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Eradication of Rabies with Mass Parental Vaccination, Post-exposure Prophylaxis and Gene Therapy: A Systematic Review

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Author's contribution

Author MLN designed the study, wrote the protocol, searched the references and wrote the manuscript. The author read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Aims: To review canine rabies, mass parental vaccination, human post-exposure prophylaxis, gene therapy and costs for fighting rabies.
Place and Duration of Study: Department of Animal Science – Other, Nelwan Institution for Human Resource Development, Indonesia, between December 2017 and March 2018.
Methodology: The author searched the Pubmed Database at NCBI for articles on rabies disease published between 2007 and 2018. All articles are open access and in English. For rabies virus examination, Seller's test was used. In this article, references written by the author and other relevant publications were included. The author reviewed a rabies dog case kept at Nelwan Institution for Human Resource Development.
Results: The dog showed clinical signs such as inappetence, urinary frequency and soaking in a small, juicy drain. Currently, to treat rabies, no drugs are available. For rabies prevention, vaccination is the best way. To eradicate rabies, mass vaccination in dogs, post-exposure prophylaxis, and gene therapy should be used. Fort rabies disease eradication, minimum 70% of

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the dog population should receive vaccination. In addition, humans with category II exposure should receive rabies vaccine and rabies immunoglobulin.
Conclusion: To eradicate rabies, vaccinations are required. In addition, gene therapy can eliminate rabies from the infected neurons by using rAAV-N796. CRISPR/Cas9 system in combination with the MMEJ-based method. Furthermore, mass parental vaccination, post-exposure prophylaxis and gene therapy can reduce costs in controlling rabies disease.
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Keywords: lyssavirus; rabies; RAVB; zoonotic.

1. INTRODUCTION

Rabies is one of the oldest diseases on the globe and most feared zoonotic disease known to humankind. The disease is a hazardous, progressive and practically deadly encephalomyelitis [1]. *Lissavirus* is the most important rabies virus (RABV) [2]. Rabies can infect both humans and domestic animals. For example, most cases of rabies in animals arise among bats, carnivores, cats, raccoons [3], mongooses, and wolves [4]. In addition, a natural rabies infection in birds has also been reported [5]. Dog (*Canis lupus familiaris*) [6,7] is the source of more than 99% of rabies cases in humans [8,9]. The animal can transmit RABV from animal to human through bites, or mucous membranes from saliva [2,6] or other potentially infectious material such as neural tissue. In domestic animals, the incubation time is normally around 1-3 months. Moreover, non-bite sources of rabies are salivating, scratches [8,10], and corneal transplantation [10]. Once symptoms of rabies begin, the disease is around 100% fatal [4,6].

In this study, the author reports canine rabies clinical signs that include heat, urinary frequency, and thirst. In addition, this study will provide an overview of the different rabies situations in other countries where the disease has been eliminated. Currently, there is no available drug for rabies [2], but this disease is 100% preventable [9] through vaccination of both dogs and humans who were exposed to the virus. According to the World Organization for Animal Health, mass dog vaccination (MDV) is the most cost efficient way to eliminate rabies. At least 70% of the dog population in the area needs to be vaccinated to maintain herd immunity. This has been proven to be effective in many countries, including Argentina, Indonesia (Bali) and Mexico. Rabies in humans is avoidable through vaccination. To prevent rabies post-exposure prophylaxis (PEP), rabies vaccine administrations and immunoglobin following contamination should be used. There have been few studies regarding possible rabies treatment for animals or humans with λ-CG P32 (carrageenan) and gene therapy. According to Luo et al. carrageenan is an anti-RABV agent that can slow down significantly RABV infection *in vitro*. It is a sulfate polysaccharide soluble in water obtained from red algae [11]. The idea of gene therapy is to use induced pluripotent stem cells (iPSCs) and CRISPR/Cas9 (clustered regularly palindromic repeats/CRISPR-associated) for rabies treatment. Indeed, rabies is a disease which requires significant financial commitment. MDV, PEP, including mass information drive for pet owners are seen to be the major components of rabies prevention and control program. Modern trends such as vaccine development and gene therapy studies hold potential for the treatment of rabies.

2. METHODOLOGY

2.1 Systematic Review

The present report follows the guidelines of the PRISMA extension statement for systematic review [12]. These guidelines also correspond to PROSPERO guidelines such as searches and risk of bias assessment [13].

2.2 Searches

The author searched articles for rabies in only one database, that is, Pubmed Database at National Center for Biotechnology Information (NCBI). These included free PMC articles in English published between 2007 and 2018 for open access. Keywords comprised: “canine rabies, human rabies, rabies PEP in human, rabies and vaccination, gene therapy, or iPSCs and CRISPR/Cas9 system, and costs for fighting rabies.” In addition, the author’s articles regarding gene therapy and other relevant publications were included.

The study included report of a canine rabies case kept at the Nelwan Institution for Human Resource Development, Indonesia. In this study, Seller's test was used. Articles used to describe this study included case study reports, research articles and review articles.

2.3 Exclusion Criteria

Criteria for the exclusion of literature included analysis of subgroups or subsets, publications other than English, publications before 2007 and rabies other than human rabies and canine rabies.

3. RESULTS

The author took 163 articles from the Pubmed Database searches and other relevant publication searches (Fig. 1). After screening titles and abstract, 128 articles were taken for full-text review of these 58 articles met the criteria for data extraction.

3.1 A Rabies Case in Indonesia

The dog was a male, and was six years old when it died. It was the only dog in the house and never received a vaccination. The dog had clinical signs that included aggressive behavior, in-appetence, urinary frequency, thirst, heat and soaking in a small, juicy drain. Based on Seller's test, the dog was positive for rabies. This case of rabies occurred in Palu, Central Sulawesi, Indonesia.

Forebears of Indonesian RABVs derived from Java. The Java's RABVs offspring transmitted these rabies viruses to Kalimantan, and then to Bali, Flores, and Sumatra. The Flores's offspring transmitted these RABVs viruses to Sulawesi and went back to Kalimantan. In Indonesia, the dog is the only source of infection of other animals [14].

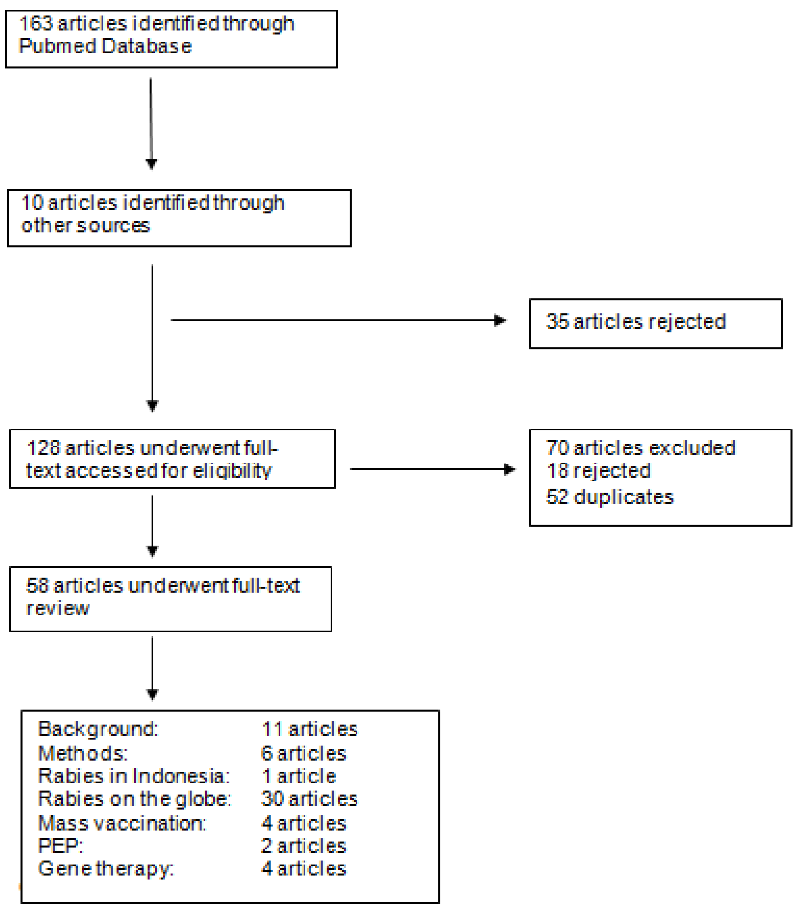

Fig. 1. A Flowchart showing articles selected in the systematic review

3.2 Rabies on the Globe

More than 3.3 billion people worldwide are at risk of being infected by the rabies virus [15]. Report in the United States estimated approximately 4.5 million dogs bite people annually [16]. In addition, the human deaths due to rabies is 59000 (25000 and 159000 (95% CI: 25000-159000) people annually. Fifteen (44.12%) of 34 publications showed 59000 human deaths from rabies [8,9, 15,23-34]. Moreover, six (17.65%) showed 55000 human deaths from rabies annually; Table 1. Furthermore, more than 95% of human deaths due to rabies occur in Asia and Africa [9,23,28-29]. Globally, around 84% of these deaths occur in rural areas [1]. Approximately, 50% of human deaths due to rabies are below 15 years old [10, 15-16]. Rabies causes 3.7 million (95% CI: 1.6-10.4 million) people lost disability-adjusted life years (DALYs) [20,31].

Human deaths in Asia due to rabies exceed 30000 annually [1,40]. For example, India has the highest incidence of rabies, even globally. Human deaths from rabies were 16450 in India and China 7450 in 2010 [40]. Rabies is endemic in Indonesia in 24 of the country's 34 provinces. This disease causes 150 to 300 human deaths annually [45]. In Africa, human deaths due to rabies are about 23000 to 23800 or 24200 annually [1,15,40]. In the Middle East and Central Asia, initial estimation for human's deaths from canine rabies is 350 and 1900, respectively. In Latin America, human rabies derived from dogs decreased from 250 in 1990 to fewer than 10 in 2010 [40].

Human rabies in the United States is rare and is only one to three cases annually. Rabies in this country may derive from bats, dogs, dog-mongoose, foxes, and raccoons. Of the 23 cases of rabies in the United States from 2008 through 2017, eleven (47.83%) derived from bats (contact, bite or unknown). Seven (30.43%) were rabies from dog bites. Dog-mongoose, fox, and raccoons were 4.3%, respectively. One (4.3%) was unknown. Eight (34.78%) of 23 cases were from outside of the United States and its territories [46]. Australia is free from carnivore rabies, and many Pacific Island nations have always been free from rabies and related viruses [1,40]. In addition, the United States [2], Canada, Western Europe, Japan [40], Argentina and Chile have succeeded controlled canine rabies [47].

3.3 Mass Parental Vaccination in Dogs

The World Health Organization (WHO) recommends that to eradicate rabies, at least 70% of the dog population should receive vaccination [24-25,35,40,48-49]. It would avoid a main disease outbreak at least 95.5%, and meets the requirements for eradicating rabies [24]. In the endemic areas of rabies, a minimum 70% of the dog population in each year during 5-7 years should receive vaccination [48]. The crucial vaccination coverage ranges between 25-40% [41]. It is essential to interrupt rabies transmission. In addition, mass vaccination under 30% is not beneficial for rabies eradication purposes [28]. For mass vaccination, vaccines such as Rabvac 1 and Inrab 1, used in the United States, can be used for vaccination annually. Route of vaccination is intramuscular or subcutaneous (Rabvac 1) and subcutaneous (Inrab 1) [3]. In a canine rabies-free country, the limit 70% threshold for eradication purposes is irrelevant. Most rabies vaccines are licensed for dogs older than 12 weeks of age [48] and re-vaccination with a booster is one year later [38,48].

Vaccination approaches include door-to-door campaigns, static point campaigns, and a combination of the two [24,40]. Such posts are usually sufficiently attended only when those posts are at less than 500 m or a 10-minute walk. The option depends on the people at the local level [40].

Table 1. Estimation of human deaths from rabies disease every year

Human deaths	Percentage	References	n = 34
50 000	5.88%	[17, 18]	2
55 000	17.65%	[10, 16, 19-22]	6
59 000	44.12%	[8, 9, 15, 23-34]	15
60 000	14.71%	[35-39]	5
61 000	14.71%	[1, 40-43]	5
70 000	2.94%	[44]	1

In Asia, several countries have successfully made significant progress in controlling rabies (Table 2). For example, Sri Lanka vaccinated about 400000 in 1990 and about 1.5 million dogs in 2015. The Ministry of Health forecasts an increase in the number of rabies vaccination from present 1.8 million to 2.4 million in 2020. In this country, the incidence of rabies cases decreased from more than 50 cases in 2010 to 5 cases in 2016 [23]. In Bali (Indonesia), mass vaccination resulted in decrease of rabies cases from 72% in 2010-2011 to 90% in 2011-2012. There are several reasons that led to the success of this project in Bali. These reasons are the implementation of vaccination for 70% of dogs in each district and municipal in Bali Province; reporting on the successful implementation of vaccination and reporting on the successful implementation of post-vaccination vaccinations by short message service and paper; implementation of daily, weekly and monthly vaccinations through government coordination; and the implementation of vaccination by trained field staffs [40].

In Africa, KwaZulu-Natal (South Africa) has vaccinated more than 15 million dogs since the commencement of the dog rabies eradication project in 2000. In 2012, more than 630000 dogs were vaccinated. In three years, the incidence of animal rabies has declined. KwaZulu-Natal reported in 2010-2011 a continuous 12-month period without a single human case [40]. Rabies was responsible for 1500 deaths annually in Tanzania. Following implementation of control activities from 2010 to 2016, human rabies deaths declined to 375 deaths (a 75% decline) [47]. Moreover, vaccination of 66% of domestic dogs in Tanzania resulted in decrease in dog rabies, human PEP, and the number of positive for rabies wild type diagnosis [50].

Many countries of Latin America have successfully eradicated rabies, (Table 2). These include such as Mexico and Trinidad & Tobago. These countries have had no rabies case for one to 10 years. However, Vilasco-Villa et al. stated that Costa Rica, Ecuador, Nicaragua, Panama, Uruguay, and Paraguay have no laboratory to assess the absence of dog maintained RABV lineages [51].

3.4 Post-Exposure Prophylaxis in Humans

There are three categories of PEP, category I, category II, and category III. Category I includes touching or feeding animals, and licking undamaged skin with secretions or excretions of a rabid animal or human. It is not an exposure, and does not require PEP. Category II includes skin biting and minor scrapes without bleeding. Finally, category III includes simple transdermal bites, multiple transdermal bites and scratching bites [40].

Table 2. New countries that have controlled rabies

Countries	Years	Case/percentage	References
South Korea	2014-2016	0 cases	[4]
Sri Lanka	2016	5 cases	[23]
Bali (Indonesia)	2011-2012	90%	[14, 40]
Visayas (the Philippines)	2012	13 cases	[40]
KwaZulu-Natal (South Africa)	2010-2011	0 cases	[40]
Tanzania	1996-2001	1 case	[47]
Argentina	2009-2017	0 cases	[50]
Chile	2017	0 cases	[50]
Colombia	2008-2018	0 cases	[50]
Costa Rica	2017	0 cases	[50]
Cuba	2009-present	0 cases	[50]
El Salvador	2009-present	0 cases	[50]
Ecuador	2017	0 cases	[50]
Honduras	2013-present	0 cases	[50]
Mexico	2006-2017	0 cases	[50]
Panama	2017	0 cases	[50]
Paraguay	2017	0 cases	[50]
Uruguay	2017	0 cases	[50]
Trinidad & Tobago	2013-2017	0 cases	[50]

Category II patients, who never been vaccinated, should receive both cell culture and embryonated egg-based rabies vaccines (CCEEVs) and rabies immune globulins (RIGs) [40]. Currently, there are available RIGs for clinical use, namely, human rabies immuneglobulins (HRIGs) and equine rabies immunoglobulins (ERIGs) [20,37]. Treatment after category III exposure is the immediate administration of CCEEVs and RIGs [37]. It requires putting HIRG into the wound or intramuscular for active immune response to vaccine antigen [2]. In addition, new RIG products have been available. Chao et al. introduced SYN023 that is derived from two novel monoclonal antibodies (MAbs) CTB011 and CTB012 [52]. Um et al. developed 16B8-Alexa MAb and evaluated it using RFFIT [39]. SYN023 and 16B8-Alexa could replace the current RIG products. Both of them are safe for PEP.

Table 3. Post-exposure prophylaxis

Regime	Schedule	Days/months
Five-dose	1-1-1-1-1	0, 3, 7, 14, 28 or 0, 3, 7, 14
Four-dose	2-0-1-0-1 or 2-1-1.	0, 7, 21
High risk	1	6 months
Not continual risk	1	24 months

Patients with category II should receive a regime with 0.5 [16] or 1 mL [2,40] doses of CCEEVs. For adults, the intramuscular administered vaccination in the deltoid area should always be administered. For children, the anterolateral aspect of the tight is also acceptable. CCEEVs should never be given in the gluteal region. The recommended dose of HIRG is 20 IU/kg (0.133 mL/kg) body weight for all ages of groups. If anatomically possible, the full dose of HIRG should be thoroughly infiltrated into the area around and into the wound. Any remaining volume should be injected intramuscularly at a site distal to the first vaccine site. However, subsequent doses of vaccine in the 5-dose series can be given in the same anatomic location where the HIRG dose was administered. Rabies PEP was 100% effective in preventing a clinical case of human rabies in the United States [2].

To manage a rabies exposure, three important methods are available. First, washing and flushing the wounds for about 15 minutes with soap and detergent of copious amounts. Iodine or 70% alcohol can be applied to the wounds. Second, for severe exposures, there are several methods of rabies vaccine use (Table 3) that is administered. Third, wounds that require suturing should be sutured loosely and after RIG infiltration [53].

3.5 Treatment with Gene Therapy

Clinical rabies in mouse model can be treated. Wu et al. created the nucleoprotein (N) gene of RABV (rAAV-N796) to fight rabies virus. In their study, the authors did their study in four groups of mice (Table 4). These groups consist of group A, B, C and D. In the first treatment group, the authors administered of rAAV-N796 or rAAV-Neg intracerebrally and administered of10 LD_{50} of lethal CVS-11 intracerebrally 24 hr later (A). In the other groups, they administered of rAAV-N976 or rAAV-Neg intramuscularly and administered of 20 LD_{50} of lethal CVS-11 intramuscularly 24 hr later (B). Moreover, the authors administered of rAAV-N796 or rAAV-Neg intracerebrally and administered of 20 LD_{50} of lethal CVS-11 intramuscularly 24 hr later (C). In the last group, they administered of 20 LD_{50} of lethal CVS-11 intramuscularly and administered of rAAV-N7960 or rAAV-Neg intracerebrally 24 hr later. The highest results were observed in the group of mice with an intracerebral administration with rAAV-N960 and administration with 20 LD_{50} of lethal CVS-11 intramuscular (C). The result was 62% alive on day 21 of infection [54].

The author did not find any reference relating to iPSCs and CRISPR/Cas9 system for treating rabies. However, Nelwan indicated that genes-delivery tools, genes-editing tools, NHEJ-based technique, for instance (M Nelwan, Nelwan Institution for Human Resource Development, INDONESIA, Unpublished results), and iPSCs technique are useful to treat monogenic disorders [55-57].

3.6 Estimated Burden of Rabies in the World

The annual cost for rabies prevention varies from one continent to another. Asia needs as much as US$ 1.5 billion for PEP only. European Union and Pan American spend US$ 6.5 million and US$ 20 million, respectively [40]. The United States needs US$ 300 million annually [1,40]. Latin America needs US$ 129 million for PEP and needs US$ 61 for mass vaccination. It is the most cost effective approach [26].

Table 4. Treatment with rAVV-N796, rAAV-Neg, 10 LD_{50}, 20 LD_{50}

	Days post infection			
	rAVV-N796	rAVV-Neg	Survival	
Treatment	Intracerebrally		rAAV-N796	rAAV-Neg
Intracerebrally	9	9	100%	100%
10 LD_{50} (A)	21	21	45%	0%
Treatment	Intramuscularly		rAAV-N796	rAAV-Neg
Intramuscularly	9	9	100%	100%
20 LD_{50} (B)	21	21	38%	0%
Treatment	Intracerebrally		rAAV-N796	rAAV-Neg
Intramuscularly	9	9	100%	100%
20 LD_{50} (C)	21	21	62%	0%
Treatment	Intramuscularly		rAAV-N796	rAAV-Neg
Intramuscularly	9	9	100%	100%
20 LD_{50} (D)	21	21	20%	0%

4. DISCUSSION

Humans have been living in fear of rabies outbreaks for thousands of years. Currently, more than half the world's population is still fearful of rabies outbreaks. Indeed, the earliest report of rabies was around 2300 BC [25]. Rabies has existed in Indonesia since 1884 [45]. In addition, this disease is endemic in provinces such as Central Sulawesi, North Sulawesi, and West Java. Rahmadane et al. [45] stated that Indonesian rabies belong to the Asian lineage; that is, *lyssavirus* genotype 1. Indonesia regularly controls rabies disease at provincial, district [45], and municipal levels. However, sufficient vaccination coverage has been hard to reach [45]. Indonesia and other ASEAN countries expect to be free of rabies in 2020.

Clinical signs of canine rabies include aggression, abnormal behavior, vocalization changes, paralysis [3,40], ataxia, cranial nerve deficits, dysphagia, inappetence [3], drooling, and convulsions [40]. The dog in this study had clinical signs such as urinary frequency and soaking in a small, juicy drain. Although, the dog had an inappetence and aggressive clinical signs, it did not have clinical signs such as ataxia and paralysis. Other clinical signs were heat and thirst. It seems that dog clinical signs are not the same as described in reference 3 and reference 16, except inappetence and aggressive behavior. It seems that heat, urinary frequency, thirst and soaking in a small juicy drain has not been described before.

The Seller's test is a rapid and a simple method for the diagnosis of rabies. The limitation of this test is that it is only suitable for fresh samples. In addition, the Seller's test has a very low sensitivity [1,45]. To detect rabies virus, Indonesia uses three methods. These are Seller's test, fluorescent antibody test (FAT), and mouse inoculation test (MIT). If the Seller's test is negative for rabies, the laboratory sends it to the FAT laboratory. If still negative, the laboratory sends it to the MIT laboratory [45]. If still negative, it means that the test result is negative for rabies. Based on the Seller's test, the dog in this study was positive for rabies. FAT or MIT was therefore not needed.

To eradicate rabies disease, mass vaccination in dogs and the administration of PEP should be done. Mass vaccination should meet the minimum 70% of the dog population. Moreover, PEP in humans should be managed immediately. Salomäo et al. [15] showed that dogs are the only animal that bit humans in Maputo and Matola cities (Mozambique). This was an expected discovery and confirmed data from other countries. It suggests that rabies eradication efforts should focus on dogs.

Currently, for rabies disease, no effective drugs are available. Medical treatments currently focus on mass vaccination and PEP for instance. However, to treat rabies in the future, gene therapy may be a very useful tool. This technique includes gene delivery vectors such rAAV [55] and CRISPR/Cas9 system [55], and iPSCs technique. For disease modeling, drug screening, and stem cell therapy; the iPSCs technique is helpful [56-58]. In addition, the iPSCs technique in combination with a CRISPR/Cas9 system or NHJE-based technique for treating rabies may also be developed. To treat rabies in wild type animals, drugs derived from this combination may be useful. Rabies outbreaks may occur in dogs and other animals such as bats and raccoons. Yang et al. [4] showed that rabies outbreaks in dogs have occurred in Malaysia and Taiwan.

Lavan et al. [50] showed that mass vaccination and human PEP are more cost saving and cost effective than human PEP only. This effective cost estimate comes from the annual cost for six years in the Bhutan government project to fight rabies. This project consisted of three stages and each stage lasted 2 years. Vaccination coverage was 70% in stage 1, 60% in stage 2, and 50% in stage 3. The number of PEP cases annually was 3440. During the stage 1, the costs of mass vaccination and human PEP exceeded the costs of human PEP only. During the stage 2, costs of mass vaccination and PEP were less than costs of human PEP only. At the stage 3, costs of mass vaccination and human PEP were lower than costs of human PEP only; US$ 730,000 against US$ 770,000.

To eradicate rabies, and respond quickly to outbreaks, three techniques are important. These are diagnosis, prevention and treatment. Diagnosis can be test tools such as FAT and MIT. Diagnosis should be as quick as possible. These tests are important for prevention of an outbreak development; animal's corpse should get immediate attention from the forestry police. The police should bring the corpses to a laboratory for diagnosis. It is also important for the diagnosis of other diseases besides rabies. Once the rabies virus has been diagnosed, vaccination and PEP if needed should be administered. Vaccination programs can help to reduce costs in fighting rabies disease. For the future treatment, genes-editing tools such as TALENs system and CRISPR/Cas9 system can be beneficial. A CRISPR/Cas9 system in combination with iPSCs method can correct erroneous strings *in vitro*. Then, genes-delivery tools such as AAV, Sendai virus and episomes can deliver the corrected genes to target organs. This technique may be able to treat rabies disease after clinical signs arise.

5. CONCLUSION

Rabies is a neglected tropical zoonotic disease. The disease is nearly 100% fatal and is 100% avoidable. Clinical signs of rabies disease include urinary frequency, inappetence, and soaking in a small, juicy drain. Vaccines are the only way to fight the rabies virus at present. In the future, to fight rabies, gene therapy, iPSCs technology, and gene editing tools may become useful. The iPSCs technique in combination with CRISPR/Cas9 system may be useful to eradicate this disease. Mass vaccination, PEP, and gene therapy can help to eradicate rabies disease worldwide. The cost to fight rabies with mass vaccination and PEP is lower than costs of human PEP only.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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The author takes the responsibility for initiating the review.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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