



Original Article

Cost-Effectiveness of Rabies Post Exposure Prophylaxis in Iran

Nahid Hatam (PhD)^a, Firooz Esmaelzade (MSc)^b, Ali Reza Mirahmadizadeh (PhD)^{c*}, Khosro Keshavarz (MSc)^d, Abdolhalim Rajabi (MSc)^e, Parvin Afsar Kazerooni (MD, MPH)^f, Marzieh Ataollahi (MSc)^f

^a Department of Health Service Administration, School of Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

^b Student Research Committee, School of Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

^c Deputy of Health, Shiraz University of Medical Sciences, Shiraz, Iran

^d Department of Health Economic School of Management and Information Sciences Shiraz University of Medical Sciences, Shiraz, Iran

^e Student Research Committee, Department of Epidemiology, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, Iran

^f Center of Diseases Control, Shiraz University of Medical Sciences, Shiraz, Iran

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* Correspondence

Ali Reza Mirahmadizadeh (MD, MPH, PhD)

Tel: +98 912 5169146

Fax: +98 711 2347315

E-mail: mirahmadia@sums.ac.ir

ABSTRACT

Background: The rabies is one of the most important officially-known viral zoonotic diseases for its global distribution, outbreak, high human and veterinary costs, and high death rate and causes high economic costs in different countries of the world every year. The rabies is the deadliest disease and if the symptoms break out in a person, one will certainly die. However, the deaths resulting from rabies can be prevented by post-exposure prophylaxis. To do so, in Iran and most of the countries in the world, all the people who are exposed to animal bite receive Post-Exposure Prophylaxis (PEP) treatment. The present survey aimed to investigate the cost-effectiveness of PEP in southern Iran.

Methods: The present study estimated the PEP costs from the government's Perspective with step-down method for the people exposed to animal bite, estimated the number of DALYs prevented by PEP in the individuals using decision Tree model, and computed the Incremental cost-effectiveness Ratio. The information collected of all reported animal bite cases (n=7111) in Fars Province, who referred rabies registries in urban and rural health centers to receive active care. Performing the PEP program cost estimated 1,052,756.1 USD for one year and the estimated cost for the treatment of each animal bite case and each prevented death was 148.04 and 5945.42 USD, respectively. Likewise 4,509.82 DALYs were prevented in southern Iran in 2011 by PEP program.

Results: The incremental cost-effectiveness ratio for each DALY was estimated to be 233.43 USD. In addition to its full effectiveness in prophylaxis from rabies, PEP program saves the financial resources of the society, as well.

Conclusions: This study showed performing PEP to be more cost-effective.

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Introduction

The rabies is one of the most important officially-known viral zoonotic diseases for its global distribution, outbreak, high human and veterinary costs, and high death rate and causes high economic costs in different countries of the world every year¹.

The disease occurs in more than 100 countries and more than 3.3 billion people have been exposed to rabies. Each year, more than 55,000 deaths from rabies occur in Asia and Africa². The highest rate of deaths from rabies occurs in Asia, where incidence rate is more than 3 cases per 100,000 people per year³.

More than 1.4 billion people are potentially at risk of rabies infection in South East Asia. In the areas where rabies is pandemic, 5-15 years-old children comprise about 40% of the people exposed to dog bite⁴. Deaths resulting from rabies in the children below 15 cause about 1.74 million DALYs to be lost in the world. Because of the lack of rabies care advanced

system, the real number of the sufferers is probably higher than the reported statistics⁵. Yet, besides the health importance in human-beings, disease outbreak among the live-stock causes significant economic losses. Despite the preventability of the rabies by effective and safe vaccines, the disease is still a healthcare problem in many countries, especially in Asia and Africa⁶. Asia bears 96.5% of the burden of the disease in developing countries by spending an annual cost equivalent to 560 million USD^{1,7}. In spite of centuries of experience in animal control and effectiveness prophylaxis after being exposed to rabies, human deaths resulting from rabies are still high. Rabies has been existing in Iran for long and is seen as endemic in Iran's wildlife causing repeated infections in pets^{8,9}. During 1994-2003, averagely, 8.4 deaths caused by rabies occurred among human-beings in Iran every year¹⁰. Moreover, about 130 thousand people annually receive PEP¹¹.

World Health Organization (WHO) recommends for the treatment of rabies vaccination classical 5 doses of intramuscular regimen (“Essen” regimen): one dose of the vaccine should be administered on days 0, 3, 7, 14 and 28. As an alternative, the 2-1-1 regimen may be used. Two doses are given on day 0, one dose on day 7 and one on day 21.^{2, 12, 13} In Iran treatment in the prevention of rabies include 5 doses on days 0,3,7,14 and 28 for wild animals bites and 3 doses on days 0,3 and 7 for domestic animals bites¹⁴.

Although PEP of rabies in Iran has reduced the death rate of rabies to a great extent, high PEP costs have imposed a heavy financial burden on healthcare and treatment systems which by itself warns the necessity to focus on the alternative policies¹⁵. For instance, rabies can be controlled or eradicated by vaccinating the animal reservoir population. Japan is the first country which successfully removed rabies by implementing the collective vaccination of dogs in 1956. Malaysia could also control rabies by obligatory vaccination and killing the stray dogs. Other countries, such as Singapore, showed that rabies could be controlled by removing dog rabies intermediates. These countries showed that the disease could be controlled even in less developed countries. Theoretical and experimental analyses show that vaccinating 70% of the dogs are enough for prophylaxis of the disease outbreak and eradicating it^{16, 17}. According to WHO’s report, the most affordable strategy to eradicate rabies is prophylaxis of human rabies by vaccination. Many of South American and Asian countries have succeeded to eradicate the rabies transfer between human being and animals using this strategy⁵.

Rabies is one of the most life threatening diseases¹⁸ and if the symptoms break out in a person, one will certainly die. Although the deaths caused by rabies can be prevented by PEP, the problem is that expensive PEP of rabies may be overused and lead to financial burden in health systems¹⁵. Moreover, the disease vaccine is expensive and often scarce and, consequently, one of the factors causing the disease breakout in developing countries is the financial inability of the victims in receiving PEP¹⁹.

In this regard, several studies have been conducted and the results are reported differently in different countries. Hampson et al. indicated that despite the treatment, only 20% of persons that bite were dying but because of the indirect costs of illness caused, PEP measured cost-effectiveness²⁰. This study also showed that using ID instead of IM can decrease the cost. Shim et al. study indicated to cost- effectiveness of PEP in comparison to reached QALY, but they approved this situation can be continued if persons who received PEP be more of 1%¹⁹.

Therefore, the present study was conducted in Fars Province, southern Iran, in order to estimate PEP costs in Iran. In addition, the effectiveness of the treatment was estimated by DALY index.

Methods

Gathering the data and estimating the parameters

We collected the information of all reported animal bite cases (n=7111) in Fars Province, southern Iran, who referred rabies registries in urban and rural health centers to receive active care. Different variables such as age, sex, occupation, animal species, bite location, vaccine dose, and amount of received serum, by following up the bitten people until the

completion of the vaccination period since 2011/03/21 to 2012/03/20, one year were also gathered.

To estimate the rabies probability in the biting animals, in case of pets, the biting animal was kept under surveillance or its head was sent to the central laboratory to be examined. On the other hand, in case of wild animals, the head of the dead animal was sent to the laboratory and the probability of rabies in the animals was estimated separately. The probability of being bitten from different parts of the body was obtained by examining the bitten cases and the probability that the bite of different parts of the body led to rabies was obtained from another study¹⁹ (Table 1). These probabilities are related to dogs, cats, and other animals which had attacked the human cases and injured them during 2011 and more than 80% of them was kept under surveillance and examined.

Table 1: The parameters needed for estimating the number of human deaths caused by rabies as a result of being bitten by the animals suspected to be rabid

Parameters description	Probability
The probability that the biting dog is rabid	0.12
The probability that the biting cat is rabid	0.08
The probability that the biting fox is rabid	0.54
The probability that the biting wolf is rabid	0.92
The probability that the biting goat is rabid	0.11
The probability that the biting sheep is rabid	0.38
The probability that the biting mouse is rabid	0.00
The probability that the biting jackal is rabid	0.90
The probability that the biting donkey is rabid	0.44
The probability that the biting horse is rabid	0.70
The probability that the biting cow is rabid	0.25
The probability that the other biting animals are rabid	0.30
The probability that head and neck are bitten	0.04
The probability that body is bitten	0.04
The probability that hands are bitten	0.45
The probability that lower body is bitten	0.45
The probability that the bite of rabid animal from head and neck lead to rabies	0.55
The probability that the bite of rabid animal from body lead to rabies	0.09
The probability that the bite of rabid animal from hands lead to rabies(hand and arm)	0.22
The probability that the bite of rabid animal from legs lead to rabies	0.12

To calculate human deaths related to rabies in Iran, decision-making tree model was used (Figure 1).

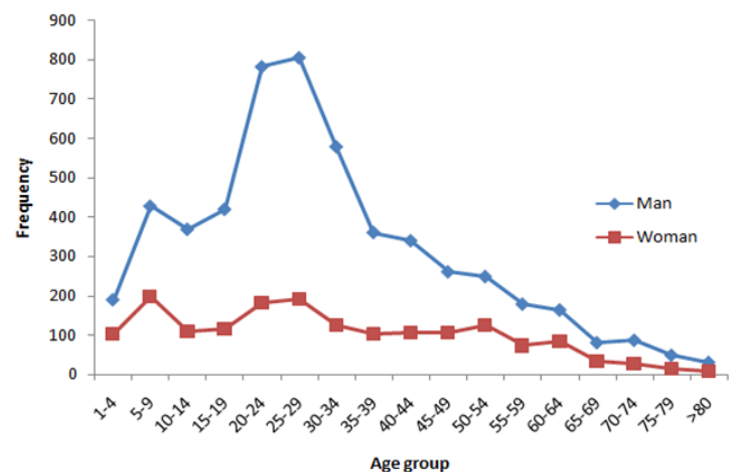


Figure 1: Bite distribution based on sex in different age groups

This model determines the cost-effectiveness ratio of PEP which people receive after being bitten by an animal suspected to be rabid. In this model, we suppose that the people who are bitten by an animal and are suspected to be rabid come to receive PEP with P1 probability, the animal is suspected to be rabid with P2 probability, and different parts of the body are bitten with P3 probability (head and neck, hands, body, lower body). Besides, if a person is bitten by an animal suspected to be rabid and does not receive PEP; s/he will die with P4 probability (Table 1). Since PEP is freely offered for all the individuals bitten by a suspected to be rabid animal, the bitten person is actively under surveillance, and if necessary the vaccinator visits the patient in his/her home to complete the vaccination period, we take P1 probability 1.

$$A = (1 - P_1) (P_2)$$

$$B = (P_{3-1})(P_4)$$

$$C = (P_{3-2})(P_4)$$

$$D = (P_{3-3})(P_4)$$

$$E = (P_{3-4})(P_4)$$

$$\text{Case Avert} = \sum_{i=1}^{7111} [A_i(B_i + C_i + D_i + E_i)]$$

In this survey, the necessary information was gathered in two parts as follows:

Cost data

In order to gather the cost information in this study, the viewpoint of the health system or healthcare provider, which is in fact the Ministry of Health and Medical Education, was used. This viewpoint considers the direct costs of the program. The costs of this survey included the costs spent for PEP proceedings in one year (2011/03/21 to 2012/03/20) including the cost related to building, equipment, wage of service provider staff, used accessories and drugs, trips, car rent, transport affairs, and so on. In addition to what was mentioned above, it is necessary to mention that the costs of each dose of vaccine and each unit of serum was calculated based on the costs spent by Iran government to import, store, and distribute them (In Iran, all the rabies vaccines and serums are provided by the government and are offered freely to the patients).

Effectiveness estimate data

To assess the effectiveness in this survey, disability adjusted life year score (DALY) was used. DALY index considers both quality and quantity of people's lives and shows the total burden of the patients. In this index, the lost years of life is obtained from the difference between the death age and standard life expectancy. According to $DALY = YLL + YLD$ formula²¹, DALY consists of two parts: YLL and YLD. In this survey, we supposed that if the person suffered from rabies after some days of symptoms outbreak, one would certainly die²². Therefore, the YLDs causing rabies were supposed to be zero. In 2001, the world organization introduced 3 ways for calculating YLL²³. In the simplest one, $YLL = N * L$ where N is the number of deaths at each age and L is the standard life expectancy at that age. As a result, the total number of the lost years of life for each death factor is obtained from the sum of YLLs at different ages. In the second way, it is supposed that the value of healthy years decreases with increase in age and, as a result, for the lost years of life, it decreases by 3% for each year of aging. This is called discounting. If the discount rate is applied to the calculation of

the lost years, the YLL formula will be as follows: $YLL = N / 0.03 (1 - e^{-0.03L})$ which was used in order to estimate YLL in the present research.

To calculate the cost-effectiveness ratio in this survey, the costs and effectiveness of PEP program was calculated with 3% yearly discount rate²⁴. Similarly, world standard life expectancy was used for estimating the effectiveness.

In order to evaluate the cost-effectiveness ratio, Incremental Cost-effectiveness Ratio Index (ICER) was used as cost for each DALY.

$$ICER = \frac{Costs_{PEP} - Costs_{NonPEP}}{Effectiveness_{PEP} - Effectiveness_{NonPEP}}$$

In this formula, the costs of not doing PEP include hospitalization and treatment costs of the people suffering from rabies (since the symptoms outbreak to death time in hospital) who have not received PEP.

The WHO has defined a standard for cost-effectiveness which is calculated based on the GDP. Based on this report, in any country, the healthcare interventions costing less than 3 times of GDP of the same country for each DALY are considered as cost-effective²⁵. In the present survey, this criterion was used for determining the cost-effectiveness of the PEP program.

At last, in order to assess and increase the accuracy of the work and because of the inherent uncertainties of the data and power of analysis, one-way sensitivity analysis was used.

Results

During the present survey, for determining the costs of PEP, the treatment costs of the 7,111 people who had been exposed to animal bite in 2011 and referred to healthcare centers to receive PEP was calculated. The results showed 75.9% of samples were male. The most of animal bites were aged between 20-24 (13.5%) and 25-29 (13.99%) years old. Finding showed 74.56% of samples bite by domestic animals.

Table 2 shows the results achieved from the cost data including the cost of doing PEP for the people exposed to the bite of a suspected-to-be-rabid animal. The results of performing the economic evaluation of the PEP program in the individuals who had been exposed to bite showed that the cost of performing the PEP program in a year was equal to 11,301,336,400 Rials (1,052,756.1 USD; USD was equal 10,735 Rials at 21st September 2011; Source: Iran's Central Bank). In addition, the total cost for treating each case of animal bite and each prevented death was estimated to be 1,589,275 Rials (148, 04 USD) and 63,824,117 Rials (5945.42 USD), respectively.

The results related to the prevented DALYs by PEP, divided into age and sex groups, are as follows:

The effectiveness index for the program was the prevented DALYs. In 2011, 4,509.82 DALYs were prevented by the PEP program in southern Iran. As a result, the incremental cost-effectiveness index for each DALY was estimated to be 2,505,939.572 Rials (233.43 USD). Furthermore, 7111 individuals were exposed to animal bite and received PEP; consequently, the prevented DALY was averagely 0.6342 for each case of biting. According to the results, the number of prevented DALYs decreased with aging; therefore, PEP cost-effectiveness decreased, too (Figure 2). Age distribution of being bitten by suspected-to-be-rabid animals in the youth was more than the adults and more in males compared to the

females (Figure 3). As a result, the number of prevented DALYs in the youth was more than the adults.

Table 2: The costs of doing Post-Exposure Prophylaxis (PEP) in Shiraz University of Medical Sciences, 2011

Items	One year cost	
	Rials	US\$
Current cost		
Personnel	11,301,336,400	1,052,756.10
Another current	5,442,474,000	506,984.07
Other costs		
Capital	2,227,475,000	207,496.51
building rent	152,530,000	14,208.66
Trip	149,157,000	13,894.45
Current affairs on building	122,103,000	11,374.29
Education	401,250,000	37,377.73
Vaccine	39,866,000	3,713.64
Serum	122,881,400	11,446.8
Total	2,643,600,000	246,259.9

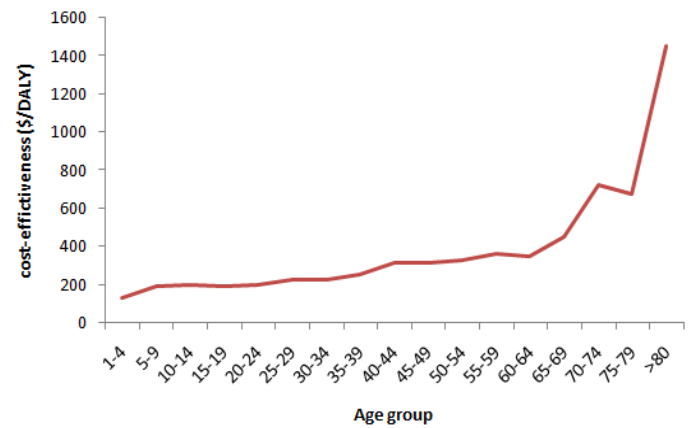


Figure 2: Cost-effectiveness ratio of PEP based on age groups

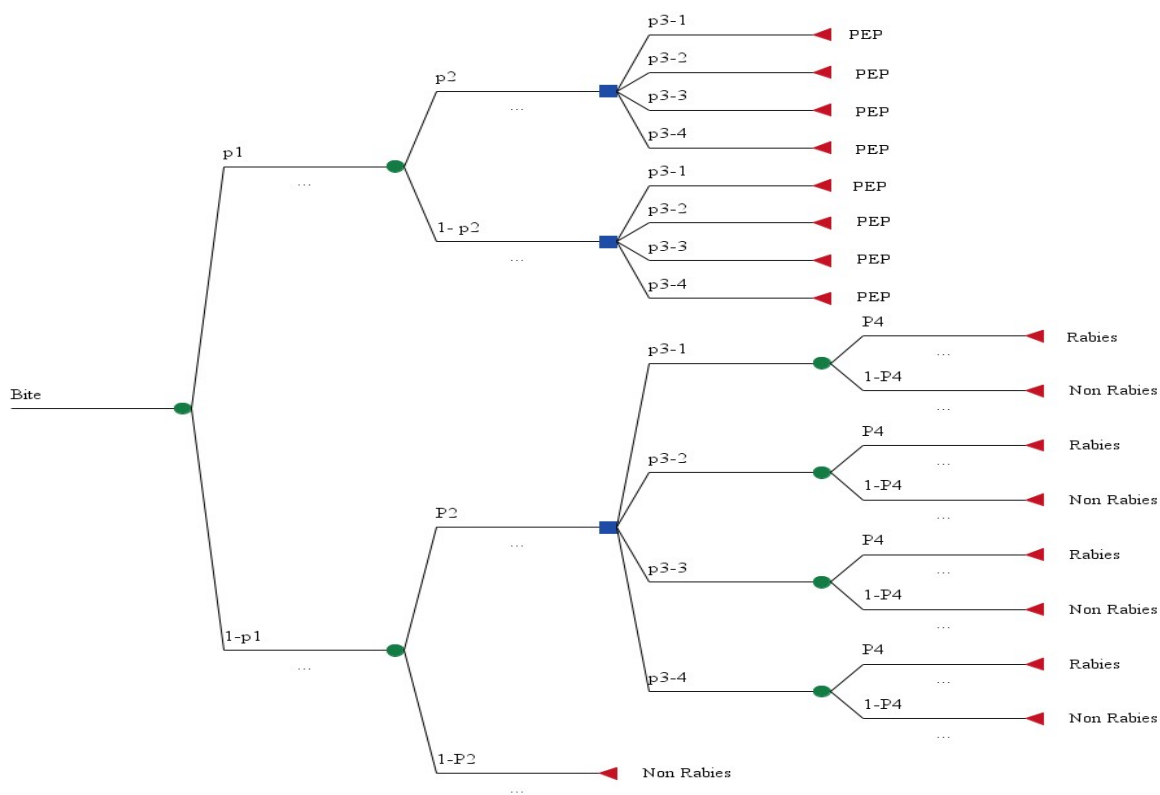


Figure 3: Decision-making tree model

Discussion

The number of deaths caused by rabies is too high and more than 55,000 individuals die due to rabies every year, which 99% of whom are in developing countries²⁶. In many developing countries, the vaccine and serum of rabies is very expensive and scarce. In addition, most of the people exposed to animal bite are the poor and villagers who do not have enough knowledge about the importance of PEP and in most cases they do not refer to receive PEP or receive just one dose and do not refer to receive the rest since the PEP provider centers are far away. In the recent years, the annual trend of animal bite is increasing in Iran; such a way that it increased from 35.1 cases per 100,000 populations in 1987 to 151 cases per 100,000 populations in 2002; however, the deaths caused by rabies have decreased in Iran²⁷. One of the most important reasons of this decrease is that the govern-

ment freely provides the rabies vaccine and serum for the bitten individuals. In addition, healthcare centers are bound to follow the bitten individuals by phone if they do not refer to them and, if necessary, the vaccination agent ought to go to their home to complete the treatment process. Although the accomplished proceedings have led to a decrease in the deaths caused by rabies, offering PEP freely and actively following the bitten individuals have imposed very high costs on the healthcare centers of Iran.

On the other hand, the shortage of resources and increasing needs and expectations in the health sector increases the necessity of optimized specification of resources and taking the performance and effectiveness of health interventions into account.

In the present survey, the results of economic evaluation of cost-effectiveness of the PEP program among the bitten

individuals showed that PEP was cost-effective. Besides, the results of performing the economic evaluation of the PEP program in the people exposed to bite showed that the cost of performing the PEP program in a year was equal to 11,301,336,400 Rials (10,502,756.1 USD) and the total cost for treating each case of animal bite to be 1589275 Rials (148.04 USD) and each prevented death, 63,824,117 Rials (5945.42 USD).

The effectiveness index was for the prevented DALYs program. According to the results, 4509.82 DALYs were prevented by the PEP program in Fars Province in 2011 and the cost-effectiveness index for each DALY was 2505939.572 Rials (233.43 USD). Based on WHO's report, in every country, the health care programs that cost less than 3 times of the country's capita GDP (GDP Per capita was 12,258 USD in 2011; Source: central bank of Iran) are economically cost-effective²⁵. Therefore, although PEP cost in humans is high compared to other treatment factors, considering the deaths and DALYs prevented by this treatment, it is very cost-effective.

Highness of the prevented DALYs to some extent reflects the age distribution of the victims; such a way that most of the bitten individuals are often of lower ages. Thus, PEP prevents deaths in lower ages and, as a result, leads to prevention from more DALYs.

In the study by Krindle et al. which was done from the society viewpoint, the average cost of the PEP for each patient was estimated to be 1646 USD (632 to 3435 USD). Likewise, by adding emergency room costs and medical room, the average cost of each patient was calculated as 2,376 USD (from 1,038 to 4,447 USD)²⁸. Although in the present survey, the treatment cost of each animal bite case was estimated to be 1,589,275 Rials (148.04 USD), it seems that one of the reasons of difference between the results is related to the different viewpoints of the surveys. In fact, in the society viewpoint, all the costs are considered regardless of who pays for it. In the government viewpoint, on the other hand, just the costs imposed on the government are considered. In fact, the study of costs from government viewpoint is a subset of the costs considered in society viewpoint.

In the study conducted by Knobble et al. in Asia and Africa, the advantages of PET program were measured by the prevented DALYs where totally 1,787,886 DALYs were prevented and the annual expenses of PET were estimated to be 485 million USD. The cost of each DALY was also estimated to be 266.18 USD²⁹. The comparison of these results with those of the present study shows that the findings are close to each other.

Shim et al. estimated the PEP cost to be 668 USD for each life and concluded that until 1% of the people who receive PEP are exposed to rabies, PEP is cost-effective¹⁹. In the present study, the needed cost for each prevented death was estimated to be 63,824,117 Rials (5945.42 USD). Perhaps the difference between the present and Shim's results can be justified by considering the fact that Shim et al. supposed most of the animals to be rabid, considered the attacker animal to be rabid with 75% probability, and, as a result, the number of prevented deaths was much higher. Thus, the cost for each prevented death decreases. In Iran, on the other hand, all the cases attacked by an animal are registered and the probabilities used for rabies in this survey were too low (the probability of the rabid dog 12%, cat 8%, fox 54%, goat

11%, cow 25%, wolf 92%, sheep 38%, mouse 0%, jackal 90%, donkey 44%, horse 70%, others 30%).

The results of sensitivity analysis showed that, except for dogs and cats (which comprise 90% of attacker animals); a change in the probability of rabies in other animals has no significant effect on the effectiveness and cost on each DALY. We considered the rabies probability of dogs between 1 and 0.052 (These probabilities are obtained from the percentage of the positive samples sent to Pastor Institute, previous studies and experts' views) and the cost on each DALY was between 1903190 Rials (177.28 USD) and 5,877,571 Rials (547.5 USD). Furthermore, with a change in the probability of cat rabies between 0.38 and 0.015, the cost on each DALY was between 2,140,112 Rials (199.3 USD) and 3,057,853 Rials (284.84 USD) and the PEP program was very cost-effective in both states. At the worst scenario, even if the rabies probability of all of the animals decreases into 0.08 simultaneously, the needed cost for DALY will be 21,193,277 Rials (1974.22 USD) and the PEP program still will be cost-effective.

Possible limitations in the study design that may affect the robustness of its results and the generalizability of its conclusions are as follows: First, we restricted our search to view of point of government as service offering and cost limited to all paid costs by government and excluded social or indirect costs. Second, measuring just one year if it could be used for a few years continuously it probably caused another results. An important point in rabies control in Iran is using IM instead of ID,² it increases extra costs and if in control program we apply ID injection it could decrease 60-80% of costs¹⁴.

Conclusions

The present survey showed performing PEP to be economically very cost-effective.

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Conflict of interest statement

There is no conflict of interest to be declared.

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