Exploring on Rabies Control and Elimination Strategy

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Abstract

Human rabies is fatal after onset; however, it can be treated through appropriate prevention tools. Implementing of personnel vaccination by pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) combined with rabies immunoglobulin (RIG), human rabies is preventable. In addition to obtain real-time information and risk assessment to facilitate the appropriateness of resources allocation; deliver accurate surveillance information, health education, and interdisciplinary communication, are the utmost priority in rabies prevention. Taiwan currently has an outbreak of rabies among wild ferret badgers with no indigenous human cases. Although 99% of human rabies deaths were associated with dogs, however, there were human rabies infections associated with exposure to ferret badgers. Therefore, the public should remain vigilant in not contacting with wild animals (including ferret badgers) and strengthen epidemic prevention via urging pet owners to acknowledge the importance of building herd immunity among canine and feline in community. For the eradication of rabies, including the assessment of the feasibility of oral rabies vaccination to eliminate rabies among wild ferret badgers, implementation of vaccination among canine and high-risk personnel, monitors and surveillance for rabies cases via reporting, and testing. An integrated, community-oriented management strategy and long-term vision under One Health strategy through a collaborative process to achieve rabies elimination in Taiwan.

Keywords：Rabies, Pre-Exposure Prophylaxis (PrEP), Exposure Prophylaxis (PEP), Ferret badgers

Introduction

Rabies is a disease of viral infection for animals. The rabies epidemic occurred in 150 countries throughout the world every year with about 50,000 to 100,000 deaths [1-2, 5]. Majority of the deaths with rabies was occurred in developing countries distributed in Asia or Africa, Nearly 31,000 deaths in Asia and 24,000 deaths in Africa annually. Thirty (30) to 50 percent of these rabies cases were young children [1-2]. In Asia, India, China and Indonesia has the largest number of cases; about 20,000 deaths in India and 2,000 deaths in China annually [1-2, 5]. In Taiwan, no human case was reported after 1951; and no record of animal case after

1961[1]. In 2002, 2012 and 2013, one human rabies case imported from China and the Philippines, respectively [1]. Recently, outbreaks of rabid ferret badgers were reported in 53 rural areas from nine counties and cities in central, southern and eastern Taiwan by the end of September 2013 [1]. The prevention control and elimination of rabies is now a new challenge to Taiwan. The purpose of this preliminary study describes the feasibility of multi-rabies immunization strategies and new emerging risks, hereby to enhance public to comprehend the awareness on rabies epidemic and facilitate the rabies elimination.

Materials and Methods

By retrieving the literatures and search for information via accessing database (e.g., PubMed, Google). Keywords used including rabies, eradication, prevention strategies. We analyzed the retrieved contents. Further information including the present epidemic related items, important opinions via consulting exchanged by Email communication, social networking, workshops including the "International Expert Meeting on Rabies" held by the Central Epidemic Command Center in August 2013, were enrolled and used herein for this study.

Results

1. Rabies epidemiology and infection

Main animal vectors accounted approximately 99% for human rabies deaths are rabid dogs, a small portion of infection are caused by other warm-blooded wild animals; usually spread and infected by the rabies virus in the saliva of rabid animals through biting, or in the wound by body contacting; few other infections, for example, from inhaled mist in the bat cave, through contact with rabid animals, the patient's mucous membranes, or organ (cornea, kidney) transplantation [1,2].

Pathological development of rabies infection through bites is shown in Figure 1 [3]. Clinical symptoms are: 1) incubation period: an average (90%) of latency is 20 to 90 days, sometimes less than a few days or as long as several years; depending on bites site and distance of wounds to the brain or the amount of virus entering. Virus replication occurs in the muscle tissue of the bitten sites; 2) the prodromal period (prodromal stage): virus invades peripheral nerve but did not arrive axons in the central nervous system, the early symptoms are not specific or obscure, possibly with fever and bitten limb showed partial palsy (flaccid paralysis), tingling, itching and other symptoms; 3) acute neurological illness phase (acute neurological phase): 1/3 patients showed paralytic (paralytic form) symptoms, including difficulty in breathing and swallowing, vomiting, polyneuritis (Guillain- Barre Syndrome), 2/3 patients present with mania type (furious form) symptoms include rabies encephalitis (encephalitic rabies), restlessness (hyperexcitability), autonomic dysfunction (autonomic dysfunction), fear of water (hydrophobia), fear of the wind (aerophobia), excess salivation (hypersalivation); 4) coma: arrhythmias, coma and fatal [3-4].

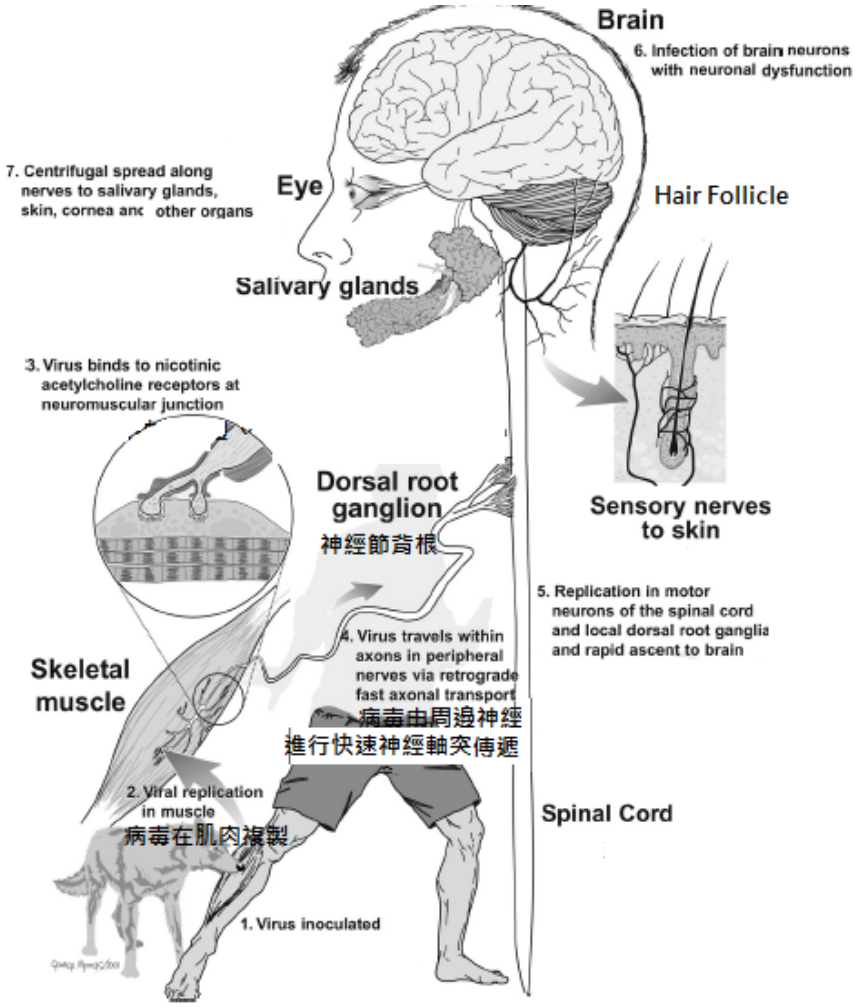

Figure 1. Pathological development of human rabies after animal bites. [3].

Being bitten into dermis by an rabid animal, the virus invades the body, and replicates in muscles of biting, via the nearby surrounding nerve axons, pass to the spine and brain, the virus multiplies in the central nervous system will then spread through the sensory nerves to head tissue (salivary glands, cornea, neck hair follicles, and skin) and other organs centrifugally. Hair follicles in neck are collected from patients with suspected rabies for examination (biopsy) recently recommended by WHO as one of the items [4].

2. Human rabies vaccination and treatment

Rabies vaccination could provide and initiate immunity approximately after 7 days of inoculation and induce neutralizing antibodies to battle against the rabies virus [1,2,5-7], provides a more long lasting protection. In case of biting by a suspected rabies animal, applying an immediate injection of rabies immune globulin could provide immediate passive immunity to curb virus A rabies vaccination could deliver a neutralization capacity against rabies virus and protection in first 0-10 days of administration, then gradually

decreased to zero on 25th day (Figure 2A) [1, 2, 5-7]. Pre-exposure prophylaxis (PrEP) in principle offers several years to whole life span's protective immunity [5-7]; however, one should refer to the manufacturer's recommendation if a booster is needed. The PrEP regimens, recommended by WHO and U.S. CDC advisory committee on immunization practices (ACIP), are vaccinations on 0, 7, 21 or 28 days, either intramuscular (IM) (1ml per dose) or intradermal (ID) (0.1 ml per dose) with tissue cultured vaccine. Even on severe exposure (biting to the dermal layer), only two additional IM injections on 0, 3 days or ID injection on four different sites (0.1 ml) on day 0; is enough to protect; rabies immunoglobulin is not necessary. Since implementation of PrEP is easy and expected to maintain immunity several years to whole life [5-7], it is recommended by the WHO and U.S. CDC to be administered on laboratory workers, veterinarians, animal control staff and those who at high-risk in remote places hard to get medical resources. The current PEP recommended by WHO and U.S.CDC (Table I) include: The Essen 5-dose formula, Zagreb reduced-4 dose formula injection treatment, mainly adopted in Europe, America, Africa, Australia and some Asian countries; the Thai Red Cross modified intradermal dose-sparing regimen (Figure 2B, Table 1) mainly adopted in Thailand, the Philippines and progressing to India and Sri Lanka [5-7].

(A) (B)

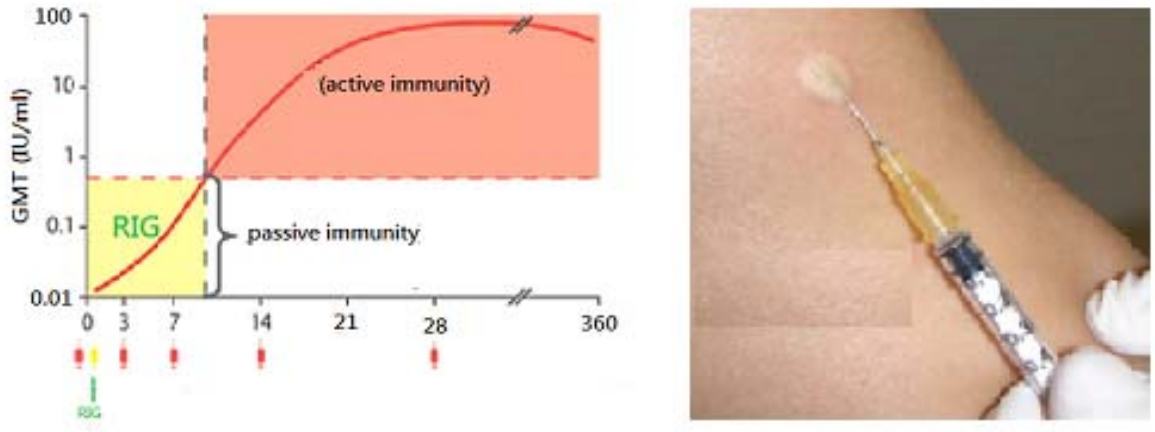

Figure 2. The illustration of rabies post-exposure prophylaxis and the vaccination schedule; partially cited [2]. (A) Rabies immunoglobuliin (RIG) provides passive immunity from 0 days to 7-10 days, a window period before the protection of active immunization; then gradually subsided; Rabies neutralizing antibodies (active immunity) is produced at 10 days after inoculation. In post-exposure prophylaxis (PEP), the use of Essen vaccination schedule on days 0, 3, 7, 14 and 28 intramuscularly inoculated with each dosage of 1ml. (B) Vaccination with intradermal inoculation: pay attention to hold the needle or syringe parallel to the skin , 0.1ml per dose, follow the vaccination schedule in Table 1.

As for PEP vaccination, according to the recommendation from WHO, if one chooses to use 5-dose IM inoculation, the best site to administer is in the deltoid muscle. First injection should be done as early as possible after being bitten by a rabid animal, inoculate simultaneously with a single dose of immunoglobulin, but must be at different site, then apply other doses on days 3,7,14 and 28 (IM, 1 ml)[5-7]. Other inoculation treatments please see Table 1. The "International Expert Meeting on Rabies " recommended to follow the WHO guidelines, to those who have completed with PrEP or PEP, if bitten again by rabid animal, then boosted either by IM 2-dose (1 ml) or ID 4-dose (0.1 ml) regardless the antibody level.

Table 1. Pre-exposure and post-exposure rabies vaccination, by intradermal injection or intramuscular injection, recommendations from WHO and U.S. CDC. [5-7].

Regimen	Total doses	Number of clinic visit (dose)	Inoculation route	Vaccination schedules (days)
Pre-exposure Prophylaxis				
Routine	3	3(1-1-1)	ID[a] IM[a,b,c]	0, 7, 21 or 28
Post –exposure prophylaxis				
Essen	5	5(1-1-1-1-1)	IM[a,b,c]	0, 3, 7, 14, 28
Zagreb	4	3(2-1-1)	IM[a,b]	0, 3 (2 doses in each deltoid),7,21
Reduced-4- Dose	4	4(1-1-1-1)	IM[b]	0, 3, 7, 14
Thai-Red Cross	8	5(2-2-2-0-2)	ID[a]	0, 3, 7, 28 (2 doses each)
Post-exposure for previously vaccinated persons				
Two-Dose	2	2(2-2)	IM[a,b,c]	0, 3 (2 doses in each deltoid)
Four-Dose	4	1(4)	ID[a]	0

a: WHO; b: U.S CDC ACIP; c: Taiwan CDC (31 July, 2013)
ID: Intradermal, 0.1ml/dose; IM: Intramuscular, 1ml/dose

3. Animal bites management

After bitten by a rabid dog, one should get treatment; the sooner the better, almost can be cured. WHO recommends the following [8]: 1) Clean and wash the wound immediately with soap and plenty of water, flush the wound thoroughly for about 15 minutes, then apply Betadine or 70% alcohol for disinfection; 2) In case of previously unvaccinated, i.e.; non PrEP person bitten by rabid animals, it is needed as soon as possible an injection of human rabies immunoglobulin (HRIG) to infiltrate the wound and neutralize the virus, this passive immunity could curb the spread of the virus to neurons, meanwhile, rabies vaccine should be injected at different site to induce active immunity; 3) HRIG provides rapid protection against a window period of active immunity induced by vaccine and should be applied simultaneously and should impose no later than seven days after the first dose of the vaccine [9] with a single dose of 20

IU/kg and closer to infiltrate the wound sites, the remaining immunoglobulin injection sites should be away from the vaccination site. If a child has multiple wounds and scratches, dilute the HRIG 2-3 x with sterile saline to be enough to apply on multiple wounds (this is a passive immunization); 4), If possible, do not suture the wounds;, if needed, the suture can be done in a few hours later to allow more infiltration of HRIG at the wound sites, which will allow the antibodies to diffuse. Other treatments, such as antibiotics, tetanus vaccine or tetanus immunoglobulin administered should follow the management procedures of scratches and wounds; 5) PEP active immunization: Please refer to Table 1 and PEP guidance from WHO.

As for the newly development in the treatment for patients after rabies onset is remaining under scientific evaluation. First, apply with hypertonic agents or targeted agents to open cerebral blood barrier (Brain Blood Barrier, BBB) channel [10-11], so that molecules of RIG could gain access and transport to the cerebrospinal fluid (Central nervous fluid, CNF) and neutralize rabies virus in nerve cells, and to deter the virus spread and infection in neurons and axons, the main principle is to reduce the expanding of brain lesions .

4. The implementation of an integration of animal and human health (One health) by prevention intervention strategies

Rabies can infect all kinds of mammals, including cats, dogs, bats and wild animals. Public health education in Taiwan at this stage should emphasize on not to touch wild animals, and beware of cross-species transmission from rabid ferret badgers to dogs. Therefore, health education should be strengthened to pet owners, register pets and vaccinate canine against rabies to at least 70% (Figure 3) [5], and to assist animal protection groups to vaccinate dogs and cats in long-term care facilities. In addition, to reduce the risk of transmission from stray dogs and cats to humans, and not to abandon pets.

Based on the implementation of an integrated strategy for animal and human health (One health) prevention; the first stage intervention aims at establishing herd immunity, including the implementation of canine health management, pets log and the rabies vaccine inoculation. Meanwhile, a pre-exposure vaccination is necessary for those who are at high risks including veterinarian, animal control staff, personnel of animal shelter and personnel in remote areas. Currently, it is needed to consider an assessment on the immune measures among wild animals (e.g., ferret badgers, bats) to reduce the overall potential risks in transmission of rabies virus among various animal groups and prevent infection. The second stage of intervention is properly transfer the suspected or confirmed cases for examination, diagnosis, monitoring, post-exposure medical treatment and care (Figure 3).

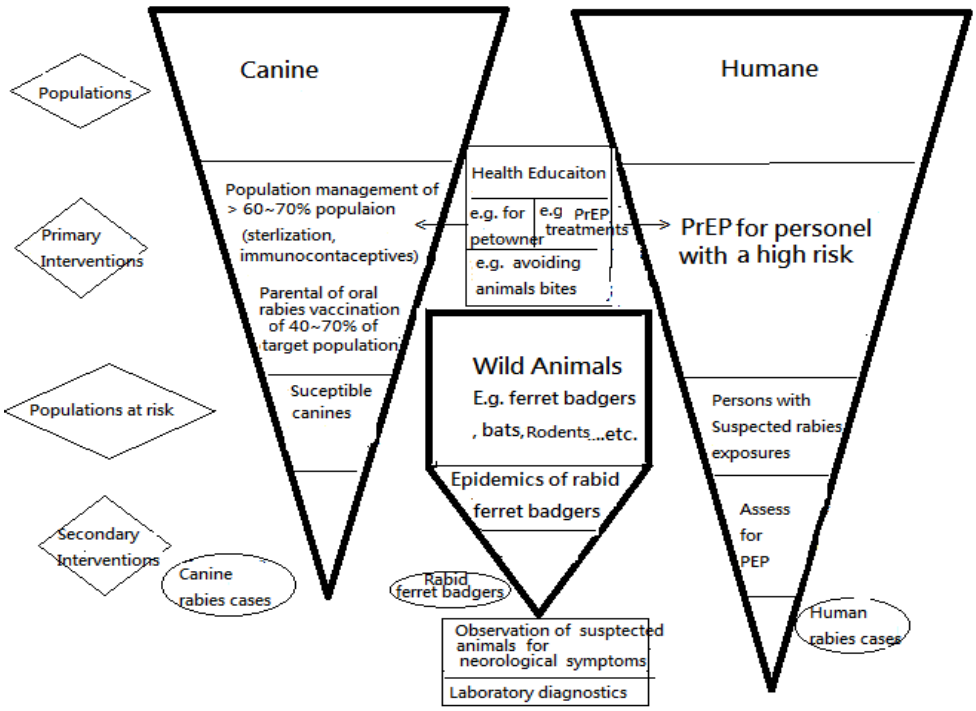

Figure 3. A concept scheme of integrated health (One health) intervention strategies for reducing the risk of rabies, partially adapted from reference [5]. Intervention refers to the first stage of the establishment of immunity among various ethnic groups, including the management of vaccination of dogs and cats in community, rabies vaccination before exposure in high-risk personnel and an assessment of immune measures among wild animals (ferret badgers). The second level of intervention is referred to examination, diagnosis, monitoring, and post-exposure treatment and care of the suspected or confirmed cases.

Discussion

Recently, multiple outbreaks of rabid ferret badgers caused fears and panic to the public. Strengthen public comprehension on rabies issues will avoid misunderstanding, reduce panic and facilitate preventive measures for a successfully epidemic control. Rabies infection is not only among canine, in general, warm-blooded animals are all susceptible, with various levels, to rabies virus. The prevention and elimination of rabies in wildlife populations is challenging because the outbreak is associated with diverse factors including animal behavior and the tracking of whereabouts of animals. Currently the presence of rabid ferret badgers has been around longer than a year [9] and appeared in different regions, it implicated that the virus has widely dispersed among ferret badger population in the island. Thus, Taiwan should be vigilant towards this issue. Besides reports of rabid ferret badgers, it was found in one shrew and one dog accidentally infected with rabies virus. It is likely the probability of rabies virus spreading from ferret badger to other species is low. Recent data from United States showed that the cause of human rabies infection related to bats is also important. In 2012, among 92% of rabies cases in wild animals, the association to rabid bats is 27% [12]. Although in recent years, test of

rabies virus in bats in Taiwan were negative, yet the number of specimen collection may be insufficient or sampling places might not be representative. Further strengthen on the appropriate selection of the area for sampling of bat specimens is needed. Nevertheless, for those whom bitten by bats, it is recommended to take the conservative approach, i.e., a post-exposure prophylaxis measure. Additionally, to remind the public avoid contacting with bats in order to ensure the health of citizens is needed.

During 1994-1995 and 2002-2004, outbreaks of rabid ferret badgers were reported in southeastern provinces of China. From 1994 to 2004, 60% (12/20) and 77% (17/22) of human rabies cases were associated with ferret badger exposure reported in Huzhou and Hangzhou, respectively [13]. Another wave of rabies epidemics might have gradually increased in 2007-2008 among ferret badgers in eastern Anhui, western Zhejiang and northern Jiangxi. That might result in a greater public health threat to the human [13]. Due to not been able to vaccinate the wild ferret badgers, the rabies epidemic in China has inevitably posed a threat to public health. Because the lack of communication or collaboration among Chinese Centers for Disease Control, Ministry of Agriculture and Ministry of Forestry to the control measures of wild animals, so that rabid ferret badgers brought a complicated situation rather than a control issue for canine rabies[13]. Genetic analysis of nucleoproteins or glycoproteins of rabies virus derived from rabid ferret badgers in southeastern provinces of China in the endemic regions revealed an 83%-89% similarity to canine rabies viruses [14]. Due to a low vaccination coverage among canines and felines in China, plus most of the ferret badger infections are mostly canine rabies strains [14], it bring tremendous threat to humans, canines and felines. We should seriously consider this issue in rabies elimination. To explore the circulating canine type of rabies virus among animals in Taiwan, a molecular epidemiologic analysis on genetic data; estimate the spreading power; animal susceptibility testing by rabies virus; ecological and population distribution study of ferret badgers and other animals and assessment of human risk of exposure should be in place.

The recent rabies epidemic in the United States, for example: 1) More than 90% of current rabies cases appeared in wild animals. There were approximately 80 rabid dogs and 300 rabid cats [15], which were primarily infected by raccoons, skunks, foxes and other wild animals. In U.S. the canine rabies vaccination rate was high, so the infection rate is low even while bitten by a wild animal [16]. 2) Before 1970s, the human rabies is majorly mediated by dogs; canine rabies disappeared after trapping stray dogs and vaccinations; however, the wildcats are not subject to the same treatment. Therefore, over the last 30 years, with 74 million pet cats, the administrations of human post-exposure rabies vaccination were associated with the risky exposure from cats,. From 2002-2012, after animal protection groups devoted to ending the killing of stray animals, the explosion in the number of wildcats reached to 60-150 millions in U.S.[16]; 3) U.S. CDC reported annually approximately 300 cases of rabies in cats; the number of PEP cases was about 40,000 people, 16 % of the cases associated with a cat [15]; 4) In 2002 - 2012, in the United States and Puerto Rico, the total cumulative number of human rabies

deaths was 33 cases [17], no death due to exposure of rabid cats [17]; more than half (19 death cases) was infected by bat type rabies virus, 8 deaths infected with canine-type viruses were imported. Lessons learned from these experiences could be useful to Taiwan's rabies prevention and control. People should avoid contact with suspicious animals, if bitten, seeking medical care as soon as possible.

In 1960, the concept of herd immunity for animals started emerging; until 1970, the oral vaccine was developed. For decades, there were a number of successful cases by using oral vaccination program to achieve regional rabies eradication. These included the bait-delivery by hand or airdrops to achieve a rabies eradication among red foxes in Western Europe or in southern Ontario. In 1990, U.S. made an oral vaccine for raccoons in the eastern states and successfully stopped rabies from spreading to the west, curbing rabid gray foxes in central Texas and cutting rabies cases in Mexican border for years [18]. Despite its apparent progress in the prevention and health innocuous for environment, oral vaccine is not a cure-all remedy but is an important supplementary technology for prevention and control. Besides the internal spread (compartmentalization) of rabies virus in Chiroptera and carnivores (Carnivora), spillover from bats to carnivores was detected, and the spread of rabies virus from bats to carnivores has been confirmed by molecular epidemiology [18]. Thus, the current oral vaccine can only work for regional carnivores rabies elimination, yet no practical methods are available to counter bats and achieve a true eradication for rabies. However, these unique fly mammals, given their biodiversity, distribution, and abundance, except with the possible exception of Antarctica, all warm-blooded inland animals may suffer from rabies, novel methods would be necessary in prevention and control, how to eradicate rabid bats is a future challenge [18-19]. In contrast, vaccination for dogs by parental injection, a traditional veterinary immunization, rabies has been extinct in developed countries [18]. Since animal immunization has exempted millions of people from this deadly disease, the World Organization for Animal Health (OIE) introduced the concept of Regional Vaccine Bank for rabies [19]. In order to improve animal welfare, the current animal rabies vaccine research aims to develop a low price vaccine by genetic recombination and tissue culture production instead of nerve tissue and no adverse side effect to animals. Therefore, the new generation of rabies vaccine will be cheap and safe for urgent uses in developing countries. This new oral vaccine will be either a single or 2-dose formulation. In addition, it is necessary to develop new adjuvants, stimulate the immune system can be applied both in parenteral and mucosal administration [19].

Rabies virus infection has been documented in organ transplantation recipients, although the probability is very low, in the "International Expert Meeting on Rabies" held in August, the experts recommended that to suspected encephalitis organ donors, the history of animal contact can be used to analyze the rabies risks, and to preserve the specimen, when necessary, laboratory tests and pathological examination can be performed to avoid the risk of rabies infection through organ transplantations; or refer to the U.S. CDC guidelines, explain the potential risks to recipients and obtain a signature consent.

After procurement of human rabies vaccine, the vaccination regimens information should provide to the public. In the recent WHO update includes the intradermal injection. The rational for ID injection is that human dermis and the epidermis are rich in antigen-presenting cells, make this layer of tissues more competent to deliver vaccine than in the muscle or subcutaneous tissue and could induce a better protection efficacy and immune response [5-8, 20,21]; and can be achieved by a smaller amounts of vaccine antigen. Thus, it will save the vaccine antigens, shorten the course, reduce clinic visits, and has protective effect (Table 1). It has been highly recommended by Program for Appropriate Technology in Health (PATH) and WHO.

Post-exposure prophylaxis (PEP), for example, the countries in Europe, America, Africa, Macao, and parts of Asia, and Taiwan are considering to adopt the IM vaccination regimens for 4~5 doses (1ml/ dose), rather than ID inoculation (0.1ml per dose) (Table I). However, the ID regimen is expected to be available to more people with the same vaccine resource.

In summary, based on the “one health” principle, prevention strategies for rabies epidemic should include investigation the distribution of rabies among wild animals (e.g., ferret badgers), evaluation of oral rabies vaccination policy, and active monitoring or surveillance of stray animals. At present time, we should continue to strengthen public health education on avoiding interacting with wild animals, enhancing awareness on wild animals with suspicious or unusual behaviors and observe the biting animal for 10-14 days, or notify early for rapid examination. Meanwhile, provide vaccination to high-risk personnel, enforce canine vaccination to prevent canine rabies and canine population management (reduce stray animals), integrate the joint public-private sector partnership to combat the current rabies epidemics [22], prevention control and elimination of rabies in Taiwan is achievable..

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