in order to control the disease and restrain the number of rabies victims, the government covers 100% of the direct costs of rabies PEP, imposing no expenses to exposed individuals. Additionally, nearly 700 health centres in 31 provinces of the country (working 24 h, 7 d per week) are involved in rabies PEP application. Trained technical staff, joined together and managed by the Center for Disease Control of the Iranian Ministry of Health and Medical Education (MoH), are responsible for the rigorous treatment and follow up of exposed subjects. These health centres are connected through a network to the MoH and routinely submit relevant data to the Zoonosis Control Department of MoH. Under-reporting is believed to be the main reason behind improper estimation of the rabies burden. Moreover, since laboratory confirmation is not ubiquitously and easily available, some cases may be misdiagnosed and disregarded accordingly. To consolidate the rabies surveillance system of the MoH, the WHO Collaborating Centre for Reference and Research on Rabies at Pasteur Institute of Iran (WHOCC-PII) fulfils the laboratory confirmation of suspected samples. In order to assure the accuracy and precision of the relevant tests, this centre has adopted specified requirements for quality and competence of diagnostic laboratories, namely the ISO 15189 quality management system. Disease burden is a factor affecting prioritization for the allocation of health resources to employ intervening measures such as prevention, control and treatment.

Therefore, both incidence reports and laboratory data are crucial for decision makers to design their action plans against rabies accordingly [27, 28]. Although rabies is being monitored, managed and prevented in human subjects by PEP, it should also be controlled in animal reservoirs in order to eliminate the risk of rabies transmission to humans. Table 1 summarizes the rabies situation in a number of countries in the region.

These data insinuate that in Croatia and Serbia, good cooperation exists between human and veterinary departments and rabies is enzootic mainly in wildlife. The absence of human victims in those countries has resulted from effective human rabies control by PEP. In Iran and Turkey, rabies is enzootic in dog as well as in wildlife. The limited number of rabies victims and high relative number of PEP applications, indicates efficient involvement of human health departments in animal bite management. Other organizations also contribute to animal rabies management and control in Iran, such as Iranian Environmental Protection Organization, Iranian Veterinary Organization and municipalities. In Ukraine, Egypt and Georgia, on the other hand, rabies is frequent in dogs, cats and wildlife. In spite of good involvement of human health departments and high PEP number, relatively high incidence of human rabies is observed. Altogether, these data demonstrate that high PEP number is not sufficiently effective without mutual involvement of human and animal health sectors and multilateral preventive measures (Table 1). However, with implementation of new preventive

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

measures, the situation in Ukraine is ameliorating as the country has been obliged to apply strict regulations for rabies control in animals in order to eradicate human rabies.

Table 1. Factors highlighting the rabies situation and management in a number of countries are presented in the table. (Data courtesy of Dr. Firouzeh Farahtaj, WHOCC-PII).

	Croatia	Serbia	Iran	Turkey	Ukraine	Egypt	Georgia
Reservoir and vector *(vector only)*	Red fox *(dog, cat)*	Red fox *(dog, cat)*	Dog, wolf, fox, jackal	Dog, fox, jackal	Cat, dog, fox	Dog	Dog, cat, (*jackal, wolf*)
Human population (million)	4.6	7.3	74.2	72.6	45.7	78.9	4.4
Number of human rabies cases in 2009 (incidence per million)	0	0	2 (0.03)	2 (0.03)	6 (0.13)	80 (1.01)	6 (1.37)
Number of human rabies cases in 2000-2009	0	0	62	21	29	880	90
Number of PEP in 2009	1,750	1,609	130,531	162,000	21,000	~200,000	28,055
Incidence of PEP in 2009 per million people	380	220	1,759	2,233	460	~2,536	6,397

The Iranian Veterinary Organization (IVO), among other duties, has the responsibility for vaccination of owned dogs. According to the deputy of health and disease prevention at the IVO, there are approximately 900,000 owned dogs in the country, of which 400,000 are vaccinated annually. It is also noteworthy that the majority of exposures in Iran occur by owned dog bites. Accordingly, data from Iran shows that in almost 80% of cases, PEP is not being completed. In the vast majority of cases, PEP has been stopped on day 10, which indicates the certainty of the suspected animal's good health. This might need reassessment by the authorities as considerable vaccine quantities are being wasted this way (Figure 4). Obviously there are also stray dogs in different regions of the country that would increase the overall number of the dog population.

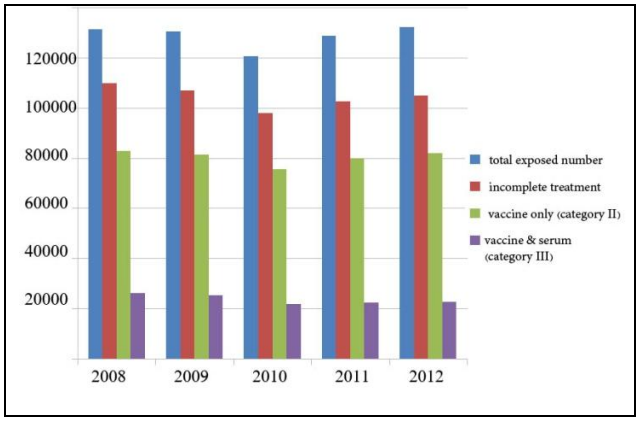


Fig. 4. Data on post-exposure prophylaxis (PEP) in Iran during 2008-2011. Incomplete PEPs are mainly due to exposure to healthy dogs and cats. Vertical and horizontal axes show number of individuals and years respectively.

The stray dog population is not easily controllable and is more prone to rabies infection and spread due to its free-ranging lifestyle. However, stray dog control and management is not included in the assignments of the IVO. According to WHO recommendations, at least 70% vaccination coverage is necessary in order to prevent canine rabies [29]. Euthanizing programs for stray dogs proved to be ineffective in some provinces since the remaining animals would repopulate the colony. Therefore, actual canine rabies control is not fully efficient and the overall results indicate annual increases in human PEP expenditure in Iran to restrain rabies victim numbers.

To eliminate canine and human rabies, it seems that broader measures such as controlling stray dog population turnover and encouraging more responsible pet ownership are needed in Iran [30].

THE RABIES AETIOLOGICAL AGENT

Rabies virus has a bullet-shaped structure, approximately 200-300 nm in length and 75 nm in diameter, with a helical ribonucleocapsid core. It belongs to the lyssavirus genus and the rhabdoviridae family. The ribonucleocapsid contains a 12 kb negative-sense single-stranded RNA genome encoding 5 viral proteins. Viral proteins play structural as well as functional roles during the virus lifecycle. The genetic material is tightly bound by viral proteins, mainly viral nucleoprotein (N), to protect it from cellular nucleases and avoid recognition by host pattern recognition receptors [31]. The large protein of the virus (L), together with the phosphoprotein (P) as its co-factor, form the RNA-dependant RNA polymerase complex [32]. Assembled rabies virions leave the host cell by budding through the host cell plasma membrane. Viral Glycoprotein (G) trimers form projections towards the extracellular surface of the lipid membrane [33]. Glycoprotein is the most important viral protein in raising virus-neutralizing antibodies and providing immune protection against rabies [34]. Viral Matrix protein forms a layer between the ribonucleocapsid and the inner portion of the glycoprotein. It also interacts with host regulatory proteins and plays roles in the regulation of cell death in the course of viral infection [35-37] as well as controlling the balance of transcription and replication of the genome [38]. Viral proteins interact with host proteins to take over control of cellular pathways in favour of viral propagation. Specific domain sequences in viral proteins are known to enable interaction with host proteins such as those involved in signalling [33, 34].

Lack of proof-reading in the viral RNA polymerase enzyme results in a high mutation rate in RNA viruses, increasing their genetic diversity which in turn, results in

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

greater adaptive potential and generates various phylogenetic lineages [39].

RABIES EPIDEMIOLOGY

Rabies infection results in more than 60,000 deaths annually. Rabies viruses spread amongst terrestrial and non-terrestrial mammals in various regions of the world causing 15-20 million exposures every year, which need administration of PEP. With the exception of a limited number of countries, members of the rabies viral family, are found in all five continents. The vast majority of human deaths occur in Asia and Africa. The incidence of rabies is estimated to be around 44% and 56% for Africa and Asia, respectively, with 30-50% of cases happening in children under 15 years of age [23]. More than 3.3 billion people across the world are at risk of acquiring this infection and in 99% of the cases, canine rabies is responsible for rabies transmission to human [24]. The global average rate of animal bites is 250 per 100,000 individuals, with an average number of rabies victims being 6.8 per million people. In Iran, exposure frequency of rabies is 180 cases per 100,000 individuals, whilst the incidence of rabies is less than 0.1 cases per million. This is due to competent surveillance and management of rabies in the country [40]. The domestic dog (Canis lupus familiaris) is responsible for nearly all cases of human rabies worldwide. Still, various other species of carnivore as well as bats can transmit rabies to humans [41]. Only a limited number of rabies cases appear in Southern and Central America and sporadic cases are reported in Europe and North America. From the epidemiological point of view, rabies is considered to have sylvatic and urban cycles. Sylvatic rabies is defined by geographic regions and the indigenous wild fauna that serve as reservoir hosts. Characteristics of reservoir hosts as well as natural barriers define the geographic distribution of rabies virus. Sylvatic rabies resides among wild animals hosting specific lyssavirus species. Example for those reservoirs are the mongoose (Cynictis penicillata) in South Africa, the polar fox (Alopex lagopus) in Alaska and north Canada, the red fox (Vulpes vulpes) in Europe and North America, the raccoon (Procyon lotor) and skunk (Mephitis mephitis) in the United States and the raccoon dog (Nyctereutes procyonides) in eastern and central Europe. Laboratory tests in the WHOCC-PII on rabies-suspected samples (2008-2012), show that dogs are the most reported rabid carnivore in Iran, followed by wolves (Canis lupus pallipes), foxes (Vulpes vulpes), jackals (Canis aureus) and cats, respectively (Figure 5). It should also be noted from this figure (column entitled "2012 PEP") that dogs and cats are responsible for around 99% of annual exposures in the country, reflecting the popularity of dogs and cats as companion animals in Iran. In dogs and cats, rabies is known to be constantly lethal. However, serological studies of wild animals in Iran showed that abortive infection may occur in the red fox (Vulpes Vulpes), which demonstrates that alternative forms of rabies infection may occur in nature [42].

(a)

	2008	2009	2010	2011	2012	PEP(2012)
dog	111	77	52	113	128	106108
wolf	17	7	10	23	14	370
fox	5	4	6	13	15	326
jackal	6	6	2	5	9	225
cat	6	2	2	2	1	18525

(b)

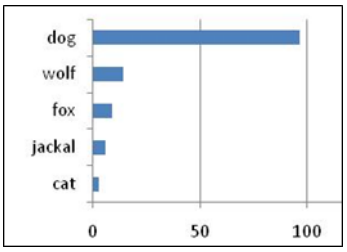


Fig. 5. (a) Data of laboratory confirmed samples from wild and domestic carnivores in Iran are presented in the table. In the left part of the table from 2008 to 2012, numbers of brain samples from each animal confirmed for rabies are indicated. In the "PEP (2012)" column of the table, numbers of exposures to each animal during one year are presented. (b) Diagram shows the average of five year results 2008-2012. In this diagram, the horizontal axis presents a five year average of the laboratory confirmed rabid animals.

Phylogenetic analyses have shown that a considerable number of lyssavirus genotypes infect bats (Table 2). The limited incidence (5% globally) of bat-mediated human rabies indicates the low frequency or efficiency of this type of transmission [41].

In the United States there is a high risk of lyssavirus transmission from particular bat species such as the insectivore bat Lasionycteris noctivagans to humans [43]. In Iran Bat rabies has never been reported, and apart from genotype 1, no other genotypes of lyssavirus have been detected among various isolates [44]. During 1990s, various bat colonies from different regions of the country were tested for rabies infection and none was detected.

However, considering the existence of about 40 species of bat in Iran [45] and the possibility of their migration through borders, where novel bat lyssaviruses were isolated [46], more comprehensive studies on bats, as possible reservoir of rabies, in the country are required. Certain numbers of recent isolates are still in the course of classification (Table 2).

RABIES MANAGEMENT AND TREATMENT: PRESENT STATISTICS AND FUTURE ESTIMATES

It should generally be considered that rabies is invariably fatal. Once the disease is confirmed, specific measures should be taken to alleviate patient suffering and prevent the risk of transmission to health workers. Strong sedation should be used to control the patient's agitation. Standard guidelines and protocols should be consulted for managing the health care staff who are likely to be in frequent contact

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

Table 2. Lyssavirus genotypes, geographic distribution and phylogenetic groups. The majority of these viruses have been isolated from bat species.

	Species	Abbreviation	Geographic origin	Phylogroup
1	Rabies virus	RABV	Many countries	1
2	Lagos bat virus	LBV	Lagos, Nigeria	2
3	Mokola virus	MOKV	Mokola forest, Oyo state, Nigeria	3
4	Duvenhage	DUVV	Kenya	1
5	European bat lyssavirus-1	EBL-1	Europe	1
6	European bat lyssavirus-2	EBL-2	Europe	1
7	Australian bat lyssavirus	ABLV	New South Wales, Australia	1
8	Aravan virus	ARAV	Central Asia	1
9	Khujand virus	KHUV	Central Asia	1
10	Irkut virus	IRKV	Eastern Siberia, Russian Far East	1
11	West Caucasian bat virus	WCBV	Caucasia	3
12	Shimoni bat virus	SHBV	Kenya	2
13	Ikoma virus	IKOV	Serengeti, Africa	3
14	Lleida bat lyssavirus	LLEBV	Spain	3
15	Bokeloh bat lyssavirus	BBLV	Germany	1

with rabid patients. If autopsy is needed for a laboratory confirmation, specific precautions should be taken for handling the deceased body. Infection can spread throughout solid organs, as well as bodily fluids, therefore an important point to consider before solid organ transplantation from an encephalitic death is to check for rabies. Several cases of rabies transmission have been observed resulting from the clinical misdiagnosis of rabies encephalitis in organ donors. In 1996, two cases of rabies transmission through corneal grafts were reported in Iran [47].

Currently, before any solid organ transplantation in Iran, a series of laboratory tests are carried out on the deceased body to check for systemic infections, including rabies.

Survival from rabies has been reported in very rare case patients, but unfortunately this has not resulted in development of any reproducible protocols, and even in survived individuals the sequelae remained after recovery. Although all rabies survivors had been exposed to bat rabies variants, control of bat rabies appears to be more difficult, which is mainly due to poor protection of available vaccines against bat lyssviruses resulting in a noticeable number of deaths in certain Latin American countries annually. In Asia and Africa however, rabies is most frequently transmitted by dogs. These regions suffer from insufficient availability of support for rabies PEP.

However, better disease prevention and more access to anti-rabies vaccines and immunoglobulins in these areas in the future are promising, as treatment protocols are being shortened and optimized. In addition, research on other aspects of the infection such as cellular and immunological characteristics of the virus could pave the way to developing new vaccines or probable cures for clinical rabies.

The importance of rabies as a fatal disease, calls for very organized and rigorous management after exposure. Exposures to rabies are divided into three categories according to severity of the wounds caused by suspected rabid animals and the risk of virus spread from wound site to nervous system.

More severe exposures require more careful consideration, and at the same time result in more expensive PEP protocols. Data on PEP in Iran from 2006 to 2011 are shown in Figure 6. General recommendations for post-exposure prophylaxis are available through WHO publications and website. Those recommendations include local treatment of the exposure site and administration of rabies vaccine and immunoglobulin. A certain number of high quality vaccines and protocols for vaccination have been approved by WHO. Preventive vaccination protocol against rabies is different from PEP. Table 3 summarizes current rabies PEP protocols for non-vaccinated individuals which apply intradermal or intramuscular routes of injection.

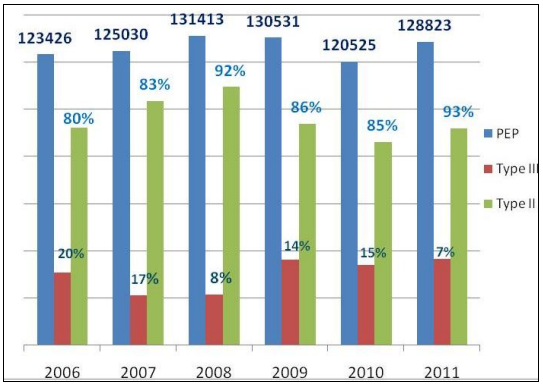


Fig. 6. Data on rabies post-exposure prophylaxis (PEP) in Iran through 2006-2011. Different exposure categories that according to WHO confirmed protocols need vaccine and serum administration are indicated in the graph as type II and type III (please see text and reference 49 for more details).

Alternative intradermal (ID) post-exposure regimens have also been studied in which 8 and 4 injections are administered during the first visit [48]. It is generally believed that regimens with multiple injections at day zero are a more practical way of raising immunity, especially in the absence of anti-rabies immunoglobulins [49]. Furthermore, ID regimens save a considerable amount of vaccine and budget in high-incidence countries and WHO recommends the application of ID regimens, wherever there is a vaccine shortage [50].

However, there are technical reasons and misgivings concerning the limited application of this type of regimen compared to intramuscular (IM) protocols [51]. Consequently, the original PEP regimen is the most commonly used protocol in the world [22].

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

Recently, the original protocol has been shortened by the Center for Disease Control and Prevention (CDC) to 4 single IM doses during 2 weeks. This PEP protocol is applied to healthy non-immunized individuals [52].

Table 3. According to the website of the World Health Organization, there are two major classes of PEP protocols based on the mode of vaccine administration. First row of this table indicates an IM protocol for rabies PEP also known as the Essen regimen. In the second row, a summarized multisite method for the first protocol is indicated. Thai Red Cross method is a multisite schedule based on ID mode of injection. Repetition of digits in multisite schedules indicates number of injections at any defined day. (I.M., Intramuscular, I.D., Intradermal)

	Post exposure regimen	Days of injection	Injection volume (ml)	I.M.	I.D.
1	Intramuscular	0- 3- 7- 14- 28	1	√	
2	Modified Intramuscular	0- 0- 7- 21	1	√	
3	Thai Red Cross	0- 0- 3-3-7-7-28-90	0.1		√

FUTURE GENERATION OF RABIES TREATMENT

By the time the clinical signs develop, rabies is invariably fatal and since there is currently no prospect for a cure, preventive measures are the most effective means of avoiding the disease. Therefore, vaccination against rabies is of primary importance in control of infection in both animals and humans. It is also a key element in the treatment of exposed individuals, as previously mentioned. Since the development of novel generations of vaccines, which are replacing old-generation nerve tissue vaccines, current rabies vaccines authorized by the WHO are limited to high quality chick embryo or cell culture-derived inactivated vaccines [53]. Generally, only vaccines of high quality and efficacy are recommended by the WHO. A study at WHOCC-IPI showed that people vaccinated with a modern cell culture-based vaccine in the course of PEP, maintained serum antibody titres up to 32 years later [54]. However, these vaccines are expensive, which limits their widespread use. Modern inactivated vaccines would need several injections for PEP, therefore, completing PEP would be very expensive, costing tens of US dollars. For this reason, certain countries in low income regions with the highest incidence of rabies might still receive nerve tissue-based rabies vaccines [55].

Vaccine formulations, capable of immunizing individuals with only one or two administrations and giving lifetime protection, would have a significant impact on controlling rabies and decreasing mortality. In order to prolong the duration of immunity against rabies, mechanisms of the immune response against rabies have been broadly investigated [56].

To produce a more effective and less expensive rabies vaccine, alternative methods of vaccine development have been evaluated. New rabies vaccines have been extensively studied for the possibility of their use in human. Traditionally attenuated rabies viruses and vaccines based on plasmid or viral vector expression systems have been developed and successfully used to control and eliminate sylvatic, as well as urban rabies [57, 58, 59]. However, administration of live rabies vaccines to humans is prohibited by the WHO. Researchers continue to find solutions for the problem of live virus application to humans. Due to the simplicity of its macromolecular components, as well as its cytoplasmic lifecycle, which avoids viral material incorporation into the host genome, rabies virus has attracted many researchers' attention. Viral vectors based on attenuated rabies virus have shown great potential for the development of other vaccines such as HIV, SARS, Ebola and hepatitis C. However, concerns regarding the safety of replicating viruses persist [60-62]. Replication-deficient laboratory rabies strains have been generated and are believed to be rapid and effective in the development of a long-lasting anti-rabies immune response. In the genome of these viruses, the matrix or phosphoprotein genes, which are necessary for normal virus replication, would be absent [63]. In animal models, these vaccines have been shown to induce a more comprehensive immune response and higher titres of neutralizing antibodies suggesting as potential replacements for current rabies vaccines [64].

ACKNOWLEDGEMENT

The authors wish to thank Dr. Marzieh FANAEI for her assistance in the proof-reading of the manuscript.

CONFLICT OF INTEREST

The authors do not have any conflict of interests.

REFERENCES

1. Wiktor T. Historical aspects of rabies treatment. Koprowski H, Plotkin SA, editors. World's Debt to Pasteur. New York: Alan R. Liss; 1985; 141-51.

2. Zinke GG. Neue Ansichten der Hundswuth, ihrer Ursachen und Folgen, nebst einer sichern Behandlungsart der von tollen Thieren gebissenen Menschen. Jena: CE Gabler; 1804.

3. Galtier V. Les injections de virus rabique dans le torrent circulatoire ne provoquent pas léclosion de la rage et semblant conférer limmunité : La rage peut être transmise par l'ingestion de la matière rabique. C R Acad Sci (Paris). 1881; 93: 284-5.

4. Roux, Émile Pierre Paul : *Des nouvelles acquisitions sur la rage*, thèse de médecine de Paris n° 398. 1883. [http://www.biusante.parisdescartes.fr/histmed/medica/page?TPAR1883x398&p=1]. Paris. Bibliothèque interuniversitaire de Santé; (c) Bibliothèque interuniversitaire de médecine (Paris) [cited 2014 July 5]

5. Pasteur L, Chamberland C, Roux PPE. Nouvelle communication sur la rage. C R Acad Sci (Paris). 1884; 98: 457-63.

6. Theodorides J. Histoire de la Rage. Masson: Paris, France; 1986; 1-289.

7. Remlinger PA. Le passage du virus rabique à traverse les filtres. Ann Inst Pasteur. 1903; 17: 834-49.

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

8. Pasteur Institut History. [http://www.pasteur.fr/fr/institut-pasteur/l-histoire/l-institut-pasteur]. Paris. Institut Pasteur ; © Institut Pasteur [cited 2014 September 18]

9. Joseph Mesnard (1886-1950). Annales de l'Institut Pasteur. 1951; t. 80: 7-8.

10. M. Baltazard (1908-1971). Bulletin de la société de Pathologie Exotique. 2004; T. 97: supplément

11. Pasteur L. Méthode pour prévenir la rage après morsure. C R Acad Sci (Paris). 1885; 101: 765-74.

12. Ghodssi M. Dix années de traitement antirabique à l'institut Pasteur de l'Iran (Téhéran) 1936-1946. Ann Inst Pasteur. 1947; 73: 900-2.

13. Habel K. Antiserum in the prophylaxis of rabies. Bull World Health Organ. 1954; 10 (5): 781-8

14. Babès V, Lepp M. Recherches sur la vaccination antirabique. Ann Inst Pasteur. 1889; 3: 384-90.

15. Comité d'experts de la rage: rapport sur la première session, Genève, 17-22 avril 1950 [http://www.who.int/iris/handle-/10665/38573]. Geneva. World Health Organization ; © WHO 2014 [cited 2014 July 6]

16. Baltazard M. L'Institut Pasteur d'Iran. Téhéran, Service de coopération et d'action culturelle de l'ambassade de France. 2004; 38 p.

17. Habel K, Koprowsky H. Laboratory data supporting the clinical trial of antirabies serum in persons bitten by a rabid wolf. Bull World Health Organ. 1955; 13 (5): 773-9.

18. Atanasiu P, Bahmanyar M, Baltazard M, Fox JP, Habel K, Kaplan MM, Kissling RE, Komarov A, Koprowski H, Lépine P, Pérrez-Gallardo F, Schaeffer M. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. Bull World Health Organ. 1956; 14 (4): 593-611.

19. Atanasiu P, Bahmanyar M, Baltazard M, Fox JP, Habel K, Kaplan MM, Kissling RE, Komarov A, Koprowski H, Lépine P, Pérrez-Gallardo F, Schaeffer M. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. Bull World Health Organ. 1957; 17 (6): 911-32.

20. Baltazard M. La rage: Etat actuel de la question. Acta Medica Itanica. 1960; 3 (4): 1-4.

21. Bahmanyar M, Fayaz A, Nour-Salehi S, Mohammadi M, Koprowski H. Successful protection of humans exposed to rabies infection. Postexposure treatment with the new human diploid cell rabies vaccine and antirabies serum. JAMA. 1976; 236 (24): 2751-4.

22. Fayaz A, Simani S, Janani A, Farahtaj F, Biglari P, Howeizi N, Eslami N. Antibody persistence 32 years after post-exposure prophylaxis with human diploid cell rabies vaccine (HDCV). Vaccine. 2011; 29 (21): 3742-5.

23. Rabies Fact Sheet N°99, Updated July 2013. [http://www.who.int/mediacentre/factsheets/fs099/en/]. Geneva. World Health Organization; © WHO 2014 [cited 2014 July 6]

24. Knobel DL, Cleaveland S, Coleman PG, Fèvre EM, Meltzer MI, Miranda ME, Shaw A, Zinsstag J, Meslin FX. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ. 2005; 8 (3): 360-8.

25. Annual reports of rabies in Iran (2006-2011), WHO collaborating centre for reference and research on rabies, Pasteur Institute of Iran. 2014.

26. WHO Expert Consultation on Rabies: second report [http://apps.who.int/iris/bitstream/10665/85346/1/9789240690943_eng.pdf?ua=1]. Geneva. World Health Organization; © WHO [cited 2014 July 11]

27. Cleaveland S, Fèvre EM, Kaare M, Coleman PG. Estimating human rabies mortality in the United Republic of Tanzania from dog bite injuries. Bull World Health Organ. 2002; 80 (4): 304-10.

28. Coleman PG, Fèvre EM, Cleaveland S. Estimating the Public Health Impact of Rabies. Emerg Infect Dis. 2004; 10 (1): 140-2.

29. Guidelines for Dog Rabies Control. World Health Organization VPH/83.43 Rev. 1. Geneva: WHO; 1987.

30. Davlin SL, Vonville HM. Canine rabies vaccination and domestic dog population characteristics in the developing world: a systematic review. Vaccine; 2012; 30 (24): 3492-502

31. Li J, Faber M, Dietzschold B, Hooper DC. The role of toll-like receptors in the induction of immune responses during rabies virus infection. Adv Virus Res. 2011; 79: 115-26

32. Emerson SU, Schubert M. Location of the binding domains for the RNA polymerase L and the ribonucleocapsid template within different halves of the NS phosphoprotein of vesicular stomatitis virus. Proc Natl Acad Sci USA. 1987; 84 (16): 5655-9.

33. Gaudin Y, Ruigrok RW, Tuffereau C, Knossow M, Flamand A. Rabies virus glycoprotein is a trimer. Virology. 1992; 187 (2): 627-32.

34. Muhamuda K, Madhusudana SN, Ravi V. Use of neutralizing murine monoclonal antibodies to rabies glycoprotein in passive immunotherapy against rabies. Hum Vaccin. 2007; 3 (5): 192-5.

35. Gholami A, Kassis R, Real E, Delmas O, Guadagnini S, Larrous F, Obach D, Prevost MC, Jacob Y, Bourhy H. Mitochondrial dysfunction in lyssavirus-induced apoptosis. J Virol. 2008; 82 (10): 4774-84.

36. Larrous F, Gholami A, Mouhamad S, Estaquier J, Bourhy H. Two overlapping domains of a lyssavirus matrix protein that acts on different cell death pathways. J Virol. 2010; 84 (19): 9897-906.

37. Han Z, Lu J, Liu Y, Davis B, Lee MS, Olson MA, Ruthel G, Freedman BD, Schnell MJ, Wrobel JE, Reitz AB, Harty RN. Small Molecule Probes Targeting the Viral PPxY-Host Nedd4 Interface Block Egress of a Broad Range of RNA Viruses. J Virol. 2014; 16 (13): 7294-306.

38. Finke S, Mueller-Waldeck R, Conzelmann KK. Rabies virus matrix protein regulates the balance of virus transcription and replication. J Gen Virol. 2003; 84 (Pt 6): 1613-21.

39. Holmes EC, Woelk CH, Kassis R, Bourhy H. Genetic constraints and the adaptive evolution of rabies virus in nature. Virology. 2002; 292 (2): 247-57.

40. Farahtaj F, Fayaz A, Howaizi N, Biglari P, Gholami A. Human rabies in Iran. Trop Doct. 2014; 44 (4): 226-9.

41. De Serres G, Dallaire F, Cote M, Skowronski DM. Bat Rabies in the United States and Canada from 1950 through 2007: Human Cases With and Without Bat Contact. Clin Infect Dis. 2008; 46 (9): 1329-37.

42. Karimi Y, Fayaz A, Teymouri H. Serological data on rabies in foxes studied in Iran. Acta Med Iran. 1975; 18 (3-4): 129-36. [In French]

43. Franka R, Constantine DG, Kuzmin I, Velasco-Villa A, Reeder SA, Streicker D, Orciari LA, Wong AJ, Blanton JD, Rupprecht CE. A new phylogenetic lineage of rabies virus associated with western pipistrelle bats (Pipistrellus hesperus). J Gen Virol. 2006; 87 (Pt 8): 2309-21.

44. Nadin-Davis SA, Simani S, Armstrong J, Fayaz A, Wandeler AI. Molecular and antigenic characterization of rabies viruses from Iran

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]

identifies variants with distinct epidemiological origins. Epidemiol Infect. 2003; 131 (1): 777-90.

45. DeBlase AF. The bats of Iran: Systematic, distribution, ecology. Chicago, Illinois: Field Museum of Natural History; 1980.

46. Kuzmin IV, Orciari LA, Arai YT, Smith JS, Hanlon CA, Kameoka Y, Rupprecht CE. Bat lyssaviruses (Aravan and Khujand) from Central Asia: phylogenetic relationships according to N, P and G gene sequences. Virus Res. 2003; 97 (2): 65-79.

47. Javadi MA, Fayaz A, Mirdehghan SA, Ainollahi B. Transmission of rabies by corneal graft. Cornea. 1996; 15 (4): 431-3.

48. Warrell MJ1, Riddell A, Yu LM, Phipps J, Diggle L, Bourhy H, Deeks JJ, Fooks AR, Audry L, Brookes SM, Meslin FX, Moxon R, et al. A simplified 4-site economical intradermal post-exposure rabies vaccine regimen: a randomised controlled comparison with standard methods. PLoS Negl Trop Dis. 2008; 2 (4): e224.

49. Shayam C, Duggal AK, Ulka Kamble, Agarwal AK. Post-exposure Prophylaxis for Rabies. JIACM. 2006; 7 (1): 39-46.

50. WHO recommends the intradermal route for post-exposure prophylaxis in all places where rabies vaccines are in short supply [http://www.who.int/rabies/rabies_post_immunization/en/]. Geneva. World Health Organization; © WHO 2014 [cited 2014 July 10]

51. Goswami A, Plun-Favreau J, Nicoloyannis N, Sampath G, Siddiqui MN, Zinsou JA. The real cost of rabies post-exposure treatments. Vaccine. 2005; 23 (23): 2970-6.

52. What care will I receive? [http://www.cdc.gov/rabies/medicalcare/index.html]. Atlanta. Center for disease control and prevention. [cited 2014 September 18].

53. Rabies: Human vaccines, [http://www.who.int/rabies/vaccines/humanvaccines/en/]. Geneva. World Health Organization; © WHO 2014 [cited 2014 September 18]

54. Fayaz A, Simani S, Janani A, Farahtaj F, Biglari P, Howeizi N, Eslami N. Antibody persistence, 32 years after post-exposure prophylaxis with human diploid cell rabies vaccine (HDCV). Vaccine. 2011; 29 (21): 3742-5.

55. World Health Organization Information Sheet Observed Rate of Vaccine Reactions Rabies Vaccine [http://www.who.int/vaccine-safety/initiative/tools/RabiesVaccine_rates_information_sheet.pdf]. Geneva. World Health Organization; © WHO 2014 [cited 2014 September 19]

56. Johnson N, Cunningham AF, Fooks AR. The immune response to rabies virus infection and vaccination. Vaccine. 2010; 28 (23): 896-901.

57. Ertl HC. Novel Vaccines to Human Rabies. PLoS Negl Trop Dis. 2009; 3 (9): e515.

58. Rupprecht C, Wiktor TJ, Johnston DH, Hamir AN, Dietzschold B, Wunner WH, Glickman LT, Koprowski H. Oral immunization and protection of raccoons (Procyon lotor) with a vaccinia-rabies glycoprotein recombinant virus vaccine. Proc Natl Acad Sci USA. 1986; 83 (20): 7947-50.

59. Cliquet F, Combes B, Barrat J. Means used for terrestrial rabies elimination in France and policy for rabies surveillance in case of re-emergence. Dev Biol (Basel). 2006; 125: 119-26.

60. Faber M, Lamirande EW, Roberts A, Rice AB, Koprowski H, Dietzschold B, Schnell MJ. A single immunization with a rhabdovirus-based vector expressing severe acute respiratory syndrome coronavirus (SARS-CoV) S protein results in the production of high levels of SARS-CoV-neutralizing antibodies. J Gen Virol. 2005; 86 (Pt 5): 1435-40.

61. McKenna PM, Koser ML, Carlson KR, Montefiori DC, Letvin NL, Papaneri AB, Pomerantz RJ, Dietzschold B, Silvera P, McGettigan JP, Schnell MJ. Highly attenuated rabies virus-based vaccine vectors expressing simian-human immunodeficiency virus 89.6P Env and simian immunodeficiency virus mac 239 Gag are safe in rhesus macaques and protect from an AIDS-like disease. J Infect Dis. 2007; 195 (7): 980-8.

62. Blaney JE, Marzi A, Willet M, Papaneri AB, Wirblich C, Feldmann F, Holbrook M, Jahrling P, Feldmann H, Schnell MJ. Antibody quality and protection from lethal Ebola virus challenge in nonhuman primates immunized with rabies virus based bivalent vaccine. PLoS Pathog. 2013; 9 (5) : e1003389.

63. McGettigan JP. Experimental rabies vaccines for humans. Expert Rev Vaccines. 2010; 9 (10): 1177-86.

64. Gomme EA, Faul EJ, Flomenberg P, McGettigan JP, Schnell MJ. Characterization of a single-cycle rabies virus-based vaccine vector. J Virol. 2010; 84 (6): 2820-31.

[Downloaded from jommid.pasteur.ac.ir on 2026-02-04]