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2013 Taiwan's Strategies in Response to Re-emergence of Animal Rabies

Ji-Jia Huang, Kai-Hsiang You, Chiung-Fang Lin, Chia-Ying Wang, Chia-Ling Liu, Jer-Jea Yen

Division of Acute Infectious Diseases, Centers for Disease Control,
Ministry of Health and Welfare, Taiwan

Abstract

Taiwan lost its rabies-free status when the Council of Agriculture (COA) reported a confirmed case of animal rabies in Taiwan in July 2013. In order to control the disease, to block rabies virus from further spreading among animals and to prevent rabies infection in human, Central Epidemic Command Center (CECC) for Rabies was established based on applicable provisions of the Communicable Disease Control Act. Ministry of Health and Welfare (MOHW), in collaboration with the COA and other relevant governmental agencies, has since been implementing the following three strategies: domestic dogs and cats rabies vaccination, pre-exposure vaccination for high risk groups and post-exposure prophylaxis for people bitten or scratched by animals. Months of response measures brought rabies under control and epidemic remains occurring only in wild ferret-badgers in mountainous areas, with neither transmission to dogs or cats nor human infection. From the viewpoint of the MOHW, this article backtracks contingency measures taken in emergency period and adapted World Health Organization (WHO) guidelines for rabies and response action taken by other countries to compile key rabies control strategies and prevention measures for medium- and long- term usage in Taiwan.

Keywords: Rabies, ferret badgers, vaccines, immune globulin

Introduction

Rabies is a worldwide zoonosis. Approximately 55,000 people die of rabies each year, mainly in Asia and Africa. In Asia, most cases occur in India, China, the Philippines and Indonesia. Each year, rabies kills approximately 20,000 people in India and 2,000 people in China [1-2]. Once clinical symptoms appear, rabies is nearly 100% fatal in human. Receiving appropriate post-exposure prophylaxis (PEP) such as rabies vaccine and human rabies

immune globulin (HRIG) after being bitten or scratched by animals can effectively reduce the risk of rabies onset. According to the World Health Organization (WHO) estimation, the number of human cases of rabies in Asia and Africa can have reached 327,000 each year without immunization intervention [3]. At present, approximately 15 million people worldwide receive PEP rabies vaccination each year, which can reduce rabies death by approximately 272,000 [4].

Literature research reveals rabies occurrences in Taiwan as early as in Japanese ruling period (1895-1945) and at least 11 cases in north and south of the island since 1900 [5]. Shortly after World War II, rabies was introduced into Taiwan from Shanghai and became epidemic in 1947. It reached its peak in 1951 with 238 human rabies cases and in 1952 with 102 cases. Subsequently, animal reservoir was brought under control by means of dog vaccination and stray dog restriction. Relevant quarantine and prevention programs were also implemented [5]. As a result, no indigenous human case of rabies occurred since 1959. Only one case each was reported from China in 2002 and 2012, and one from the Philippines in 2013 [6,7]. Animals such as dogs and cats have been monitored for rabies in Taiwan and no animal rabies cases were detected during the five decades between 1961 and 2012. Taiwan had thus been one of the few rabies-free territories in the world [8].

The Council of Agriculture (COA) began commissioning academic institutions to conduct wildlife surveillance in 2011, to which rabies monitoring program was added later in 2013. The same year in June, a ferret badger was tested and suspected of rabies. Based on diagnosis confirmed by the COA Animal Health Research Institute, animal rabies occurrence in Taiwan was officially declared on July 16 and reported to the World Organization for Animal Health (OIE) the next day. The COA also designated towns and townships where rabies virus was detected as top risk areas and other mountainous townships as secondary risk areas.

Taiwan is currently classified by OIE as rabies endemic territory. May 23rd, 2012, the day its first case in ferret badger was reported, became official onset date of current animal rabies outbreak in Taiwan [9]. The agriculture authorities in Taiwan had long been ignoring wildlife disease surveillance and failed therefore to take promptly action in the early stages when rabies virus was introduced. It might be the cause of ongoing discovery of rabid ferret badgers in the central, southern and eastern mountains. For MOHW, this is an important turning point to control human rabies. The target of human rabies control used to be preventing imported cases and is now switching and aiming at preventing indigenous cases. In this article, inter-ministerial rabies control platform construction and relevant responding strategies are discussed from MOHW's perspective.

Strategies and Interventions

Human living environment is highly correlated to that of canine and feline animals. According to the WHO and other sources, over 99 % of human rabies cases are associated with dog and cat bites [4]. Hence, once rabies is detected in animals in an area, agricultural

authorities will give priority to control measures such as increasing dog and cat rabies immunization coverage, improving stray dog and cat control and enhancing animal rabies surveillance, while MOHW's primary aim will be preventing human from being infected through high risk animal bites or scratches. After the rabies outbreak in animals in July 2013 in Taiwan, MOHW and COA, through inter-ministerial cooperation mechanisms, jointly took three control measures, including: "promoting domestic dogs and cats vaccination", "providing pre-exposure vaccination protection for first line animal disease control workers" and "PEP for people bitten or scratched by animals". In addition to increasing immunization coverage of dogs and cats to reduce the risk of dogs and cats from being infected by rabid ferret badgers, providing pre-exposure vaccination (PrEP) and PEP for people with high risk of exposure can protect human from rabies infection and onset of disease.

1. Crisis Management

Crisis caused by current epidemic situation of animal rabies in Taiwan can be divided into two levels: "substantive disease hazards" and "public panic effect". The former includes epidemic expansion to dogs, cats and human and can be controlled with professional intervention from the MOHW and the COA. The latter is caused by lack of knowledge and leads to pet abandonment, vaccination-run and rational/irrational public and media criticism. In order to ease public panic, authorities have to alleviate public concerns on epidemic management and build credit by releasing epidemic update, disclosing response policies and improving health education.

2. Establishment of Command System

Rabies is a zoonotic disease and rabies control requires, therefore, coordinated efforts from relavant agencies including the COA and the MOHW. Optimal outcome of control can only be achieved when the government acts as one body. For this reason, the COA and the MOHW invited related agencies to set up an inter-ministerial commission on rabies prevention on 24th July. Daily inter-ministerial meeting, co-hosted by heads of the COA and the MOHW, has been held since 27th July under direction of Mao, Vice Premier and Chairman of the National Disasters Prevention and Protection Commission (NDPPC). Latest epidemic control policies will be declared at press conference after each meeting. Furthermore, resources, facilities as well as staffs from related agencies across the country need to react promptly in coordination to protect public health and prevent public panic. Therefore, the Central Epidemic Command Centre (CECC) for Rabies was approved and organised by the Executive Yuan in accordance with Article 17, Item 1 of the Communicable Disease Control Act. From 1st August, the CECC has been holding weekly command meeting as inter-ministerial communication platform. Efforts from different agencies are integrated through face-to-face discussions and prompt transmission of orders, and partnership between central and local governments is also reinforced by local governments' participation via teleconference system. Accelerated implementation and efficiency of control methods ensure effective outcomes of outbreak management.

3. Human Rabies Surveillance

Rabies is classified as category 1 communicable disease in Taiwan. Article 39 of the Communicable Disease Control Act requires physicians or forensic physicians who detect rabies or suspected rabies in patients to report such cases to the competent authorities within 24 hours so that government control measures can be duly initiated. Statistics from the Communicable Disease Reporting System of the Centers for Disease Control (CDC), MOHW, show that Taiwan found only three imported cases [6-7] and no indigenous human rabies case. Additionally, in order to provide evidence of no indigenous human rabies cases in Taiwan, the Taiwan CDC called for its Research and Diagnostic Center in "Forum on Human Exposure Risk and Management in Regard to Rabies Virus Detection in Animals" on 12th July, to conduct retrospective testing on previous specimens of encephalitis of unknown causes to determine whether the cause was rabies virus infection. Among the 205 specimens of encephalitis with unknown causative pathogens reported from 2010 to July 2013 of which sufficient quantities of cerebrospinal fluid specimens remain, high-throughput sequencing had been completed and no rabies genetic sequence was detected.

Animal bites and scratches are the major transmission route of rabies virus infection. Therefore, since first animal rabies reported, the Taiwan CDC has been providing PEP to those who are bitten or scratched by high risk animals, individual health follow-up and compile statistics of types of animal exposed and the frequency to intensify human rabies surveillance.

4. Human Rabies Vaccine and RIG Reserves

Taiwan had been rabies-free for more than 50 years, and therefore no rabies vaccination was required after animal bites in the past. In the beginning of ongoing animal rabies outbreak, the country had only a small number of rabies vaccine and HRIG in stock (privately imported vaccine included) which were used mainly as PEP booster for whose who had been bitten by animals in rabies endemic countries overseas.

As the Taiwan's rabies free status change, the Taiwan CDC took charge of overall control and dispersion of vaccine since mid-July to prevent rapid depletion of vaccine stocks caused by panic and surged demand. Meanwhile 82,500 doses of rabies vaccine, 2,870 bottles of HRIG as well as horse serum backup were imported through emergency procurement, and weekly consumption has been monitored to ensure sufficient supply of rabies PrEP and PEP in Taiwan. To ensure a both efficient and safe response to pandemic emergency, the Taiwan Food and Drug Administration (TFDA), MOHW provided the CDC with regulated assistance in sealing testing of rabies immunization products at procurement clearance to complete building national human rabies vaccine reserves in time.

5. Development and Implementation of Human Rabies Vaccination Policy

Providing appropriate medical care, such as rabies vaccination, for everyone bitten or scratched by animals is the most important key to prevent rabies occurrence in humans. At the beginning of the ongoing outbreak, the Taiwan CDC convened an MOHW Advisory Committee on Immunization Practices (ACIP) extraordinary meeting immediately. Recommended target groups for rabies vaccine and HRIG was revised in accordance to COA animal surveillance data (Tables 1 & 2.) and eligible population would be provided government-funded vaccination. A "Ferret-Badger Bite Safety Program" came into effect since 1st August to protect the health of previously unvaccinated people who were bitten or scratched by a ferret badger in the past year. The Taiwan CDC also increased the number of hospitals with rabies vaccine stockpile. Rabies vaccine is now available in as many as 60 hospitals: one hospital each in Penghu, Kinmen and Lienchiang offshore county and at least two or three in every city or country on the main island. Vaccine accessibility has been significantly improved.

Table 1. Post-Exposure Rabies Vaccination Target Group (effective from 31st July, 2013)

Category of Animal Exposed	Vaccination recommendations	Remark
Wild mammals (including shrew)	Immediate medical care and vaccinations	No need for subsequent vaccine dose if tested negative.
Stray dogs and cats	Immediate medical care and vaccinations	No need for subsequent vaccine dose if no symptoms are observed in the dog or cat in the following 10 days.
Domestic dogs and cats	No vaccination in general	Administrate vaccine if suspected rabies symptoms are observed in the dog or cat and the case is highly suspected by animal quarantine authority.

Table 2. Post-Exposure HRIG Administration Target Group (effective from 25st August, 2013)

Category of Animal Exposed	Vaccination recommendations
1. ferret badgers 2. moles (in Taitung City only) 3. animals that display certain abnormal behaviours (such as unprovoked attack) and are suspected by central agricultural authorities).	1. HRIG is recommended for category III exposure. 2. HRIG is recommended for category II exposure to positive ferret badger bites.

Definition of exposure: an animal bite or scratch or contamination of open wounds or mucous membrane with animal saliva and other secretions.
Definition of category II exposure: a minor bite on bare skin, scratch or abrasion without bleeding.
Definition of category III exposure: one or multiple bite(s) or scratch(es) into dermis layer of skin, animal licking on damaged skin, or contamination of mucous membranes with animal saliva.

To ensure occupational safety of animal disease control workers, all relevant central and local governments provided funding for their eligible staff to receive a complete PrEP series in designated hospitals. Besides, indigenous people are potentially exposed to rabid wildlife as many live in remote mountains. Accordingly, indigenous people at high risk were identified by the Council of Indigenous Peoples (CIP) and provided with PrEP assistance based on the criteria of "living in an area with rabies-positive ferret badgers", "has been engaged in hunting (traps) activities for years in remote mountains" and "identified as high risk group by township government",

The CECC published also "Guidelines for Clinical Management of Suspected Rabid Animal Bite and Scratches" as a reference for physicians to enhance the ability of diagnosing and treating suspected rabid animal bites or scratches in hospitals and clinics, including how to identify target group and administrate human rabid vaccine and HRIG. The CECC also collaborates with various medical associations in organizing intensive training for medical professionals. Also, as surveillance and investigation of adverse reactions to rabies vaccine or HRIG ensures early detection of hazards of vaccination and timely response, the Taiwan CDC has set up the "Rabies Vaccine and HRIG Adverse Event Reporting and Response Process". Medical institutions are required to report immediately such cases to local health authorities.

As of 30th September, 3,942 people have been approved and received government -funded rabies vaccine and 35 people have received HRIG. A total of 20 adverse events have been reported, and none was serious adverse event. All cases were closed when follow-up found no discomfort in the individuals. In addition, approximately 4,000 people at high risk have received rabies PEP vaccination, and 500 indigenous villagers at high risk have received rabies PEP vaccination.

6. Health Education

A Health Education and Outreach Working Group was co-organised by the COA and the MOHW to provide the public with real-time information and correct knowledge of rabies prevention. Various risk communication programmes are designed for different target groups, using multiple communication channels, to prevent panic by enhancing health knowledge. To strengthen public advocacy, regular press conferences have been held to publish latest epidemic situation and declare response measures since the beginning of ongoing outbreak in animals. Other channels include press release, media interviews and letters to medical community. Anti-rabies education materials such as video clips were also produced and distributed to relevant units. The materials are downloadable from the Rabies pages in the CDC website for public use. Besides, reporting and consultation services are available through the 24hr hotline 1922 of Taiwan CDC. The CECC also urged the Ministry of the Interior (MOI), the CIP, the Ministry of Education (MOE) and other ministries to reinforce awareness through their respective operation in village systems, indigenous villages and schools.

7. International Cooperation

Taiwan CDC and the Bureau of Animal and Plant Health Inspection and Quarantine (BAPHIQ) of COA, have invited international rabies experts from the U.S. CDC, the Global Alliance for Rabies Control, the WHO Collaborating Center and China to visit Taiwan and provide advices on epidemic prevention and control in regard to rabies surveillance, wildlife oral vaccination, high-risk group management, health education, surveillance for unexplained encephalitis in human and laboratory diagnosis. International expert meetings were also held to share experiences in rabies control and prevention with other countries.

Discussion

The most important source of rabies virus transmission is from rabid dogs and mainly caused by canine rabies virus, especially in developing countries. According to WHO statistics, 99% of rabies in human are caused by rabid dog bites. Disease control interventions are feasible as there is one dominant source [10]. It is proven that risk in human occurrences reduces significantly with increased and well-managed rabies vaccination coverage in animals that live closely with humans, such as dogs and cats.

On the eve of the first World Rabies Day on 7th September, 2007, the U.S. CDC officially announced the eradication of canine rabies virus in the U.S., which had been achieved through promotion of vaccination program, improvement of animal vaccination coverage and proper management of stray dogs, etc. [11]. In recent years, over 90% of rabies are found in wildlife, such as raccoons, skunks, bats and foxes, and relatively less in dogs and cats. The cases of dogs and cats were all caused by wildlife bites [12]. In developed countries, such as the U.S. and Europe, the majority of human rabies cases are importation-associated, with a few cases caused by wildlife bites or scratches or organ transplantation. As raccoons and bats rabies virus variants still spread among wild animals and constitute threat to humans, dogs and cats in the U.S., the U.S. government continues to keep a close eye on rabies control strategies such as surveillance of animal rabies, rabies vaccination for animals, rabies PEP for humans and prevention of dog smuggling.

The primary human rabies prevention and control objective lies in "Prevention of symptom appearance". Rabies is present in most of the developed countries in the world and only a small number of countries are rabies-free. Rabies endemic data in developed countries show that few fatal cases occur as long as a correct prevention is carried out, which includes vaccination of pets such as dogs and cats, avoidance of wildlife as well as immediate and appropriate medical treatment such as PEP after bitten or scratched. The healthcare and public health are fairly good in Taiwan, and therefore its rabies prevention and control planning can adopt the same model used by developed countries to ensure the nation's health and safety.

Due to long-neglected rabies surveillance in animals, the COA was unaware of and unable to obtain relevant endemic information, especially on status of virus infection in ferret badgers and other wildlife populations, on geographical distribution, and on circulation in other mammalian species. Reliable statistics of numbers of stray dogs and cats living closely to humans is also absent, and consequently the actual animal vaccination coverage can not be obtained and risk of rabies in human increase. The COA is recommended therefore to start immediately proactive rabies surveillance of wildlife, stray dogs and cats to provide immunization parameters for related agents. In accordance with epidemic updates provided by the COA, the MOHW will adjust the recommended target group of rabies vaccine and HRIG, reinforce health education for high-risk groups and ensure PEP vaccination in order to effectively prevent occurrence of human rabies.

Human rabies vaccine and HRIG preparedness is key to human rabies prevention. In the past, as Taiwan was rabies-free, the demand was so small that international companies were reluctant to supply this market, and no human rabies vaccine was manufactured in Taiwan. Allocation of human vaccine in the early stages of current epidemic was extremely difficult. Emergency procurement was achieved and facilitated with assistance provided by the TFDA in line with regulations, so that demand for PEP vaccine is supplied. Front-line animal rabies control workers were thereafter able to receive occupational PEP to ensure their safety at work. Likewise, self-paid vaccination should be encouraged for high-risk groups, such as veterinarians; as soon as sufficient vaccines are imported and supplied to prevent shortage of vaccines should outbreaks occur.

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Human Surveillance in Response to the 2013 Re-emergence of Animal Rabies in Taiwan

Chiu-Mei Chen, Ni-Chun Yeh, Hung-Wei Kuo, Ding-Ping Liu

Epidemic Intelligence Center, Centers for Disease Control,
Ministry of Health and Welfare, Taiwan

Abstract

On July 16, 2013 Taiwan announced that the rabies virus had been found in wild ferret-badgers. Taiwan's Ministry of Health and welfare and Council of Agriculture strengthened the monitoring of human and animal rabies and launched various preventive interventions in accordance with their responsibility. In response to the ongoing rabies outbreak, in human rabies surveillance, besides the notifiable infectious disease surveillance system, use vaccine apply mechanism to collect human cases information of animal bite or scratch, and gather rabies vaccination information and Council of Agriculture animal laboratory data , to provide intact information for risk assessment and the intervention for prevention and control. This article analyzes 5,335 cases of animal bites or scratches that led to an application for a vaccine from July 21, 2013 to September 30, 2013. Male (55.0%), particularly those aged 25-49 years old (40.2%), were predominant. Overall, 78.6% had been exposed to dogs or cats the majority (56.1%) of which was stray dogs or cats. Eastern area had a higher number of cases than the other areas, with male accounting for 60%, and 65.4% having the category 3 wounds. Analysis of the Taiwan's Real-time Outbreak and Disease Surveillance System (RODS) found that the number of emergency room due to dog bite is consistent with the applications for rabies vaccines. 205 specimens from cases of encephalitis of undetermined etiologies from January 2010 to September of this year were all ruled out as being infected with rabies. There has been no confirmed case of human rabies as of September 30, 2013. Only central, southern and eastern districts have animals been found to have rabies and are classified as potential risk areas. In the future, the will be an improved surveillance mechanism for animal bites or scratches, the establishing of a platform for the collection of data to strengthen risk assessment and risk communication, and the reduction of exposure and probability of infection, are directions for future work.

Key word: Rabies, animal bite or scratch, Surveillance

Introduction

Rabies is a zoonotic infectious disease. The virus exists in the saliva of an infected animal, and is transmitted to humans through scratches, bites, or incidentally through wounds or mucous membranes. Human rabies is widely distributed around the world, with most cases occurring in Africa and Asia. WHO estimates that rabies causes about 60,000 human deaths a year, 95% of which take place in Asia and Africa; the major animal vector are dogs. In the cases of being bitten or scratched by a suspected rabid animal, 40% are children under the age of 15[1].

Rabies was introduced to Taiwan from China in 1947. There were epidemics occurred continually after the first human rabies case found at Taipei city in 1948, regard 238 cases in 1951and 102 cases in 1952 as most. Though dog vaccination countrywide, put out stray dogs and the quarantine of dog imported, controlled the epidemic effectively, no more e human case appeared since 1959 [2], the confirmed cases were imported in recent years; Animal's epidemic situation, Taiwan had not occurred animal's case since 1961, till July 16, 2013, Council of Agriculture's Animal Health Research Institute reported to World Organization for Animal Health (OIE) on July 17 that the wild ferret-badger was contagious with the rabies virus[3]. The reoccurrence of rabies after in Taiwan after 50 years led the Ministry of Health and Welfare and the Bureau of Animal and Plant Health Inspection and Quarantine to establish a rabies prevention inter-ministerial working group on July 24, which reported to the Executive Yuan on 1 August, leading to the setting up of a Central Epidemic Command Center (CECC) for Rabies, and launched follow-up monitoring, controlling and preventive interventions. This article analyzes data from the period of July 21 to September 30 during the setting-up of relevant monitoring systems by the surveillance team of the CECC.

The surveillance of human rabies

1. Collection and monitoring the information of animal bite and scratch

(1).Database of applications for human rabies vaccine for animal bites and scratches.

Taiwan was rabies free in the past and did not have a surveillance system for animal bites and scratches. The majority of those who applied for the human rabies vaccine had been bitten or scratched by animals abroad and had to finish the vaccination after returning country, while the minority were pre-exposure prophylaxis. The use of the human rabies vaccine was low, and the vaccine was allocated to travel medical clinics countrywide, and managed and dispatched through the National Immunization Information System(NIIS) of the Taiwan CDC (TCDC). It was unable to provide complete epidemiological information of the cases animal bites or scratches. In response to this rabies outbreak, the TCDC assessed the area and animals at risk, widened the criteria of those eligible for vaccination for those suspected of being exposed to rabies, and provided free post-exposure vaccination to

people at a high risk of infection. The six regional centers of Taiwan TCDC recorded information on the applicants for the vaccination according to the application forms submitted by the hospitals under their jurisdiction. The content of the database included gender, age, the county or city inhabited, exposure time, place, animal, wound grade, etc. Besides relevant analysis, the surveillance team of the Central Epidemic Command Center gathered laboratory data from the Bureau of Animal and Plant Health Inspection and Quarantine and vaccination data of NIIS in order to understand the laboratory results and follow the vaccination situation of the people bitten or scratched by animals.

(2).Recall Project for ferret-badgers bite or scratch

The incubation period of rabies is one to three months, but may be shorter than one week or over one year, depending on wound severity and volume of virus. Once onset, the fatality rate is nearly 100%. Treating the wound as soon as possible after exposure, with either a rabies vaccine or immunoglobulin, can effectively induce the onset of rabies and death [1].

According to the retrospective research of the Council of Agriculture, the earliest rabies infected ferret badger was found in July, 2010, people who had risk to be bitten or scratched by ferret -badgers during July, 2010 to September 30, 2013 could register voluntarily through the TCDC 1922 hotline to get further risk assessment and medical referral at the same time.

The project was conducted during August 1 to September 30, 2013. People who have bitten or scratched by ferret-badgers in previous years will get the rabies vaccine by the general application.

2. Surveillance of notifiable infectious disease

According to degrees of risks and hazards such as case fatality rate, incidence rate, and transmission speed, human rabies is categorized as a Category 1 communicable disease. The criteria for reporting are: a person who has been to a rabies affected area and been bitten or scratched by mammals such as dogs, cats, bats, raccoons, etc., or who has accepted an organ transplant from a suspected rabies case, or worked in a rabies virus laboratory during the incubation period, etc., and suffers from anxiety, headache, fever, and an unusual sensation in at the site of an animal bite. A diagnosis of a suspected rabies case should be reported by a doctor within 24 hours in order to strengthen the surveillance; if the case is not in accordance with the definition, but requires testing, the doctor can also report it as ' other '.

3. Real-time Outbreak and Disease Surveillance System (RODS)

RODS was launched formally in November 2006, to collect and convey information between the TCDC and over 150 emergency rooms in the hospitals every day and monitor epidemic trends of relevant infectious diseases every week [4]. People who have bitten or scratched by animals will usually seek emergency intervention at hospitals first,

and this system can detect the possible clustering or particular situation from frontline emergency medical units. It can also monitor the weekly trends of gender, age and areas of cases of animal bites or scratches. This report used ICD-9-CM Code: E906.0 (bitten by dogs) for analysis. By reviewing the RODS data, another relevant disease code E906.3 (bitten by cats, rodents, except mice, sharks or eels) was not adopted in this report for analyzing due to rare notification and various species.

4. Sentinel surveillance for encephalitis of undetermined etiologies

To detect emerging and re-emerging infectious diseases, the TCDC has cooperated with hospitals since 2010. Physicians should report cases on the infectious disease system as an 'encephalitis of undetermined etiologies ' under “others”, and submit serum, throat swab and CSF from patients with either encephalopathy or ataxia of unknown etiologies, plus any one of the following: fever, seizure, focal neurological signs, abnormal CSF profile, abnormal electroencephalography (EEG) and brain images.

Taiwan was rabies free for approximately half century, so that cases of ' encephalitis of undetermined etiologies' were not test for rabies regularly. In response to the outbreak which can be traced back to the detection of rabies animals in July 2010, the specimens from cases of unexplained encephalitis have been examined for rabies since January 2010 to ensure no human case infected by rabies.

The surveillance of animal rabies by the Bureau of Animal and Plant Health Inspection and Quarantine, Council of Agriculture

According to the data from World Organization for Animal Health (OIE), the types of rabid animals differ by country, including dogs, cats, other domestic animals, and wild animals such as skunks, raccoons, foxes, etc.. Bats also have become a rabies reservoir in Africa, Australia, Central Asia, Southeast Asia and Europe. In 2010, Europe notified more rabid animals than other areas, followed by Africa and America. In Asia animals infected by rabies were mostly dogs, cats and other domestic animals [3]. Thus, to control animal epidemic can be helpful to reduce the risk of human infection.

The Bureau of Animal and Plant Health Inspection and Quarantine started the disease mortality and morbidity surveillance of wild animals in 2012. Besides general monitoring, the monitoring of rabies in carnivorous animals began in 2013 [5], this bureau responds to public notices of dead animals or reports of unusual behavior. The TCDC and Bureau of Animal and Plant Health Inspection and Quarantine set up a single point of contact from July 26, daily exchange of laboratory information of animals by mobile phone text message , besides providing the Central Epidemic Command Center and local government with risk assessments, and also offering real time tests and results informing, so as to ensure that animal bites or scratches are treated.

Results

1. The collection and analysis of applications for human rabies vaccine for animal bites and scratches:

(1). Database of applications for human rabies vaccine for animal bites and scratches.

We obtained details of 5,335 applications for the human rabies vaccine (not including the cases of exposure abroad and those unidentified) for the whole country from July 21 to September 30. 3,923 (73.5%) met the criteria for vaccinations. The cases are exposed mostly in central area (23.5%) and followed by Taipei area (20.3%). The number of applications rose daily in the beginning of the outbreak, and peaked on August 1. Although the eligibility criteria for the vaccination were set wider in response to the outbreak of animal rabies, the number of vaccination applications was declined (Fig. 1).

Among the applications for human rabies vaccines 55.0% were male, mostly aged 25-49 years old (40.2%) and followed by 24.9% aged 50-64 years old. The animals responsible for exposure were mainly by cats and dogs (78.6%), followed by mice (9.5%) and house shrews (6.0%). The majority animals were stray dogs and cats (56.1%), followed by domestic animals (24.3%) and wild animals (19.2%). The legs (52.4%) were the most often site of the wound, followed by arms (42.7%) and 1.1% had multiple (two or more) wounds. More than half (52.6%) cases were belong category 3 contact type.

Males are higher than females. Analyzing the exposed area, male in the eastern area accounted for 60%, higher than other areas. Those bitten or scratched by animals were mostly aged 25-49, followed by those aged 50-64 years old in all areas. Those aged 13-24 year old were the third highest in Taipei and the Kaohsiung-Pingtung area, while males over 65 years old were the third highest in other areas. Those in 0-12 years old were accounted for 10.6% in eastern area, noticeably higher than other areas.

Dogs and cats were accounted for more than 75% of the cases in all areas and mice are the second. Those bitten by mice are accounted for 14.6% among all animals in Taipei area, higher than other areas. 47 cases were bitten by high risk ferret-badger and the case number in central area (15 cases), Kaohsiung-Pingtung area (13 cases) and eastern area (10 cases) are higher than other areas. However, cases bitten by ferret-badger were accounted for 3.2% among all animals in eastern area, higher than other areas. Stray cats and dogs were responsible for most of cases in all areas, followed by domestic animals and wild animals. 61.9% of cases were exposed by stray cats and dogs in Taipei area, which is higher than other areas. More than 22% of cases were exposed by wild animals in southern and eastern areas.

Analyzing the categories of wound, category 2 was predominant in northern and central areas while category 3 was predominant in other areas. 65.4% of cases were belonged category 3 in east area, higher than other areas.

The legs were most likely to be bitten or scratched, followed by the arm in all areas (table 1). There is significant difference after cross analysis with the gender, age and exposed area. Among the cases bitten by the ferret badger, most were 50-64 years old (15 cases) and 25-49 years old (14 cases). Males (31 cases) were twice than females (16 cases).

(2).Recall Project for ferret-badgers bite or scratch

As of September 30 2013, the project had finished and received 15 cases. Investigation found that one case was not a ferret-badger bite and another was of the consumption of ferret-badger blood without high risk exposure – these were excluded. 13 cases have completed all rabies vaccinations. Among these 13 cases, over 50 years old (61.5%) and males (76.9%) were predominant, while the most area with the highest number of cases is the southern area (30.8%) , and the arm was the common site of the wound (69.2%). All were category 3 wound, and exposure time was between October 2012 and June 2013.

Table 1. Characterization of applicants for the human rabies vaccine in Taiwan, July 21 to September 30, 2013

area exposed	case number (n=5335)	Taipei Area (n=1083)	Northern Area (n=811)	Central Area (n=1252)	Southern Area (n=941)	Kaoping Area (n=936)	Eastern Area (n=312)
gender							
female	2399(45.0%)	517(47.7%)	384(47.3%)	549(43.8%)	409(43.5%)	418(44.7%)	122(39.1%)
male	2936(55.0%)	566(52.3%)	427(52.7%)	703(56.2%)	532(56.5%)	518(55.3%)	190(60.9%)
age							
0-12	331(6.2%)	64(5.9%)	57(7.0%)	73(5.8%)	60(6.4%)	44(4.7%)	33(10.6%)
13-24	778(14.6%)	183(16.9%)	99(12.2%)	174(13.9%)	137(14.6%)	141(15.1%)	44(14.1%)
25-49	2147(40.2%)	482(44.5%)	349(43.0%)	515(41.1%)	323(34.3%)	372(39.7%)	106(34.0%)
50-64	1331(24.9%)	241(22.3%)	206(25.4%)	313(25.0%)	242(25.7%)	249(26.6%)	80(25.6%)
over 65	748(14.0%)	113(10.4%)	100(12.3%)	177(14.1%)	179(19.0%)	130(13.9%)	49(15.7%)
animal exposed							
dog and cat	4195(78.6%)	865(79.9%)	678(83.6%)	968(77.3%)	714(75.9%)	731(78.1%)	239(76.6%)
mouse	507(9.5%)	158(14.6%)	57(7.0%)	105(8.4%)	89(9.5%)	74(7.9%)	24(7.7%)
house shrew	320(6.0%)	6(0.6%)	33(4.1%)	97(7.7%)	87(9.2%)	79(8.4%)	18(5.8%)
squirrel	65(1.2%)	11(1.0%)	7(0.9%)	17(1.4%)	19(2.0%)	8(0.9%)	3(1.0%)
ferret-badger	47(0.9%)	5(0.5%)	1(0.1%)	15(1.2%)	3(0.3%)	13(1.4%)	10(3.2%)
bat	35(0.7%)	2(0.2%)	5(0.6%)	14(1.1%)	7(0.7%)	7(0.7%)	-
gem-faced civet	24(0.4%)	2(0.2%)	2(0.2%)	7(0.6%)	6(0.6%)	2(0.2%)	5(1.6%)
others	63(1.2%)	13(1.2%)	9(1.1%)	10(0.8%)	14(1.5%)	9(1.0%)	8(2.6%)
unknown	79(1.5%)	21(1.9%)	19(2.3%)	19(1.5%)	2(0.2%)	13(1.4%)	5(1.6%)
source of animal exposed							
stray dog and cat	2992(56.1%)	671(61.9%)	443(54.6%)	702(56.1%)	480(51.0%)	535(57.2%)	161(51.6%)
domestic animal	1298(24.3%)	220(20.3%)	254(31.3%)	289(23.1%)	247(26.2%)	209(22.3%)	79(25.3%)
wild animal	1025(19.2%)	187(17.3%)	112(13.8%)	258(20.6%)	211(22.4%)	188(20.1%)	69(22.1%)
others/unknown	20(0.4%)	5(0.5%)	2(0.2%)	3(0.2%)	3(0.3%)	4(0.4%)	3(1.0%)
exposure of wound[1]							
category 1	45(0.8%)	6(0.6%)	10(1.2%)	20(1.6%)	5(0.5%)	2(0.2%)	2(0.6%)
category 2	2273(42.6%)	459(42.4%)	441(54.4%)	542(43.3%)	384(40.8%)	342(36.5%)	105(33.7%)
category 3	2804(52.6%)	607(56.0%)	353(43.5%)	511(40.8%)	551(58.6%)	578(61.8%)	204(65.4%)
no exposure/unknown	210(4.0%)	11(1.0%)	7(0.9%)	179(14.3%)	1(0.1%)	14(1.5%)	1(0.3%)
exposure position[2]							
leg	2817(52.2%)	563(51.5%)	418(51.0%)	655(51.9%)	490(51.2%)	527(55.6%)	164(51.9%)
arm	2307(42.7%)	475(43.4%)	363(44.3%)	542(42.9%)	412(43.1%)	377(39.8%)	138(43.7%)
head and neck	84(1.6%)	17(1.6%)	15(1.8%)	18(1.4%)	15(1.6%)	13(1.4%)	6(1.9%)
hip	72(1.3%)	13(1.2%)	5(0.6%)	16(1.3%)	16(1.7%)	17(1.8%)	5(1.6%)
trunk	88(1.6%)	22(2.0%)	14(1.7%)	18(1.4%)	18(1.9%)	13(1.4%)	3(0.9%)
shoulders	12(0.2%)	3(0.3%)	2(0.2%)	2(0.2%)	4(0.4%)	1(0.1%)	-
unknown	17(0.3%)	1(0.1%)	2(0.2%)	12(1.0%)	2(0.2%)	-	-

1. Categories of wound: category 1: Touching or feeding animals; licks on intact skin; category 2: nibbles on uncovered skin; minor scratches or abrasion with no bleeding; category 3: Single or multiple bites or scratches that break the skin; licks by animals on broken skin; contamination of mucous membrane with saliva from licks; contact with bats.

2. Exposure position: Multiple bites are counted individually.

2. Analysis of notifiable infectious disease surveillance

There have been 6 suspected human rabies cases notified in the past ten years, 3 of which were confirmed cases, and all of which were contracted abroad (2 from China and 1 from the Philippines): all three patients died. Between July and September 2013, only one case was notified as ' other ' and ruled out after being tested for rabies. There has been no confirmed case of human rabies.

3. Analysis of Real-time Outbreak and Disease Surveillance System

Between January up until July 20, before there rabies outbreak, there were 263 weekly cases of dog bites or scratches (ICD9: E906.0). After July 21, 2013, the number of cases began to rise rapidly, gradually dropping after peaking at the end of that month. 3.65 per thousand saw a doctor: 2.77 per thousand females were slightly higher than the 2.67 per thousand males. The highest group was 50-64 years old, with 25-49 years old second; 13-24 years old, males over 65 years and children under 13, were all relatively low. 3.86 per thousand in the eastern area were higher than other areas, and the central area second highest. The rate of dog bite case among the emergency cases was consistent with the trend in applications for a rabies vaccine. (Fig. 1)

4. Analysis of sentinel surveillance of encephalitis of undetermined etiology

During January 2010 to September, 2013, the TCDC was notified 365 cases with encephalitis of undetermined etiologies. Of 205 available stored samples, none tested positive for rabies virus.

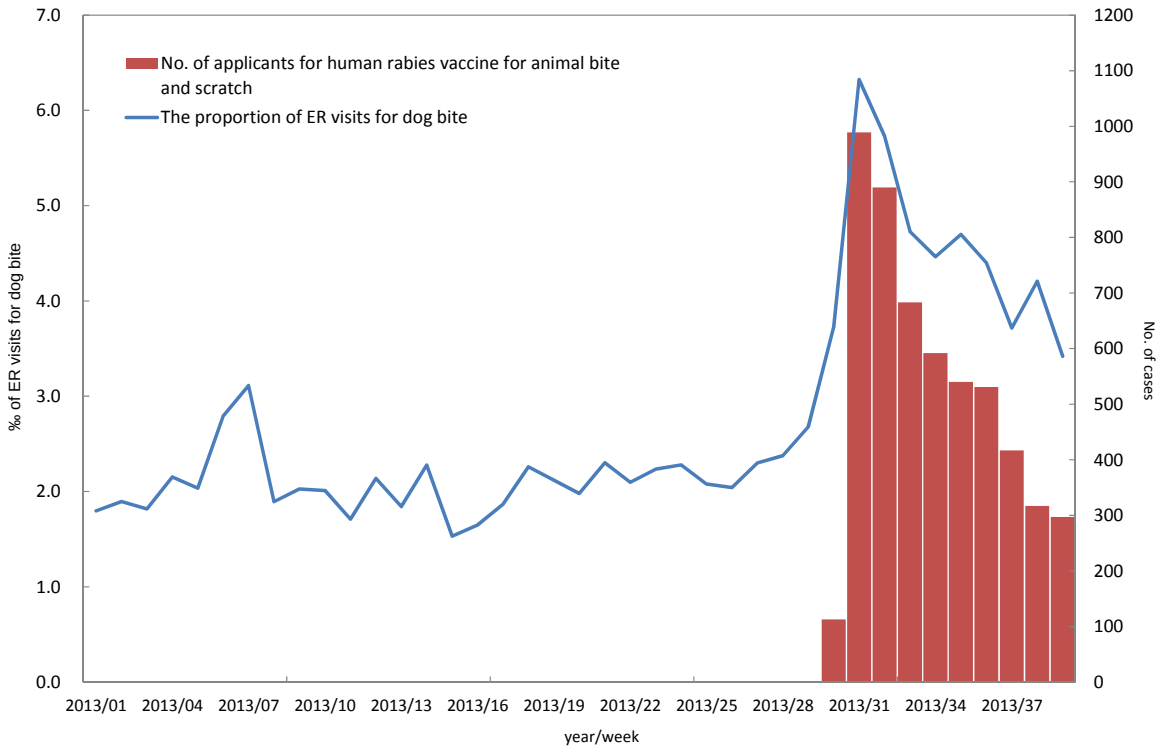

Figure 1. Number of applicants for human rabies vaccine and the proportion of emergency room visits for animal bites or scratches in Taiwan, 2013

Analysis of the surveillance of animal rabies by the Bureau of Animal and Plant Health Inspection and Quarantine

As of September 30, the Bureau of Animal and Plant Health Inspection and Quarantine had examined 627 wild carnivorous animals, 284 other wild animals, 862 dogs, 61 cats and 44 bats. Other than the 155 ferret-badgers(98.7%), 1 house shrew and 1 isolated dog bitten by a ferret-badger and confirmed as having the rabies infection, none of the other animals had rabies. The area covered 9 counties and cities, 53 townships/districts, including10 mountainous indigenous townships, in which the ferret-badger was predominantly the infected animal.

The central area detected 64 (40.7%) rabid animals, followed by the eastern area with 44 cases (28.0%). The area covered included the counties and cities from Heping District in Taichung City in the north, to Majia Township in Pingtung County in the south, and from Chenggong Township, Donghe Township, Yanping Township in Taitung County in the east, to Liouying District in Tainan City and Tianliao District of Kaohsiung City in the west. Taitung county and Nantou County with 41 cases are the highest (both account for 26.1% each), Taichung City with 23 cases (14.6%) is second (see table 2); the combined distribution of cases involving ferret-badgers and rabid animals is shown in Figure 2. As of September 30, there were 7 cases of people being bitten or scratched by a rabid animal, all of which were ferret-badgers. These were at Dongshih District of Taichung City; Renai Township, Yuchih Township and Shueili Township of Nantou County; and Chenggong Township, Donghe Township and Beinan Township of Taitung County. All cases have already inoculated with immunoglobulin and a rabies vaccine. A woman in Taitung City was bitten by a house shrew on July 27, which was confirmed as being infected with rabies. No wound was found by the doctor and there was no need for a rabies vaccine.

Table 2. Distribution of rabid animals in Taiwan, July 21 to September 30, 2013

area	county and city	Township and District	case no.	%	cases of Township and District
central area	Taichung City	7	23	14.6%	Sinshe District(6)、Taiping District(5)、Heping District(4)、Dongshih District(3)、Wufong District(3)、Dali District(1)、Beitun District (1)
	Nantou County	10	41	26.1%	Renai Township(3)、Yuchih Township (8)、Sinyi Township (2)、Shueili Township (3)、Lugu Township (7)、Guosing Township (6)、Jhushan Township(7)、Caotun Township (2)、Puli Township (2)、Jhongliao Township(1)
southern area	Yunlin County	1	6	3.8%	Gukeng Township (6)
	Chiayi County	4	10	6.4%	Fanlu Township (5)、Jhongpu Township (2)、Jhuci Township (2)、Alishan Township (1)
	Tainan City	9	17	10.8%	Nanhua District(4)、Longci District(3)、Zuojhen District(3)、Nansi District(2)、Lioujia District(1)、Danei District(1)、Dongshan District(1)、Guanmiao District(1)、Liouying District(1)
Kaoping area	Kaohsiung City	10	12	7.6%	Neimen District(1)、Tianliao District(2)、Cishan District(2)、Meinong District(1)、Yanchao District(1)、Liouguei District(1)、Alian District(1)、Jiasian District(1)、Shanlin District(1)、Maolin District(1)
	Pingtung County	2	4	2.5%	Majia Township (3)、Wutai Township (1)
eastern area	Hualien County	2	3	1.9%	Jhuosi Township (2)、Yuli Township (1)
	Taitung County	8	41	26.1%	Donghe Township (14)、Taitung City (2)、Chenggong Township (7)、Haiduan Township(3)、Chihshang Township (6)、Guanshan Township (2)、Yanping Township (1)、Beinan Township (6)
Total		53	157		

Note: Under line is the mountain indigenous township.

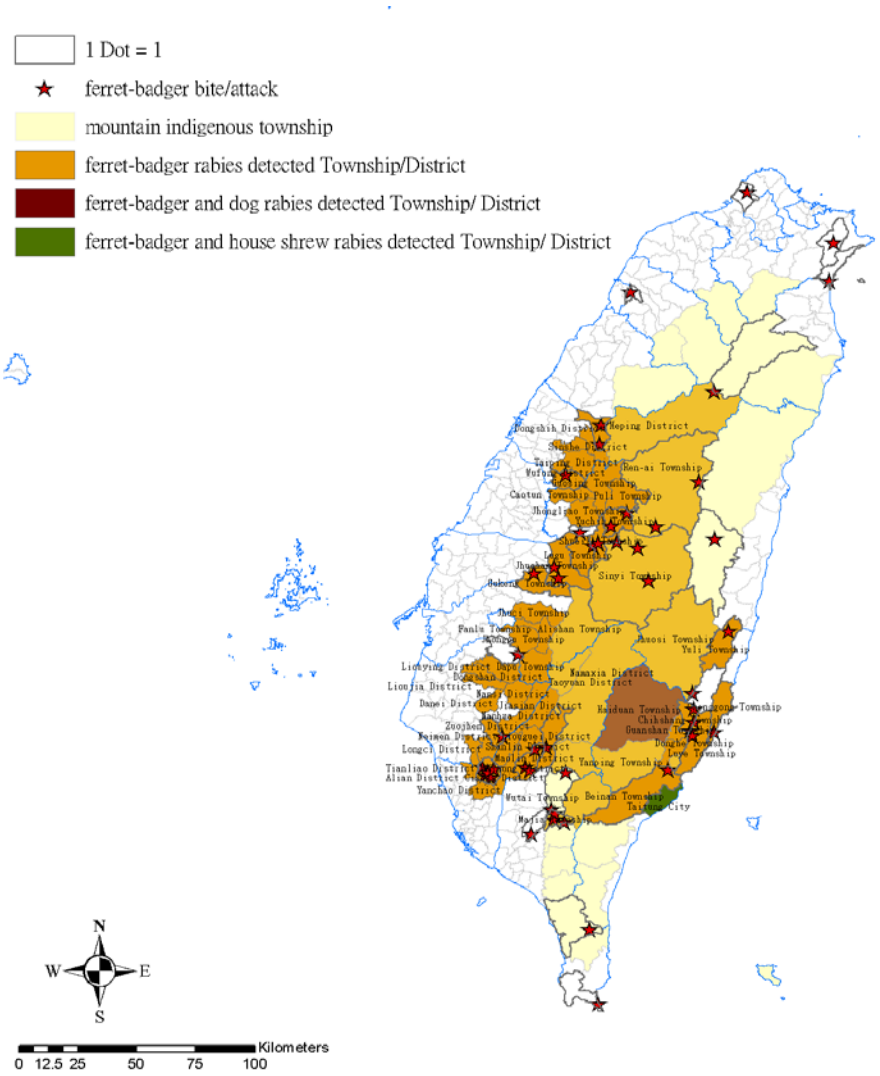

Figure 2. The geographic distribution of rabid animals and the occurrence of ferret-badger attack events in Taiwan, July 21 to September 30, 2013

Discussion

1. Risky population and area

Our data revealed that the male had higher risk to be bitten by animals than the female. Persons aged 25-64 years old were more likely to be bitten by animals this is different from other countries that the 5-14 years old children are the highest risk group of being bitten or scratched by animals [1]. This may reflect the different cultural and attitudes toward nature in other countries. Dogs and cats were the main source of animal bites or scratches, while the detection of rabid animal was mainly in wild animals: this is similar to the U.S.A.'s experience, only the rabid animals are often raccoons rather than ferret-badgers [6]. China has had many human rabies cases due to being bitten or scratched by ferret-badger since 1997[7, 8]. In addition, surveillance in Georgia, U.S.A., shows that females are more apt to be bitten by cats, but males are more likely to be bitten by wild animals (raccoon); most often was the hand was the site of the wound (40%), followed by the head and neck (19%) [9]. This result is different from Taiwan’s experience.

In Taiwan, the predominant rabid animal was ferret-badgers, rabid ferret badgers were mainly detected in central, southern and eastern parts of Taiwan especially in the mountainous areas in Nantou County, Taichung City and Taitung County. Researches revealed that in Taiwan the ferret-badger is one of the main species of small carnivorous animals widely spread in low mountainous area above sea level and in these areas there has been closer interaction between ferret-badgers and human [10-11]. The mountainous area of Nantou County, Taichung City and Taitung County had a high ferret-badger detection rate, including 8 remote mountain indigenous townships where it is difficult to transmit information. This suggests that to raise the awareness of the resident in these remote areas to avoid contact with ferret-badger is needed.

2. Potential risk areas

Rabid animals may appear sick, behave unusually even attack human initiatively [12]. These were similar to the main symptoms shown by the rabid ferret-badgers in 7 cases. The ferret-badger is a nocturnal animal [10-11], therefore ferret-badgers haunt during the day, as well as unprovoked attack human is unusual behavior.

In our database, there were also many reports of suspected rabid animals or ferret-badger attacks from the northern part of Taiwan such as New Taipei City, Yilan County and Hsinchu County, up to the end of September 2013. The Bureau of Animal and Plant Health Inspection and Quarantine examined about 160 specimens from these area but all the specimens were tested negative for rabies. Because of rivers, mountains and other natural barriers exist, which might be the reason why rabies has not spread to northern Taiwan. However, we suggest to conduct an active surveillance program in the townships neighboring to the epidemic area for monitoring the rabies epidemics in wild animals. The townships located in central, southern and eastern parts of Taiwan which nearby where the rabid ferret-badgers had been detected should be classified as a potential risk area.

3. Potential risk species

In other countries, dogs, cats, raccoons, foxes, and other animals are reported to be infected by rabies virus, and bats are also reservoirs for the virus. In 2002, a case of human rabies due to ferret-badger bite was reported from Chunan county in Zhejiang Province, China, and a case of rabies in a domestic dog in 2008, but has not reported any case of human rabies since 2005. It reveals that transmission of the virus from wild animals to domestic animals cannot be excluded [7]. It shows that rabies has the possibility of being transmitted across species: dogs and carnivorous animals are potentially the main species at risk. A study that interviewed people working in the lower mountainous areas of Miaoli and Hsinchu Country shows that there are still some wild animal hunting, in which the residents will take domesticated dogs which may be used to catch various wild animals. There is a risk of infection and spreading the disease [10].

4. Analysis of human behavior

The surveillance data for animal bites and scratches from Georgia in the US reveals that regardless of the age, the main cause of animal bites and scratches is provoking the animal, accounting for 61-80% in all age groups [9]. The present surveillance has not collected the relevant information of this human behavior, so we are unable to offer comparable statistics.

Suggestion

1. Set up the surveillance mechanism for being bitten or scratched by animal

In order to classify the high risk area and to detect clusters of incidences promptly, surveillance of rabies should include human and animal. In addition, the use of rabies vaccine should be included [12,14]. The U.S. has adopted an animal bite and scratch notification mechanism, and has human and animal laboratory information in hand at the same time[6, 9,13] to ensure comprehensive surveillance.

Taiwan was previously rabies free. Although human rabies was classified as a Category 1 communicable disease and was to be monitored, there were no other monitoring mechanisms. Advanced countries in rabies affected areas monitor animal bites and scratches and collect epidemiological information from these cases. The only information collected at present is through the rabies vaccine application and reviewing mechanism. The hospital fills out an application form for each case, and the staff of regional control center of TCDC will enter the data into the database. Rabies vaccination will be included in the National Health Insurance (NHI) coverage. Besides integrating the existing surveillance systems, one suggestion is to use the NHI database and RODS to analyze the trend of animal bites and scratches. If an unusual rise is detected, other than providing warning, it can alert relevant government institutes to strengthen monitoring and find the causes. Integrating long-term NHI surveillance data and RODS can help understand the demographic characteristics of the population bitten or scratched by animals, so as to help focus on the target population and provide the relevant information of risk, as well as help prevention and control if necessary. In addition to the reporting mechanism for infectious diseases, we suggest testing patients with unexplained encephalitis in intensive care units for rabies and collect epidemiological information from the NIIS, in order to have information on the risk of animal bites and scratches.

Relevant information from animal laboratory testing, vaccination and management, also are helpful for assessing the areas at risk of rabies and the data from surveillance systems will be stronger if these data are integrated.

2. Set up an information consolidating platform for animal surveillance and human bitten or scratched by animals.

The rapid and complete exchanging of information is an important point in the control and prevention of infectious disease. We suggest that information from human rabies surveillance, animal bites and scratches surveillance, application for rabies vaccinations, animal laboratory testing, active surveillance and vaccine inoculation and management, currently done separately by government departments and agencies is consolidated. In order to understand the outbreak the epidemic intelligence is considered longitudinally, can connect horizontally information such as human and animal surveillance, laboratory data and vaccine inoculation. Integrated information sees the overall epidemic situation, and is a basis for the evaluation of the risk of different areas and animals to the wider population for prevention, and provides a reference for physicians in the diagnosis and treatment of patients bitten or scratched by animals. It can also be regarded as a reference for decision-making for prevention and control policies.

3. Investigation and analysis for the model of human behavior

Chingtien county in Zhejiang Province in China has recorded a case of rabies from catching and eating a ferret-badger[8]. When the field investigation for this outbreak, found that the residents in southern and eastern mountain area have habits of catching and eating ferret-badgers, and drinking the blood of ferret-badgers. These risky behaviors can result in being bitten or scratched by ferret-badgers and subsequently being infected with rabies. In addition, the hunting of wild animals for eating, pest control, selling and breeding, is practiced in some mountainous areas. The higher proportion of small carnivorous animals hunted are gem-faced civets, followed by ferret-badgers[10]. This shows that human behavior is related to animal bites and scratches.

In depth interviews and field observations will have more value for reference, so a case study method in the future is recommended, along with active surveillance of animals in mountainous areas, going deeper into remote townships and indigenous districts, to study the risks to specific populations and behaviors.

Limitation

This article studies the surveillance of animal bites and scratches by analyzing the vaccine application database; it is not representative of the wider population.

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Diagnosis, Management, and Prevention of Rabies

Hoa-Hsin Wu[1], Kai-Hsiang You[2], Hsiu-Yun Lo[2]

1. Office of Preventive Medicine, Centers for Disease Control, Ministry of Health and Welfare, Taiwan
2. Division of Acute Infectious Diseases, Centers for Disease Control, Ministry of Health and Welfare, Taiwan

Abstract

Since the Council of Agriculture reported three rabid ferret-badgers in July 2013, Taiwan has become rabies enzootic area after being rabies-free for 50 years. About 40% persons exposed to rabid animals will be infected and the mortality is extremely high. This article introduces the symptoms, diagnostic tests, management, pre-exposure and post-exposure prophylaxis of rabies. Rabies is an acute progressive encephalomyelitis. The typical clinical symptoms involve neurological presentations predominantly, including agitation, convulsion, and confusion, etc. The laboratory techniques include viral antigen detection, virus isolation, viral antibody detection, and viral ribonucleic acid detection. Due to no proven standard therapy, it is important to prevent rabies after suspect exposure to the virus, consisting of local treatment of wounds, rabies immunoglobulin (RIG) administration, and rabies vaccine injection. In response to re-emergence of rabies, Taiwan CDC has controlled and coordinated the distribution of rabies vaccines and RIG in Taiwan since July 2013. Other implemented strategies include increasing designated hospitals for rabies vaccines storage, enhancing the healthcare providers training about rabies prophylaxis.

Keyword: rabies, management, prophylaxis

Introduction

Since the Council of Agriculture, Executive Yuan identified three positive rabid ferret-badgers in July 2013, Taiwan has become rabies enzootic area after being rabies-free for 50 years. About 40% persons exposed to rabid animals will be infected and the mortality is almost 100% [1]. To facilitate the healthcare providers (HCP) to manage persons exposed to rabid animals, this article summaries the symptoms, diagnostic tests, management, pre-exposure and post-exposure prophylaxis of rabies.

Diagnosis

Rabies is an acute progressive encephalomyelitis. The clinical diagnosis is simple in a person presenting with a compatible illness (e.g. aerophobia, and hydrophobia) after documented animal exposure history [2]. In the absence of a history of exposure or paramount signs, however, the diagnosis on clinical grounds alone is difficult and laboratory testing is necessary to establish the diagnosis.

1. Clinical diagnosis

(1). Incubation: The incubation period for rabies is typically 3 - 8 weeks, but may vary from <1 week to >1 year。

(2). Prodrome:The virus moves centripetally from the periphery to dorsal root ganglia in this stage, and causes neuropathic pain at the bite site, presenting as burning, itching, pruritus. Prodromal symptoms last a few days, generally not more than a week.

(3). Acute neurological phase：Classic rabies can be classified to two forms in this phase as follows:

a. Encephalitic form: about two-thirds of patients have an encephalitic form and manifest as hyperactivity, confusion, spasm, and autonomic stimulation signs (e.g., hypersalivation, anisocoria). The spasms can be incited by tactile, auditory, visual or olfactory stimuli (aerophobia, and hydrophobia)

b. Paralytic form: the remainder present with paralysis; they generally start in the bitten limb but progress to all limbs, the bulbar and respiratory muscles. Phobic spasms may appear in only 50% of such patients and the presentations mimick other neurological disorders, such as Guillain-Barré syndrome (GBS). The following features may serve to differentiate this disorder from GBS: persistent fever from the onset of limb weakness; intact sensory function of all modalities except at the bitten region; percussion myoedema; and bladder dysfunction.

(4). Coma: The patients become comatose after 1-2 weeks of acute neurological phase and die of arrhythmia or myocarditis [2].

2. Laboratory diagnosis

The rabies diagnostic tests include viral antigen detection, virus isolation, viral antibody detection, and viral ribonucleic acid (RNA) detection (Table 1). The last two methods are available in Centers for Disease Control (CDC), Taiwan.

3. Image study

Computerized tomography of the brain is of little diagnostic value [2], but magnetic resonance imaging (MRI) when performed with adequate precautions can be helpful [13]. Typical MRI abnormalities are hypersignal T2 changes involving the spinal cord, brain-stem, thalamus, limbic system, and white matter during the non-comatose phase. During the comatose phase, widespread T2 hyperintense lesions in the forebrain can be seen. Such progressive patterns can help to differentiate rabies from other viral encephalitides [2].

Management

The mortality rate of rabies is extremely high. Due to no proven standard therapy, current management for rabies patients is mostly symptomatic and palliative [2, 3, 13], including adequate sedative agents, setting the patients in a private, quite area, and emotional support. Some therapeutic agents, such as combination therapy with immunoglobulin plus vaccination, ketamine and interferon-α, or large doses of intravenous human rabies immunoglobulin (RIG)

had been advocated with limited success [13]. There is a survived rabies patient under the treatment of the "Milwaukee protocol", developed by the Medical College of Wisconsin, consisting of supportive care, therapeutic coma, and antiviral agents. However, data about the protocol have been conflicting. In the protocol, the rabies vaccine and immunoglobulin are considered to be avoided if possible, due to slow natural immune response and may not penetrate blood-brain barrier, respectively [15]. Some researchers are concerned about clinical deterioration after receipt of rabies vaccine and immunoglobulin [16].

Table 1. Laboratory assays for rabies diagnosis

Method	Description	Advantage	Disadvantage	Sensitivity / Specificity
Antigen detection				
Direct fluorescent antibody technique, (DFA)	1. Gold standard for rabies diagnosis 2. The test is based on microscopic examination of smears of brain, skin from the nuchal area of the neck, and salivary gland biopsy samples after incubation with anti-rabies polyclonal or monoclonal antibodies.	Lower cost, rapid (2-4 hours).	* The sensitivity is influenced by the sample type, experience of the performer, and quality of the used antibodies and equipment. *It may not be practicable in decomposed tissues.	98.3% / 97.3% [7]
Enzyme-linked immunosorbent assay(ELISA)	1. Useful for large epidemiological surveys. 2. Provides results of high agreements with the DFA (96%) [8].	* Lower cost, rapid (few hours). * Practicable in decomposed tissues. * Easy to perform. * Do not need for microscopy * Suitable for large numbers of samples.	* Less sensitive than DFA, and not suitable for confirmative diagnostic test.	95.0% / 99.9%[a][8]
Antibody detection				
Rapid fluorescent focus inhibition test(RFFIT)	1. Neutralizing antibodies tend to appear on average 7-8 days after clinical symptoms, and are considered of little value as a confirmatory test. 2.Useful in the detection and quantification of rabies antibody in animals and humans post vaccination. 3. Serum is the commonly used specimen due to viral antibodies seldom found in the cerebrospinal fluid.	* Reference test to monitor neutralizing antibodies.	* Longer turnaround time (24-48 hours). * Requirement for specialized labs capable of handling live virus. * Higher cost.	74% / 98%[9]
Fluorescent antibody virus neutralization test (FAVN)		* Reference test to monitor neutralizing antibodies. * Appropriate for dealing with the large numbers of samples.	* Longer turnaround time (48 hours) * Requirement for higher cost and larger volumes of examined serum than the RIFFT * Requirement for specialized labs capable of handling live virus	88.6% / 100%[b][10]
ELISA		* Lower cost, rapid (4 hours) * Easy to perform * Do not need specified labs	*Not specific to neutralizing antibodies *Less sensitive than RIFFT	66%/ 100%[9]
Virus isolation				
Inoculation of laboratory animals	Isolation of virus following intracerebral inoculation of weaned mice with homogenized suspensions of brain, spinal cord or salivary gland from suspected rabid cases.	* Confirmation test for the samples with negative or uncertain DFA results. * Amplification of virus for further characterization of the isolate. * Useful in labs without cell culture facilities.	*4 weeks or even longer for final results (It can be shortened to 10-21 days if the suckling mice were used).	
Isolation of rabies virus in cell culture	Homogenized specimens can be inoculated directly onto monolayer cell cultures.	* Confirmation test for the samples with negative or uncertain DFA results. * Lower cost, rapid (1-2 days) when compared to animal inoculation. * Do not involve the use of live animals.	* The sensitivity varies with different cell lines used.	
Viral ribonucleic acid detection				
Reverse Transcriptase-Polymerase chain reaction (RT-PCR)	Despite not recommended if DFA available, RT-PCR is playing an increasingly important role in diagnosis, strain characterization, and epidemiological surveys.	* Useful in decomposed samples or liquid specimens, e.g., saliva, tear. * To discriminate between rabies virus and other *Lyssaviruses*. * Rapid (few hours).	* Serial samples of saliva and urine should be tested, as the virus is excreted intermittently. * The sensitivity is influenced by the sample amounts and specimen types.	8.0 – 100% / 100%[c] [11, 12]
Histopathology	Rabies virus causes encephalitis with limited cellular damage. However, Negri body, an intracytoplasmic, eosinophilic inclusion body, can be found in rabies-infected tissues.	* Easy to perform * Pathognomonic feature of Negri body.	* Low sensitivity, influenced by samples from different site. * Longer turnaround time * More expensive than DFA.	50 - 80% / 93.5%[7]

a. compared to DFA; b. compared to RIFFT; c. The sensitivity varies between different specimens

Prophylaxis

1. Post-exposure prophylaxis (PEP)

Due to no effective therapy nowadays, it is important to prevent rabies after suspect or proven exposure to the virus, including timely local treatment of wounds, passive immunization (RIG), and active immunization (rabies vaccines) [2, 17, 18]. The recommendations regarding PEP between U.S. Centers for Disease Control and Prevention and World Health Organization (WHO) are different. The Advisory Committee on Immunization Practices (ACIP) in Taiwan, following recommendations of WHO, established the guidance for PEP according to categories of exposure and types of exposing animals (Table 2, 3). The guidance will be modified timely according to surveillance data of rabid animals from the Council of Agriculture. For example, after the positive rabid house shrew identified on July 30th, 2013, which was the first trans-species infection in Taiwan, people exposed to house shrews, stray dogs and cats have become eligible to government-funded PEP.

Table 2. Recommendations for administration, brands, dosages, and adverse effects of rabies immunoglobulin (RIG)

Exposing animal species	Recommendations
1. Ferret-badger 2. House shrew (Taitung County only) 3. Animals behaving abnormally (e.g., unprovoked attack) and tested positive for rabies by the Council of Agriculture	1. Administer RIG for all persons with category III exposures 2. Administer RIG for immunocompromised cases with category II exposures or for immunocompetent cases with category II exposure to positive rabid ferret-badgers

Immunoglobulin	Human RIG	Purified equine RIG
Brand	Hyperrab	Favirab
Dose	20 IU/kg	40 IU/kg
IU/ml	150 IU/ml	200 IU/ml
Contraindication	No	History of allergy to equine protein
Adverse reactions	Soreness and mild temperature elevations may be observed at the site of injection. Sensitization to repeated injections has occurred occasionally in immunoglobulin - deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported.	Adverse effects are observed in less than 10% of subjects. The immediate reactions are anaphylactic reactions with hypotension, dyspnea, and urticaria. In rare cases (less than 1 case in 10,000), more severe reactions such as angioneurotic edema or anaphylactic shock may develop. Delayed-type reactions may occur about six days after the injection, consisting of fever, pruritus, erythema, urticaria, adenopathy, and arthralgia.

Table 3. Recommendations for rabies vaccination according to exposing animals

Animal types	Recommendations	Notes
Wild mammals (including house shrew)	Administer vaccine for categories II and III exposure	The vaccination can be discontinued if the exposing animals is tested negative for rabies
Stray dogs and cats	Administer vaccine for categories II and III exposure	The vaccination can be discontinued if the exposing animals are confined for 10 days remaining alive and healthy
Domestic dogs, and cats	Vaccination is not recommended	Administer vaccine if the exposing animals present signs suggestive of rabies during the 10 days observation period, and are confirmed positive for rabies by the official laboratory

(1).Management of wounds:

Irrigate the wounds immediately and thoroughly with running water or soap water for at least fifteen minutes, and sterilize the wounds with povidone-iodine solution. Suturing of wound should be avoided as far as possible. If surgically unavoidable, minimum loose sutures should be performed for debris discharged smoothly. If RIG has been administered, suturing should be performed several hours later (more than 2 hours) for antibodies infiltrating into tissues properly [18]. Thorough wound cleansing alone markedly reduce the likelihood of rabies in animal studies [17].

(2).Passive immunization:

RIG provides rapid immunity to tide over the initial phase after vaccination before neutralizing antibodies inducted. The ACIP in Taiwan proposes guidance for the RIG administration according to categories of exposure [2] and types of exposing animals (Table 2). The full dose of RIG, according to body weight of the cases, should be thoroughly infiltrated in the area around and into the wounds if possible. Any remaining volume should be injected into deep muscles at the wounded limb (e.g., deltoid or anterolateral thigh). If wounds were severe and multiple (most likely in children), dilute the RIG in sterile normal saline two to three fold to be able to permit infiltration of all wounds.

RIG can be administered concomitantly or up to seventh day after vaccination. However, RIG should be administered at a site distant form the site of the first vaccine dose as it may suppress the antibody production. Beyond the seventh day after vaccination, RIG is not indicated since an antibody response to vaccine is presumed to have occurred. There are two classes of RIG available in Taiwan: human rabies immunoglobulin (HRIG) and purified equine rabies immunoglobulin (pERIG), both recommended by WHO (Table 2).

(3).Active immunization:

Rabies vaccines, inducing active neutralizing anti-rabies antibodies, should be administered as soon as possible after exposure. The five-dose regimen consists of one dose each on days 0 (the date of the first dose of vaccine administration), 3, 7, 14 and 28. The vaccination should be administered in the deltoid area or the anterolateral thigh and avoid the gluteal area due to lower neutralizing antibody titers production. For previously vaccinated persons, whether complete pre-exposure (PrEP) or post-exposure prophylaxis, who are exposed to rabies, two doses of vaccine should be administered, one immediately and one 3 days later. In the “International Expert Meeting” on August 2013 [19], the experts suggested that such persons should be re-vaccinated regardless of the last vaccination date or the neutralizing antibody titer.

Because the high fatality of rabies, the benefits of the vaccination outweigh the risks in pregnancy, lactation, and infantile, and these conditions are not contraindication for vaccination [2, 17].

(4).Immunosuppression:

The immune response to vaccination in immunocompromised individuals might be inadequate and PEP recommendations for such persons are different from those for immunocompetent persons [2,17]. The definitions of immunosuppression are [18]:

a. Patients with human immunodeficiency virus infection, post-transplantation within 2 years or receiving immunosuppressive agents continuously.

b. Patients with congenital immunosuppression, asplenia, autoimmune disease under corticosteroids or other immunosuppressive agents, malignancy under chemotherapy, malaria under chloroquine treatment.

c. Patients with other medical conditions which might influence immune functions, including chronic kidney disease, diabetes, liver cirrhosis, chronic liver disease, etc.

If these persons have not received complete PrEP or PEP previously, RIG and a complete series of five intramuscular doses of rabies vaccine should be administered regardless of category II or III exposures according to the recommendations of WHO [2]. The guidance for immunocompromised individuals in Taiwan is tailored according to epidemiologic data of animal rabies, mostly similar to the guidance for the immunocompetent persons, except that RIG and a complete series of vaccination will be prescribed for immunocompromised cases with category II exposure to ferret-badgers. If these persons have received complete PrEP or PEP previously, a complete series of five doses of rabies vaccine is required and RIG is unnecessary. In capable labs with optimal resource, neutralizing antibody titers should be determined 2-4 weeks after completion of PEP (≥ 0.5 IU/mL or 1:5 serum dilution by RFFIT [2]; ELISA can be used as an alternative test [9]) for decision-making about a single booster dose of vaccine. Experts should be consulted if the titer less than the reference value. For immunocompromised individuals, intradermal vaccine injection or schedules other than five-dose regimen are inappropriate, and the PEP should be considered as incomplete.

2. Pre-exposure prophylaxis

U.S. CDC and WHO both recommend PrEP for anyone who is at continual, frequent or increased risk for exposure to the rabies virus as a result of their occupation, such as laboratory worker dealing with rabies virus, veterinarians, and wildlife workers. Three-dose regimen can be administered, one injection each on days 0, 7, and 21 or 28 [2, 17]. For the safety of animal disease control professionals, wildlife workers, stray animal-control officials, Taiwan CDC offers PrEP to these populations according to the lists provided by central departments and local county governments after risk assessment.

Table 4. Rabies pre-exposure prophylaxis guidelines - U.S. Centers for Disease Control and Prevention [18]

Risk category	Nature of risk	Typical populations	Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below a 1: 5 serum dilution.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, veterinarians and staff, animal-control and wildlife worker in area where rabies is enzootic. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below a 1: 5 serum dilution.
Infrequent	Exposure nearly always episodic with source recognized.	Veterinarians and animal-control staff in areas where rabies is uncommon to rare. Veterinary students, travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care is limited.	Primary course. No serologic testing or booster vaccination.
Rare	Exposure always episodic with source recognized. Bite or nonbite exposure.	General populations.	No vaccination is necessary.

3. Establishment of vaccine supply plan

People who had been bitten by animals did not receive PEP during the past fifty years when Taiwan had been listed as rabies-free. Hence, only about 300 doses of human rabies vaccines and 10 doses of HRIG are stockpiled annually in Taiwan CDC for PEP for travelers returning from overseas area with enzootic rabies. In response to re-emergence of rabies, Taiwan CDC have controlled and coordinated the distribution of all stored rabies vaccines and RIG (including official and of manufacturers) in Taiwan since 2013 July. To implement a complete prophylaxis campaign, the other strategies include emergent importation of vaccines and RIG, increasing designated hospitals for rabies vaccines storage, enhancing the HCPs training about PrEP and PEP. PEP is funded by government since 2013 July 24 if exposed persons are eligible by the guidance, and is scheduled to be covered under National Health Insurance in 2014.

(1). Importation:

The future requirement for rabies vaccine and RIG is under assessment according to the medically-attended animal bite surveillance data from “Real-time Outbreak and Disease Surveillance system”. For rapid expansion of the rabies vaccine stockpiles to fulfill the demands of persons who are indicated for PEP or PrEP, Taiwan CDC has maintained a close liaison with manufacturers to seek the supply of rabies vaccines and RIG since July 10th. Special importation projects have been implemented and the vaccines had been issued to the designated medical facilities since July 26th. Till September 24th, about 42,500 doses of vaccines have been purchased from Norvatis Taiwan and Sanofi Pasteur Taiwan to ensure the availability of vaccines for PEP and PrEP.

To be prepared and response to the re-emergence of rabies, pERIG has been purchased and delivered to regional centers of Taiwan CDC since August 4th. Till September 24th, there are 1,946 doses of HRIG (2 ml/vial), 250 doses of HRIG (10 ml/vial), and 2,000 doses of pERIG available.

(2). Regulation:

For precise and effective prescription of vaccines and RIG, the PEP administration was once regulated by application and verification individually according to the ACIP recommendations. Besides, persons in high risk groups are offered with PrEP according to lists from the Council of Agriculture and local county governments. For long term disease control and preparation, the regulatory policy has been changed to *ad hoc* audit, which means that the application would be reviewed randomly by authorized officials, since September 9.

(3). Distribution:

Before the rabies resurfacing in Taiwan, the rabies vaccines had been stored in twelve Taiwan CDC-contracted hospitals with travel medicine services. Since the first three rabid positive ferret-badgers were identified on July 18th, another three medical facilities in Nantou and Yunlin County have become the vaccine stockholders. The numbers of medical facilities with rabies immunizations increased to 28 on July 26th, 54 on August 5th, and 60 on August 9th. There is a vaccine-stored hospital in each of island counties, including Penghu, Kinmen, and Lianjiang, and 2-3 stockholders on average in other counties. Current accessibility of PEP and PrEP has increased remarkably [20].

(4). Training:

Taiwan CDC has published the “Guidance of human exposure to suspected rabid animals” [17], and cooperated with several medical associations to conduct series of education courses and seminars to strengthen the capacity of HCPs to manage persons exposed to suspected rabid animals.

Conclusion

Despite the high fatality of rabies, the disease can be prevented with adequate post-exposure prophylaxis. The burden of rabies can be reduced if the general populations and HCPs are capable of recognizing the exposure risks and are familiar with prophylactic measures.

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Exploring on Rabies Control and Elimination Strategy

Mei-Mei Kuan[1], Muh-Yong Yen[2]

1. Chief Secretary Office, Centers For Disease Control, Ministry of Health and Welfare, Taiwan
2. Taipei City Hospital, Kun Ming Branch

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].

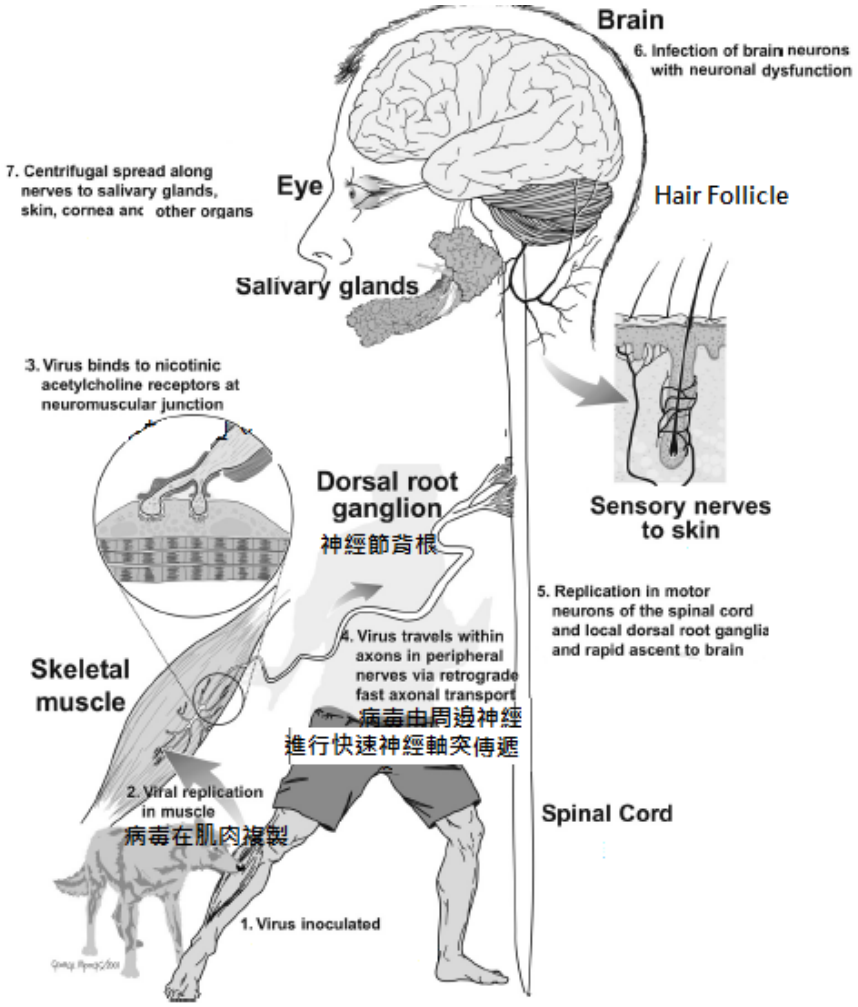

Figure 1. Pathological development of human rabies after animal bites. [3].

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)

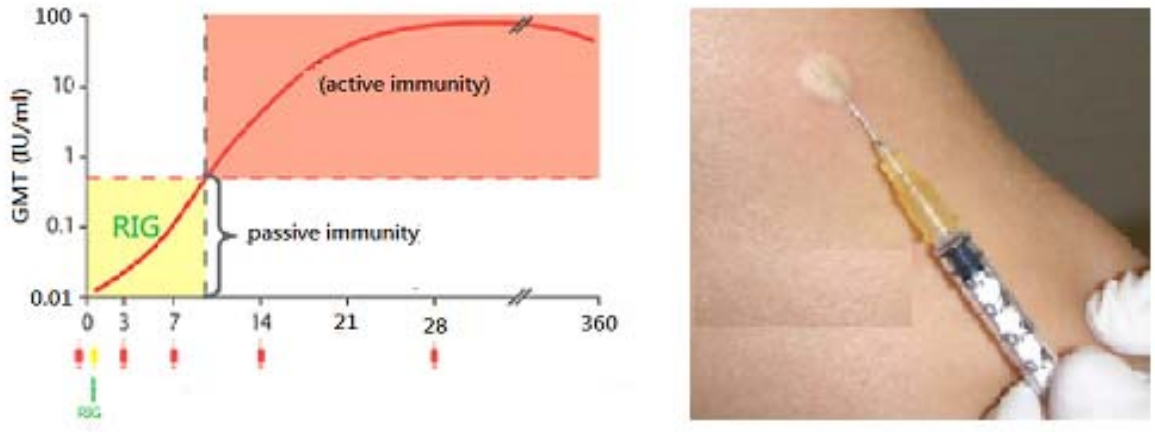

Figure 2. The illustration of rabies post-exposure prophylaxis and the vaccination schedule; partially cited [2]. (A) Rabies immunoglobuliin (RIG) provides passive immunity from 0 days to 7-10 days, a window period before the protection of active immunization; then gradually subsided; Rabies neutralizing 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).

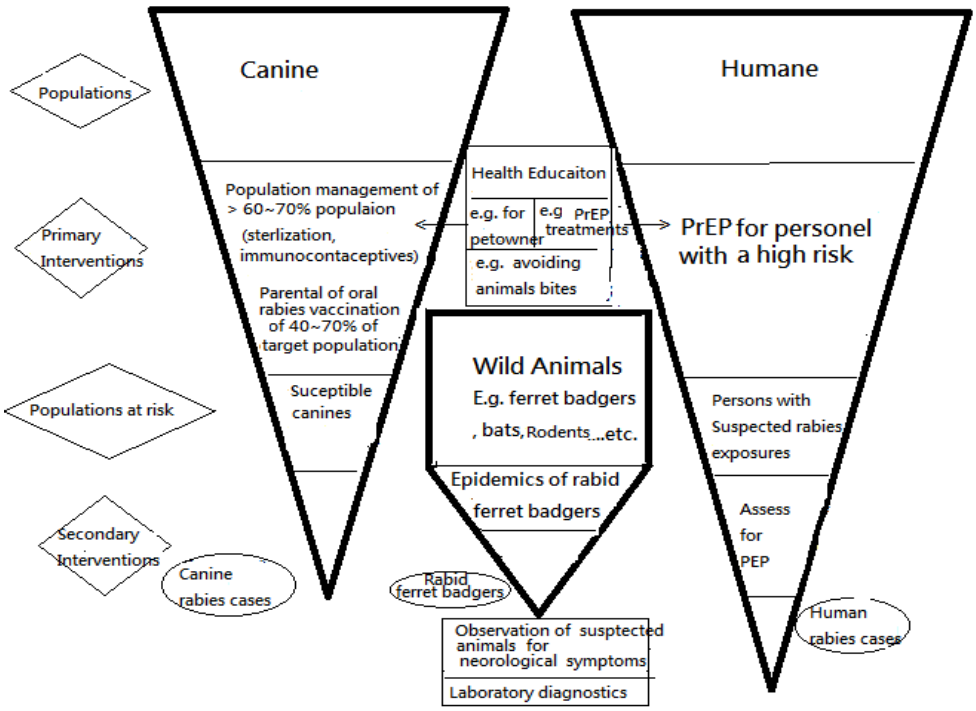

Figure 3. A concept scheme of integrated health (One health) intervention strategies for reducing the risk of rabies, partially adapted from reference [5]. Intervention refers to the first stage of the establishment of immunity among various ethnic groups, including the management of vaccination of dogs 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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History of Rabies Control in Taiwan and China

Chen-Hsuan Liu

1. Graduate Institute of Molecular and Comparative Pathology, School of Veterinary Medicine, National Taiwan University
2. Animal Cancer Research Center, School of Veterinary Medicine, National Taiwan University
3. National Taiwan University Veterinary Hospital

Abstract

Rabies is one of the top ten causes of death from infectious diseases in the world; it is also an ancient global zoonosis. The first case of rabies was recorded in 2300 BC. In China, the earliest report of rabies was recorded in "Zhuo Zhuan", written during the Spring and Autumn Period and the Warring States Period in 556 BC. China has the second highest number of rabies deaths in the world, just behind India, with 90% of the deaths occurring in farmers, students, and children. Most deaths are caused by dogs, followed by cats and other animals. Rabies virus isolated from humans and animals are all of genotype 1. Rabies caused 782 deaths in Taiwan during 1948 - 1959. In 2002, 2012, and 2013, there was an imported human rabies case each year. In 1956, Taiwan began rabies control by vaccinating dogs. Along with the control of domestic and stray dogs, rabies was successfully eradicated in 1961. However, in July 2013, following the detection of rabies in ferret-badgers, a house shrew and a dog also tested positive for rabies virus. On August 1, 2013, the Rabies Control Central Epidemic Command Center was established. Through inter-ministerial collaboration, increased health education, vaccination of dogs and cats, and the use of pre- and post-exposure prophylaxis in humans, there have been no human infections reported. The response phase is now largely completed. Follow up actions are also being planned. History has shown that as long as the people are united in disease prevention, rabies may become a historic term in Taiwan once again.

Key words: rabies, rabies virus, ferret-badger

History of rabies in China

Rabies is an ancient global disease. The first recorded case of rabies is reported in the Eshnunna Code in Mesopotamia in 2300 BC [1]. At that time, if rabies occurs, dog owners would be notified to put the dog under strict custody. If the dog attacks and causes infection and death, the owner would be heavily fined. Rabies was rampant during the middle ages. It was found in dogs and wild animals in Europe during the1500's. The disease was brought to the Americas by immigrants during the middle of the 18th century. Rabies in Africa may be traced to 1772, when the British brought in the disease, which slowly spread to the entire

African continent. Rabies is more prevalent in northern and eastern Africa. Currently, rabies is one of the top ten causes of death from infectious disease in the world. Each year, an estimated 55,000 people die from rabies, of which, 31,000 occurred in southeast Asia, 24,000 in Africa. This is more than the deaths caused by Japanese encephalitis, dengue fever, and yellow fever combined.

Rabies has been circulating in China for a long time. The earliest report of rabies was recorded in the ancient text of "Zhuo Zhuan", written during the Spring and Autumn Period and the Warring States Period. It was written "in November of the 11th year of Xianggong (556 BC), a person was chasing a rabid dog". This indicated that rabies has been around in China for 2500 years. Later on, Han and Jin dynasty history texts also recorded the danger posed to humans by rabid dogs, and rabid dogs were driven out. Old medical texts, including books from the Jin, Tang, and Song dynasties all have texts on diagnosis, treating, and preventing rabies. The earliest medical text, the "52 Prescriptions" included treatment for "bites by rabid dogs" and "bites by dogs", indicating that even then, the distinctions were made between bites by rabid dogs and non-rabid dogs [2-4].

During 1911 - 1949, rabies was rampant in all provinces. With incomplete recording of cases, there were approximately 5,000 cases a year, with a mortality rate of 1.2/100,000 persons. After 1949, there were cases reported in accordance with the Communicable Disease Control Act, which listed rabies as a category II reportable disease. In 1956, there were 24 provinces reporting 1,942 cases, resulting in the first epidemic peak. During 1980 - 1989, there were 55,367 deaths caused by rabies, resulting in the second epidemic peak. This was an increase of 266% compared to the 1970's. On average, there were 5,500 deaths each year. Mortality rate was the highest among all infectious diseases in China. During the late 1990's, rabies rose once again. During 2000 - 2006, there were 13,104 cases reported. Compared to 519 cases reported in 2000, having 3,279 cases reported in 2006 represents a 513.8% rise. The only places with no rabies reported were Tibet and Qinghai province. Provinces with the most severe epidemic, in descending order, were Hunan, Guangxi, Guizhou, Guangdong, Jiangxi, Jiangsu, Hubei, Anhui, and Henan. These 9 provinces reported 89.3% of the cases. In 1996, there were 98 counties reporting rabies; by 2007, there were 910 counties in 195 regions, located in 23 provinces, reporting rabies. Overall, the number of rabies cases in China rose quickly, spreading from provinces with high incidence. Since the 1980's, China's rabies deaths has been the second highest in the world. There were 4,000 – 8,000 rabies deaths reported annually, just behind India,

which has approximately 20,000 deaths each year. In recent years, the number of dogs has been estimated to be close to 200 million. Because 95% of the human rabies cases is associated with exposure to dogs, this runaway situation must be reversed, or rabies control will become more difficult. In addition, because of the complex geographical and ecological environment, controlling rabies will also have to rely on effective immunization and surveillance of the disease in wild animals [2-4].

History of rabies in Taiwan

Rabies was first reported in Taiwan in 1903, when the Capitol Church News (now Taiwan Church News) printed an article on “crazy dogs”, describing rabies. This indicated that Taiwan had rabies, but most people did not understand its seriousness or have the knowledge of the disease [5]. During colonial Japanese rule, literature also documented rabies. Since 1900, there were at least 11 cases, occurring in southern and northern Taiwan. Starting in 1930, the Japanese began to control rabies by producing inactivated vaccine for canine use at the then Danshuei Manufacturing Institute for Animal Antisera, instituting strict dog registration, and poisoning stray dogs; human rabies vaccines were produced by then Research Institute of Tropical Medicine for the prevention and treatment for rabies. Human rabies cases decreased gradually, eventually disappearing completely. According to literature, before 1948, there were decades when Taiwan had no rabies. However, after the end of World War II, there were frequent traffic between the ports in Taiwan, Shanghai, Hongkong, and Hainan, where rabies were present. On June 17, 1948, the first case of rabies was diagnosed by Dr. Tsung-Yi Lin of the Taiwan University Hospital. In the “Health Statistics, 1984” published by the Department of Health, it was also recorded that rabies in Taiwan, at the time, came from Shanghai. The record stated that during 1948 – 1958, there were no infectious disease specialist, and most dog bites were treated by surgeons. Other than catching and observing dogs and cats that bit humans, patients did not receive immunoglobulin or human rabies vaccine following exposure, and animal catchers also did not receive pre-exposure vaccination. Therefore, there were 782 deaths in Taiwan. The highest number of deaths occurred in 1951, when 238 deaths were reported, followed by 1952, with 102 deaths. In 1956, the Joint Commission on Rural Reconstruction and the Taiwan Provincial Health Department instituted rabies control measures including vaccinating dogs with vaccines imported from the United States and culling stray dogs to control animal reservoir. These policies successfully controlled rabies. The last human death from rabies occurred in 1958. The dog brain sent from Bali in Taipei County on January 13, 1961 became the last case of rabies in animals. After that, no more animal rabies was reported, and Taiwan proclaimed to have eradicated rabies. Since the last human rabies case occurred in 1959, there were cases of imported human rabies case from China occurring in both 2002 and 2012. In 2013, a case was imported from the Philippines. All three cases died. The Domestic Animal Hospital of the National Taiwan University College of Agriculture (now National Taiwan University Veterinary Hospital) was established on June 15, 1955. The hospital actively provided free chick-embryo live attenuated rabies vaccines to dogs. In addition, Professor Rong-biao Liu, Dean of Veterinary Medicine, instructed chief of laboratory, Dr. Si-Kwang Liu, to provide testing for all suspected rabies specimens sent in by veterinary hospitals, health stations, or individuals. They contributed to the rabies eradication in Taiwan. The first case was sent in on July 18, 1958. On December 21 of that same year, a dog brain sent in by the health bureau in Chiayi became the first confirmed rabies case, and the first rabies case in animals.

The Bureau of Animal and Plant Inspection and Quarantine of the Council of Agriculture has contracted National Taiwan University to conduct surveillance of wild animals since 2011. In 2013, rabies was added to the disease under surveillance. In 2013, National Taiwan University received dead ferret-badgers. Autopsy of the animals showed severe encephalopathy, but repeated testing for etiologies causing encephalopathy, including canine distemper and measles, failed to identify the cause of death. The University used RT-PCR to test for rabies in June 2013 which turned out positive, and reported the finding to the Bureau of Animal and Plant Inspection and Quarantine on June 24. On June 26, the specimens were sent to the Animal Health Research Institute, Council of Agriculture, for confirmation. After the Council of Agriculture convened a meeting of rabies experts on July 16, which confirmed the diagnosis of rabies, the incident was reported to the World Organization of Animal Health (OIE) on July 17. May 23, 2012, the date the first rabid ferret-badger was found, became the onset date of the current epidemic [7]. Comparison of the rabies epidemics in different eras is listed in table 1.

Table 1. Comparison of the rabies epidemics in different eras.

	1941–1961	2002–2013
Method of importation	Imported from Shanghai in 1948.	1. Unknown source of infection in ferret-badgers. 2. 3 human cases were all imported from abroad.
Confirmed infections	Humans, dogs, and apes. (Anecdotal report of disease in cattle, goats, and pigs, but no literature documentation). Transmission in urban cycle.	Other than a house shrew and a dog bitten by ferret-badger, all animals with confirmed disease were ferret-badgers. Ferret-badger and house shrew infection considered sylvatic cycle transmission.
Cases	1. 1947: spread by rabid dog brought in from Shanghai. 2. 1958: last rabies human case died. 3. 1959: last dog case died.	1. 2002, 2012, 2013: 3 human cases imported from abroad. 2. 2013: ferret-badgers, house shrew, dog confirmed to be infected. The 7 persons bitten by rabid ferret-badgers all received rabies vaccination and immunoglobulin; none had become ill.
Control measures	1. Rabies vaccines imported from the United States. 2. Stray dogs culled. 3. Other coordinated policies.	1. Increase awareness and increase rabies vaccine coverage among dogs and cats. 2. Stockpile supplies prior to July 2013, because Taiwan was considered rabies-free, approximately 200 doses of human rabies vaccine were stockpiled for travel clinic use. After rabies was reported in Taiwan, there was an emergency procurement of rabies vaccine. 3. Post-exposure prophylaxis for humans bitten by high risk animals and pre-exposure prophylaxis for personnel working in animal disease control.
Virus strain	Unknown (Speculated to be genotype 1).	1. Genotype 1 isolated from ferret-badgers, house shrew, and dog. 2. Genotype 1 found in the 3 imported human cases.
Treatment of animals bites	1. No infectious disease specialists were available at the time; most patients were treated by surgeons. 2. Observation of dogs and cats that bit humans. 3. No post-exposure prophylaxis; sedatives and supportive treatment given.	1. Treatment in accordance with guidelines published by the Centers for Disease Control, Taiwan. 2. Clean wound with water and soap, followed by disinfection using iodine-containing solutions. 3. Post-exposure prophylaxis: provide human rabies immunoglobulin and rabies vaccines.
Mortality rate	100%	Deaths in ferret-badgers, house shrew, and dog. No locally-acquired human fatal case reported. All imported cases died.
Note	To prevent rabies, since 1930 (during Japanese colonial rule), inactivated canine vaccines have been produced by the then Danshuei Manufacturing Institute for Animal Antisera. Human vaccines for treatment and prevention were produced by the then Research Institute of Tropical Medicine. At that time, dog registration and poisoning of stray dogs were instituted and rabies was thus controlled (Annal of animal disease control in Taiwan, 1988, published by the Department of Agriculture and Forestry, Taiwan).	

Rabies control in China

Statistics show that farmers (65%), students (16%), and children (8%) make up 90% of the rabies cases. Among them, 92.5% of the infected live in rural areas, which indicate that residents in the countryside are at high risk of disease. Furthermore, rabies occurrence is also increased in summer and autumn, when both humans and animals have increased outdoor activities. Main reasons for increased incidence include:

1. Increased number of dogs and cats with decreased vaccine coverage: dogs are the main source of infection. Farming communities use dogs to guard their homes and frequently do not leash the dogs. Farming communities in the south have high pet density, up to 15-20 dogs per 100 persons, and 5-10 cats per 100 persons. Vaccine coverage among dogs only 10-20%, and nearly no vaccination among cats, the low vaccine coverage could not establish effective immune shield.
2. After being bitten by dogs or cats, because of the limited knowledge and financial support, many people do not receive wound management or post-exposure prophylaxis with rabies immunoglobulin and vaccine.
3. Lack of knowledge on preventing rabies: surveys show that only 50% of the residents in farming communities know that rabies has a 100% mortality rate; 30% know that wounds must be treated after animal bites. Only 65% of the people sought medical attention after bite. In addition, healthcare personnel also need to have strengthened capabilities on wound treatments.
4. Poor vaccine quality and management [2-4].

Epidemiological studies in China show that 95% of rabies cases were bitten by dogs, 3% by cats, and 2% by other animals. In some areas, this proportion has changed. For example, in Zhejiang, during 1994 - 2004, there were 114 rabies cases, of which, 108 (75%) were caused by dogs, 31 (21.5%) were caused by ferret-badgers, and 5 (3.5%) by cats; and in Hangzhou and Huzhou, ferret-badgers caused 77.3% (17/22) and 60% (12/22) of the rabies cases, respectively. Other than dogs and cats which can be infected with rabies, the disease has also been found in pigs, cattle, goats, horses, and deer. Regarding rabies in wild animals, after the first human rabies case caused by ferret-badgers was reported in 1994 in Huzhou, Zhejiang, the epidemic continued for 3 years. Hangzhou also continued to have cases. Most people reported being bitten in the hands. Dogs, cats, and pigs in the area were also bitten by ferret-badgers. During 2008 - 2009, Wuyuan, Jiangxi, also reported 6 human rabies cases caused by ferret-badgers. Therefore, ferret-badgers became the only wild animal proven to be an independent reservoir for rabies in China. Cases of rabies have also been reported in wild animals including rats, foxes, yellow weasels, wolves, and badgers. These are most likely spillover infections, and do not play a significant role in the overall epidemiology and control of rabies. Only one bat in Tonghua, Jilin has been found to cause rabies death after biting a human. Rabies virus isolated from humans and animals all belong to genotype 1. Virus nucleoprotein from the

isolated viruses shared 86.6% - 99.9% similarity. China uses genotype 1 vaccines strain. The effectiveness of the different vaccine strains used in China is similar to the rest of the world, and is effective in preventing rabies infections [3,4,9].

China has prohibited the use of nerve tissue vaccines (NTV) since 1991. In 2006, cell cultured vaccines were completely replaced NTV. According to the 2009 China Department of Health statistics, approximately 12 - 15 million doses of rabies vaccines were given each year, making China the country with the most human rabies vaccines provided in the world. Rabies control agency is collaborating with the international societies with a goal to eradicate rabies in China by 2025. Recently published "Mid- to long- term animal disease eradication plan for 2012 - 2020" has set target date 2020 for rabies control. The plan identified 12 provinces (cities, and regions) with rabies epidemics for strengthened rabies control, including Hebei, Shanxi, Jiangxi, Shandong, Hubei, Hunan, Guangdong, Guangxi, Chongqing, Sichuan, and Guizhou. Rabies is now reported mainly in the southeast. Inter ministerial collaboration is an important characteristic China's rabies control program. For example, the Ministry of Health, Ministry of Agriculture, Ministry of Public Security, and the Bureau of Food and Drug Monitoring and Control jointly published the "Memorandum for strengthened rabies control and prevention" in 2003.

Rabies control in Taiwan

Literatures have documented numerous rabies control measures implemented in the 1930's. There was no rabies reported until June 17, 1948. The case was reported by the National University Hospital doctor, Tsung-yi Lin, who identified the first case of rabies in Taiwan. In 1956, the Joint Commission on Rural Reconstruction and the Taiwan Provincial Health Department instituted rabies control measure including vaccinating dogs with vaccines imported from the United States and culling stray dogs to control animal reservoir. These measures successfully controlled the rabies epidemic. In 1961, the government pronounced that rabies was eradicated. At that time, there were no effective methods such as pre- or post- exposure prophylaxis for the control of human rabies infection. In both 2002 and 2012, a case of human rabies was imported from China. Then in 2013, a case was imported from the Philippines. None of the cases received post-exposure prophylaxis, and died after disease onset, despite best medical management [7,8].

In July 2013, after the incident of rabid ferret-badger was discovered, in order to protect the health of the citizens and avoid panic among the public, the Executive Yuan established the "Central Epidemic Command Center" in response to rabies outbreak, in accordance with item 1 in the Communicable Disease Control Act. Deputy Premier Chi-Kuo Mao was appointed as the Commander General, Chief of the Council of Agriculture, Bao-Ji Chen, and Ministry of Health and Welfare Minister, Wen-Ta Chiu

were appointed co-commanders. Inter-ministerial collaboration accelerated rabies response. After the establishment of the Central Epidemic Command Center, the first meeting was convened. All ministries began action to prevent rabies, to protect the health of the people. In the first meeting on August 1, chaired by Commander General Mao, he assigned the responsibilities among different ministries, and instructed all ministries to use the most strict criteria in response, implement control measures, closely monitor the epidemic, and, depending on the severity of the epidemic, to communicate with the public [7,8].

To prevent the spread of rabies, health education for residents living in rural and mountainous areas must be increased, dogs and cats should be vaccinated against rabies regularly, pets should not be abandoned. International literature indicates that abandoning pets increases the population of stray animals. These animals may stray into the territory of wild animals, become infected, and bring diseases back into the city. This will in turn worsen the epidemic. To prevent pets from coming into contact with wild animals, it s recommended to avoid taking dogs or other susceptible animals to go hiking. The prevention measures are as following:

(1). All dogs and cats should be vaccinated against rabies and do not abandon pets. If vaccine coverage reaches 70% among dogs and cats, it can effectively prevent 96.8% of rabies in animals. Literatures also point out that abandoning pets increases the population of stray animals. These animals may stray into the territory of wild animals, become infected, and bring diseases back into the city. This will in turn worsen the epidemic.

(2). Avoid all contacts with wild animals, including hunting, eating, or keeping them as pets.

(3). Immunity in humans: some persons are at high risk of being infected by rabies because of their work or occupation, including veterinarians and those who work with wild animals. These people should receive rabies immunization [7-9].

The Central Epidemic Command Center continues to remind people to practice "2 don'ts and 1 do". That is, please don't contact, hunt, or keep wild animals as pets; don't abandon pets, but vaccinate pets regularly; and do report to animal disease control authorities when finds animals with abnormal behavior, such as the animal has stopped eating or drinking, has become anxious, has more urinary frequency, is afraid of the light, or has become aggressive (reporting hotline: 0800-761-590). For more information on rabies, please visit the rabies pages www.cdc,gov.tw at the Taiwan CDC webpage at, or call the public inquiry hotline, 1922 or 0800-001922. For information on animal's rabies, please go to the website for the Council of Agriculture (www.baphiq.gov.tw), or call the Council of Agriculture hotline at 0800-761-590. If one comes across dead animals, please do not touch the animal, but call the Bureau of a Animal and Plant Inspection and Quarantine hotline at 0800-761-590, or call the local animal disease control center.

If one is scratched or bitten by animals, please remember the following steps: remember, rinse, go, and observe.

(1). Remember: please keep calm, and remember the characteristics of the animal.

(2). Rinse: rinse the wound with copious amount of water and wash with soap; then disinfect the wound with iodine-containing solution.

(3). Go: go to the hospital to be evaluated for possible need for post-exposure prophylaxis.

(4). Observe: if possible, observe the animal for 10 days and see if the animal develop symptoms consistent with rabies. If animal has rabies, symptoms will usually appear in 5 - 8 days. If the animal is very aggressive, please do not venture to catch the animal.

If one receives correct treatment before symptom onset, the likelihood of becoming ill decreases dramatically. The prodromal symptom of rabies is not specific. Patients may have fever, nausea, vomiting, or have pain or numbness at bitten site. One should use soap to clean the wound following animal bites and see a doctor be evaluated for the possible need for post-exposure prophylaxis. Post-exposure prophylaxis includes active immunization with rabies vaccine and passive immunization with rabies immunoglobulin. Immunoglobulin infiltrated at the wound provides passive immunization and neutralizes viruses in the wound. Active immigration through the use of vaccines induces the body to develop anti-rabies antibodies. Both types of immunization can effectively decrease the viral load in the body [7,8].

Conclusion

Many emerging and reemerging disease in animals and humans, including many zoonoses, had major influences on human history. Literatures have shown that 38%-57% of non-immunized human die from rabies after being bitten by rabid dogs. This did not result in significant decrease of human population. However, humans are still fearful of rabies because of the frightful symptoms and inevitable death caused by rabies. Mortality following rabies disease onset is very high, but the disease is 100% preventable. The preparedness and response plan to rabies reemergence is mostly completed. The work to be accomplished could not be done immediately. But, history has proven that as long as the people are united in disease prevention, rabies may be eradicated from Taiwan once again.

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