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## WORLD RABIES DAY ISSUE

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This week's issue was organized by Guest Editor Qiulan Chen.

## Foreword

## Accelerate the Progress Towards Elimination of Dog-Mediated Rabies in China

Rabies is an ancient zoonotic disease first recorded over 4,000 years ago. Globally, over 99% of human rabies cases were caused by rabid dogs. Rabies is fatal once symptoms appear. However, rabies is preventable through mass dog vaccination and post-exposure prophylaxis (PEP), including wound treatment, vaccine injection, and passive immunization when necessary. Sustained vaccination coverage of 70% among dog populations can interrupt dog-mediated rabies and is regarded as a first-line defense against human rabies for its cost-effectiveness. PEP is almost 100% effective in preventing human rabies death if carried out promptly and properly.

Rabies still affects over 150 countries and regions and caused annual human deaths of about 59,000 worldwide with about 40% of deaths occurring in individuals under 15 years old and 95% occurring in developing countries within Asia and Africa (1). India ranks at the top in the number of human rabies cases globally, and China is also one of the highest burdened countries, with several hundred human mortalities due to rabies each year (1).

Rabies also causes a heavy economic burden to both individual families and society as a whole. It is estimated that rabies had caused annual economic losses as high as 8.6 billion USD worldwide (1), while PEP only cost 1.5 billion USD in Asia yearly (1). Over 70% of human rabies cases in China were reported in rural areas. The average disposable income of China's rural population in 2020 was 17,131 CNY. PEP services cost about 300 CNY per person for injecting the vaccine alone but over 1,000 CNY if rabies immunoglobulin is needed, not including expenses of wound treatment, transportation, and delayed work. This has caused a heavy economic burden to low-income populations in the case of dog bites.

The World Health Organization (WHO), the World Organisation for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), and the Global Alliance for Rabies Control (GARC) jointly held the International Conference on the Elimination of Rabies' in Geneva in December 2015 to endorse the vision of eliminating dog-mediated rabies globally by 2030 ("Zero by 2030") and jointly issued a global strategic plan in 2018 (2). "Zero by 2030" is also aligned with the United Nation Sustained Development Goal (SDG) 3 and specifically Target 3.3 (to end the epidemics ... of neglected tropical diseases) and Target 3.8 [to achieve universal health coverage ... and access to safe, effective, quality and affordable essential medicines and vaccines for all (2)].

Great progress had been made in the prevention and control of rabies in China under the coordination of all parties led by the Chinese central government in the last decade. In 2020, 202 cases were reported nationwide, affecting 143 counties and districts, which decreased by 94% and 86%, respectively, compared with the peak of 3,300 cases and 984 affected counties and districts in 2007. It showed a sporadic state of rabies nationwide, which laid the foundation for the elimination of dog-mediated rabies.

In addition, as the world's second largest economy, China has institutional advantages with both a complete public health system and veterinary service system and is also capable of mass production and supply of rabies vaccines for animal and human use that meet international standards. It is therefore feasible for China to put forward the goal and road map to realize the target of rabies cases reaching "Zero by 2030".

Currently, the major challenge to achieving "Zero by 2030" in China is the management and immunization of dogs, especially in rural areas, as well as a lack of a robust and sensitive animal surveillance system and a more flexible multisector cooperative mechanism at all levels (3). In 2021, the newly revised version of the Animal Epidemic Prevention Law of the People's Republic of China was released (4), which clearly stipulates the duties of dog owners to manage and vaccinate dogs against rabies, providing a national legal guarantee for the elimination of dog-mediated rabies in China. Recent studies indicated that within China existed complex rabies transmission dynamics, including in dogs, wildlife, and livestock, which may become increasingly complicated once spread to other species, such as badgers, raccoons dogs, and foxes (5). It is also necessary to strengthen health education, as well as to promote and maintain the accessibility and standardization of PEP services in rural areas where the risk of rabies still exists.

In this World Rabies Day Issue, we invited colleagues from China CDC, China Animal Disease Control Center, Changchun Veterinary Research Institute (National Reference Laboratory for Animal Rabies), China Institute of Veterinary Drug Control, and Tianjin CDC to report their recent studies about the progress, challenges, and opportunities of rabies control in China in the past decade. Liu ZR et al. analyzed the epidemiological characteristics of human rabies in China in the most recent five years (6). Feng Y et al. analyzed the epidemiological characteristics of animal rabies, including animal species, geographic distribution, and transmission sources in the past decade (7). Liu YF et al. analyzed the epidemiological characteristics of 126,133 outpatients in rabies PEP clinics in Tianjin Municipality, China in 2020 (8). Yin CS et al. reviewed the progress of development of animal rabies vaccines in China since the 1950s (9). Yin WW et al. summarized the strategies and measures, achievements, challenges, and prospect of rabies control in China (10). The findings from this issue highlighted the feasibility, necessity, and urgency to accelerate progress towards eliminating dog-mediated rabies in China and clearly outlined the next steps, i.e., based on a one health approach, focusing on dog management and immunization coverage in rural areas, as well as combatting threats from other wildlife.

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## Vital Surveillances

## Epidemiology of Animal Rabies — China, 2010–2020

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## ABSTRACT

**Introduction:** Rabies is a fatal zoonotic infectious disease that poses a serious threat to public health in China. Since 2005, a National Animal Rabies Surveillance System has been operating to understand the rabies situation in animals in China with a view to control and eventually eliminate dog-mediated human rabies.

**Methods:** From 2010, the brain tissues of dogs, livestock, and wild animals showing rabies-like clinical signs were collected and tested by the National Reference Laboratory (NRL) for Animal Rabies to analyze the epidemiological characteristics of rabies, including animal species, geographic distribution, and transmission sources. Over the same period, clinically suspected animal rabies cases were collected by Animal Disease Control Centers through the National Animal Disease Monitoring Information Platform (NADMIP) and then reported in the *Veterinary Bulletin*.

**Results:** During 2010–2020, 170 of 212 suspected animal rabies cases were submitted to and confirmed by NRL as rabies virus-positive. Of these confirmed cases dogs, especially free-roaming and ownerless dogs in rural areas, were major transmission hosts (71/170). A total of 51 infected dogs attacked humans with 45 biting more than one person. The dog cases were reported all year round, but with significantly more in spring and summer. The majority of livestock rabies cases (70/80) being caused by rabid wild foxes in Xinjiang and Inner Mongolia revealed that foxes play a pivotal role in animal rabies epizootics in the north and northwest of the country.

**Conclusion:** Dogs were the main transmission sources of rabies in China, and along with the recent increase of rabies in foxes and other wildlife, presented an increasing threat to livestock and public health.

## INTRODUCTION

Rabies is a zoonotic disease caused by rabies virus (RABV) and rabies-related lyssaviruses (1). It is a

serious public concern in China with the majority of human rabies cases caused by rabid dogs (2). Since 2005, to understand the epidemiology of animal rabies and to establish a comprehensive control strategy, animal rabies surveillance throughout the country has been implemented under the National Animal Rabies Prevention and Control Plan by the Ministry of Agriculture and Rural Affairs of China (MARA) (3). According to the Rabies Surveillance Plan, animal rabies surveillance must be conducted across the country to identify the major transmitters, their geographical distribution, and roles in transmission of rabies to human and domestic animals. Through the National Animal Disease Monitoring Information Platform (NADMIP), details of suspected animal rabies cases based on clinical signs have been collected and reported to the China Animal Disease Control Center by provincial and municipality Animal Disease Control Centers, and then published in the *Veterinary Bulletin*, an official journal of MARA for the dissemination of monthly information on animal infectious diseases in China since 2010 (<http://www.moa.gov.cn/zwllm/tzgg/gb/sygb/>). Most of these suspected cases were diagnosed by clinical observation and investigation, with only a small part being subjected to brain tissue collection for laboratory diagnosis in National Reference Laboratory (NRL). Here, only evidence-based data have been used for analyzing the epidemiological characteristics of animal rabies in China.

## METHODS

According to the Rabies Surveillance Plan, brain tissues of rabies-suspected animals (dogs behaving abnormally or biting humans, livestock showing rabies-like clinical signs, dead foxes, wolves, and raccoon dogs) with background information submitted to NRL by provincial and municipality Animal Disease Control Centers (CADCs) as well as Forestry and Grassland Administrations of China, were examined by the direct fluorescent antibody test (DFA) using

fluorescein isothiocyanate (FITC)-conjugated anti-rabies monoclonal antibody (Fujirebio Diagnostics Inc., USA) (4). Concurrently, information on suspected animal rabies based on clinical observation and investigation was collected by provincial CADCs, reported through NADMIP to the National CADC, and published monthly in the *Veterinary Bulletin*.

## RESULTS

Over the period 2010 to 2020, brain tissues (80.2%, 170/212) of suspected animal rabies cases submitted from 16 provincial-level administrative divisions (PLADs) to NRL were confirmed to be rabies positive by DFA (Table 1). Over the same period, the *Veterinary Bulletin* reported 1,132 suspected rabies deaths (Figure 1), showing a trend similar to that of the laboratory-confirmed findings (Figure 2). The data showed a rapid increase of animal rabies in 2020.

Among the positive cases, dogs were the main rabid animals, accounting for 41.8% of total cases (71/170), followed by cattle (28.2%, 48/170), sheep (13.5%, 23/170), foxes (*Vulpes vulpes*) (9.4%, 16/170), camels (4.1%, 7/170), badgers (*Meles leucurus*) (1.2%, 2/170), a raccoon dog (*Nyctereutes procyonoides*) (0.6%, 1/170), a horse (0.6%, 1/170), and a donkey (0.6%, 1/170).

Further analysis showed that infected dogs, and especially those that were free-roaming or stray, were major transmission sources in rural areas (45/71). The

ratio of rural dogs to urban dogs was 1.7 (45:26). Of the 51 rabid dogs that attacked people, 45 (88.2%) bit more than one person, with one even biting 63. All victims received timely post-exposure prophylaxis (PEP). The number of animal rabies cases varied seasonally, with higher incidences in spring (28) and summer (20) than in autumn (15) and winter (8).

Yearly numbers of infected and dead animal rabies cases reported in the *Veterinary Bulletin* varied, but with a marked increase in both during 2020 (Figure 1). There was a high correlation with increases in confirmed rabies cases reported by Changchun Veterinary Research Institute (CVRI). According to CVRI surveillance, the majority of livestock rabies cases (70/80) were caused by rabid wild foxes, which served as a major transmission source and reservoir in Xinjiang Uygur and Inner Mongolia autonomous regions. Rabies in badgers and a raccoon dog were also confirmed in Inner Mongolia Autonomous Region in 2020, revealing the diversity of animal reservoirs.

## DISCUSSION

Reported human rabies cases in China have steadily declined from 3,300 in 2007 to 202 in 2020 (5), benefiting from improvements in the governmental supervision system as well as the ready availability of PEP (6). Nevertheless, animal rabies continues to

TABLE 1. The ratios of confirmed animal rabies cases in China, 2010–2020.

Item	IM	CQ	SH	XJ	SX	ZJ	GD	TJ	HeN	GS	HLJ	JS	SN	GX	HN	JX
2010	–	3/3	3/4	–	6/6	–	–	–	–	–	–	–	–	–	–	–
2011	–	6/6	1/2	–	1/1	–	–	–	–	–	–	–	–	–	–	–
2012	–	2/3	–	–	1/1	–	–	–	–	–	–	–	–	–	–	–
2013	3/3	3/3	1/1	2/3	1/1	–	0/1	–	–	–	–	–	–	–	–	–
2014	8/12	2/4	1/2	4/6	1/1	–	–	1/1	–	1/1	–	–	–	–	–	–
2015	2/2	5/6	–	2/2	2/2	–	–	–	1/1	–	–	–	–	0/2	0/1	–
2016	4/4	–	2/2	1/1	–	2/2	1/1	–	–	0/1	1/2	–	0/1	–	–	–
2017	3/4	4/4	–	2/2	–	–	1/1	1/1	–	–	–	–	–	–	–	–
2018	4/4	0/1	1/1	0/1	–	1/3	–	–	1/1	–	–	1/1	0/1	–	–	–
2019	3/4	–	9/10	1/1	–	0/5	–	–	–	–	–	–	–	–	–	0/1
2020	59/64	–	5/6	–	–	0/1	–	–	–	–	–	–	–	–	–	–
Positive rate	(86/97)	(25/30)	(23/28)	(12/16)	(12/12)	(3/11)	(2/3)	(2/2)	(2/2)	(1/2)	(1/2)	(1/1)	(0/2)	(0/2)	(0/1)	(0/1)

Note: ratios=positive samples/total samples submitted.

–: No sample submitted.

Abbreviations: IM=Inner Mongolia Autonomous Region; CQ=Chongqing Municipality; SH=Shanghai Municipality; XJ=Xinjiang Uygur Autonomous Region; SX=Shanxi Province; ZJ=Zhejiang Province; GD=Guangdong Province; TJ=Tianjin Municipality; HeN=Henan Province; GS=Gansu Province; HLJ=Heilongjiang Province; JS=Jiangsu Province; SN=Shaanxi Province; GX=Guangxi Zhuang Autonomous; HN=Hainan Province; JX=Jiangxi Province.



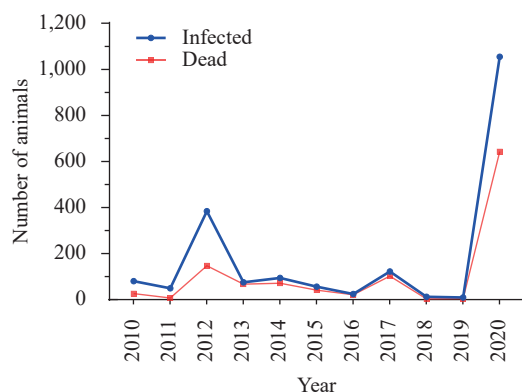


FIGURE 1. Domestic animal rabies cases reported in the *Veterinary Bulletin*, 2010–2020.

Note: The domestic animal species include dogs and livestock.

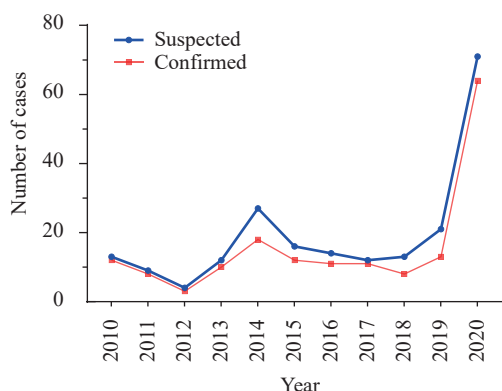


FIGURE 2. Confirmed animal rabies cases in China, 2010–2020, reported by the National Reference Laboratory.

expand geographically over the country, and emerging and reemerging cases have been reported over the last decade in previously rabies-free or low-incidence regions such as Heilongjiang, Xinjiang, Inner Mongolia, Tibet, and Qinghai PLADs and Taiwan, China (7–9). Even though animal rabies is spreading, however, the reported animal cases were still less than the number of reported human cases, likely due to inadequate surveillance and a lack of awareness of reporting and laboratory procedures. Animal rabies cases were therefore likely to have been underestimated. Evidence for this was provided by the numbers of reported cases of laboratory-confirmed animal rabies (Figure 2 and Table 1), which were much lower than those reported in the *Veterinary Bulletin* (Figure 1); i.e., the majority of suspected animal rabies cases in China were not diagnosed in laboratories. However, the fact that the rabies positive detection rate in suspected cases was generally high, as

shown in Table 1 and Figure 2, indicating that clinical judgement on rabies based on nervous system symptoms and aggressiveness of suspected animals was acceptable in the absence of laboratory methods, and therefore can be used to predict animal rabies status.

Our results have also revealed that rabid dogs, particularly from rural areas, continue to be the main sources of transmission of rabies virus in China. In addition, dogs showing strange behavior or biting more than one person (mostly free-roaming or stray) were usually confirmed as being rabid. There being no effective management of the health of free-roaming and stray dogs, it is difficult to implement dog vaccination in rural areas (6). To date, cat rabies has not been reported nor identified during our surveillance. This may be due to cats exploiting a rather solitary existence, resulting in cats not playing a significant role in rabies transmission as reported in a previous study (10).

The data reveal a remarkable increase in 2020 (Figures 1–2), which has been ascribed to increasing numbers of cases of rabies in livestock in Inner Mongolia (Table 1) since it was first confirmed there in 2013 in wild foxes (8). Since then, animal rabies has been increasing in Inner Mongolia Autonomous Region with cases in 25 livestock (cattle, sheep, and camels) diagnosed between 2013 and 2018 (11). This trend continued in 2020 with 59 laboratory-confirmed cases by NRL and 597 clinically-judged cases in Inner Mongolia Autonomous Region published in the *Veterinary Bulletin*. Our previous study showed a spillover of fox RABV strains to other rabies transmitters such as dogs, badgers, and raccoon dogs, with the field RABVs in Inner Mongolia Autonomous Region showing a broad genetic diversity and with fox-origin variants closely related to strains circulating in Xinjiang Uyghur Autonomous Region and the surrounding countries including Mongolia and Russia (11). A case of fox-mediated human rabies was confirmed in Xinjiang Uyghur Autonomous Region in 2016 (12). These observations not only demonstrated the spillover of wildlife RABVs into dogs in the past decade but have also indicated that the risk of spillover is increasing and threatening public health in northwestern China.

In addition to terrestrial animals, a bat (*Murina leucogaster*) harboring Irkut virus was confirmed in Jilin in 2012 (13). This was the first bat-borne lyssavirus identified in China, suggesting that public warnings regarding bat bites should be increased.

This study was subject to some limitations. Although national surveillance systems for animal rabies have been established in China, the animal rabies case reporting is not comprehensive. The reported and confirmed dog rabies cases in this study were far below the human cases, especially in high incidence provinces of human rabies. The infrequent information sharing between the human and animal health sectors was identified as major gap. Cross-department cooperation should be enhanced. Furthermore, the national reference laboratory is responsible for diagnosis of animal rabies at the national level; however, the laboratory diagnostic capacity of most provincial CADCs remains weak.

MARA has made substantial progress in dog rabies control in last decade. A National Medium- and Long-term Plan for Animal Epidemic Prevention and Control (2012–2020) was issued by the General Office of the State Council in 2012 (14). To implement this plan, MARA has published every year since 2005 a National Animal Disease Surveillance and Epidemiological Survey, which includes animal rabies surveillance across the country. In addition, the National Animal Rabies Prevention and Control Plan (2017–2020) implemented by MARA in 2017 further strengthens prevention and control strategy (15). Nevertheless, there remain major challenges for China to achieve the goal of eliminating dog-mediated human rabies by 2030. Compulsory dog vaccination covering the entire country must be initiated in a multiple-sector based collaborative manner, including participation of the public.

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## Vital Surveillances

## Epidemic Characteristics of Human Rabies — China, 2016–2020

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## ABSTRACT

**Introduction:** The epidemiological characteristics of human rabies in China in 2016–2020 were analyzed in order to provide the scientific basis for the formulation of the prevention and control policy of rabies at next stage.

**Methods:** The data of China's National Notifiable Disease Reporting System (NNDRS) from 2016 to 2020 were collected and analyzed by using a descriptive epidemiology method.

**Results:** A total of 2,074 cases of human rabies were reported from 2016–2020 in China, there were year over year decreases in total number of cases. Human rabies appeared throughout the year, among which the highest in incidence happened from August to October, while March and December months were months in which the epidemic was weakest.

**Conclusion:** Though decreases were observed for human rabies in China, further steps should be taken to maintain these results. Management should be strengthened and the immunity of dogs should be prioritized to control this situation from the source. In addition, all reported cases should be monitored and reported to achieve the accurate prevention and control.

## INTRODUCTION

Rabies is a fatal infectious disease that has comorbidity of human beings and animals and the mortality is nearly 100%. In each year, there were about 59,000 human deaths worldwide. In China, the latest epidemic peak was in 2007, totalling 3,300 cases (1). After this, the situation has been in a constant decrease state. In this paper, a statistical analysis for 2016–2020 data for human rabies and the research of five-year epidemic characteristics were made to provide the foundation for further accurate prevention and control and subsequent policy preparation.

## METHODS

The data is from China's National Notifiable

Disease Reporting System (NNDRS), and the adopted data includes the reported incidence, mortality, occupation, and other various indexes of all provincial-level administrative divisions (PLADs) in the mainland of China.

All statistical analyses were performed using Microsoft Excel (version 2019, Microsoft Corporation, Redmond, Washington, USA) and the geographic distribution map was drawn using ArcGIS (version 10.3, Environmental Systems Research Institute, Inc., Redlands, California, USA).

## RESULTS

From 2016 to 2020, there were 2,074 reported human rabies cases in the NNDRS, and the number of cases decreased year over year; the reported incidence rate also decreased from 0.047/100,000 population in 2016 to 0.014/100,000 in 2020 (Figure 1).

Currently, human rabies mainly affects China in the southern and central regions, having a trend of gradually spreading over the north. From 2016 to 2020, the number of PLADs with reported cases in China gradually reduced from 28 PLADs in 2016 to 21 PLADs in 2020. The top 5 PLADs with total cases for 5 years were successively Hunan (327 cases), Henan (240 cases), Guangxi (160 cases), Guizhou (139 cases), and Hubei (138 cases), accounting for 48% in total cases reported in the nation. There were no reported cases in Jilin and Liaoning. The epidemic situation within most PLADs and regions was consistent with national trends, i.e., having a trend of decreasing year over year; while in Hunan, Jiangsu, Anhui, and Sichuan, etc., the trends were less stable. In Hunan, the trends in 2017 and 2018 constantly rose and in 2019, the number of cases was significantly reduced. However, in 2020, the number of cases increased again. The trends in Jiangsu and Sichuan were the same as in Hunan, i.e., in 2020, the number of cases slightly increased. In Guangxi, Guizhou, Hubei, and Yunnan, etc., the number of cases greatly decreased in 2020 of over 50% less than that of the previous year.

The onset of human rabies appeared throughout the

year. According to the count of each month in 2016–2020, the months of August, September, and October had the highest incidence, while March and December had the lowest incidence (Figure 2).

The number of human rabies cases in 2016–2020 primarily affected farmers (73%), among which students, homemakers and unemployed, and scattered children comprised 8%, 5%, and 5%, respectively. The male-to-female ratio of cases was 2.39:1; the incidence rate of the 40–70 years old group was higher, accounting for 69% of the total number of cases (Figure 3).

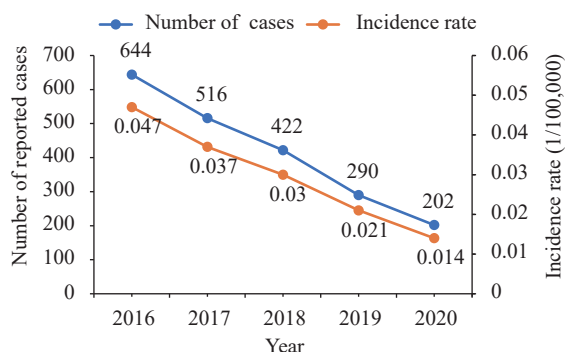


FIGURE 1. The number of reported human rabies cases and incidence rate in China, 2016–2020.

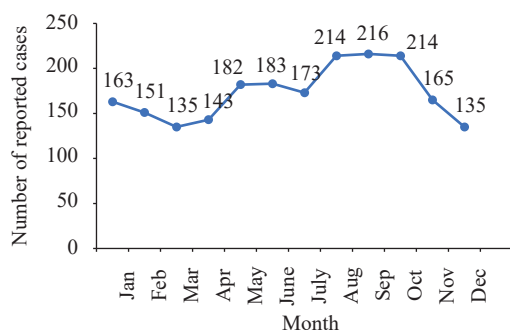


FIGURE 2. Total number of reported human rabies cases in each month in China, 2016–2020.

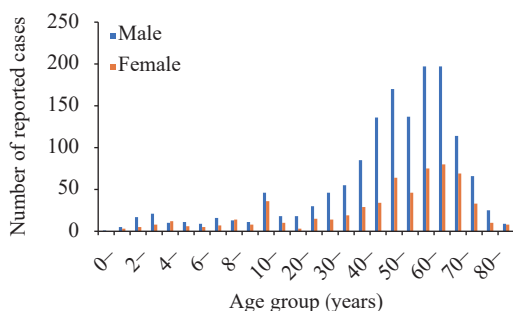


FIGURE 3. Age and sex distribution of human rabies incidence reported in China, 2016–2020.

## DISCUSSION

From 2016 to 2020, the number of human rabies cases in China constantly and stably decreased from 644 cases in 2016 to 202 cases in 2020, which was mainly attributed to China's implementation of continuous monitoring and active prevention and control.

The spatial distribution of cases in China gradually narrowed from 28 PLADs in 2016 to 21 PLADs in 2020. However, some PLADs without new human rabies cases for several years began to have new reports, such as in Xinjiang, which had no reported cases for 4 years but had 1 in 2016, and in Heilongjiang, which had no reported cases from 2014–2018 but had 1 in 2019. For regions with sporadic cases, rabies awareness should be promoted and the public kept vigilant.

For some portion of PLADs, the epidemic situation was properly controlled, and the number of cases constantly decreased or has been reduced to zero. The number of cases in Henan and Shandong reduced year by year. In Shandong, the number of human rabies cases in 2020 reached zero, and the number of cases in Guangxi, Guangdong, Yunnan, and Shanxi has stably decreased for roughly 10 years, which was likely due to strict local policies. Yunnan, for example, had strict management of dogs with the policy of “management, immunity, and elimination”, which achieved good results (1). Hunan, Henan, Guangxi, Guizhou, Hubei, Jiangsu, and Anhui stably maintained approximately 10 cases occurred each year from 2016 to 2020 and Sichuan maintained 20 cases for 5 years. Human rabies mostly affected the southern and central regions of China, which was distributed roughly the same as reported in previous studies (2–4). Since 2007, reported cases of human rabies in Hunan, Henan, and Guangxi generally decreased, but in the most recent 5 years, these PLADs were still the top 3 most affected PLADs, which indicated that progress was slow. For high-incidence PLADs and regions with the slow decreasing number of cases, rabies prevention should be prioritized by enhancing health education, awareness, and multisectoral cooperation, as well as the adaptation of relevant policies and measures to local conditions.

Due to rabies comorbidity, reducing opportunities for contact and exposure of hosts to an infectee is pivotal to prevention. Children and middle-aged and elderly men in rural areas are high-risk groups and need to be prioritized as they have lower awareness of self-protective measures, awareness of rabies and related

medical knowledge, and awareness of seeking prompt medical treatment post exposure (2–3,5). Therefore, we will strengthen the publicity and education in rural areas, especially in the summer and autumn seasons with high incidence. Governmental departments should enhance the management of dogs and properly capture and treat stray dogs to improve the immunity rate. Meanwhile, the provincial range of reimbursement on NCMS should be expanded to prompt the exposed crowd to timely and correctly accept prevention and disposal measures and better promote the prevention and control work of rabies.

In China, the main animal causing the injury is dog (3–4). The management and immunity of dogs are radial measures of eliminating the epidemic situation. With the good effect on control of rabies, Europe and America, Japan, and the Republic of Korea and other developed countries implemented the dog-object large-scale inoculation movement to eliminate rabies of dogs. In 2015, the World Health Organization (WHO) proposed that in 2030, the target of eliminating dog-to-human rabies by reaching 0 global cases, while the core strategy of elimination lies in comprehensively carrying out the large-scale dog immunity. Currently, the immunity rate of dogs is still low (2–3), the average immunization rate of dogs in national rabies monitoring points is about 30%, which is still of great difference with 70% of the targeted immunity rate. The management of dogs, especially in rural areas, centers on free-range farming, and the proportion of tying and confining of dogs is relatively low (6). Therefore, actively promoting the vaccination for livestock, enhancing the management of dogs, strengthening the management regulations of dogs will be more contribute to reduction of number of exposed outpatients and death cases. With the strengthening of publicity and education, people's self-protection awareness has been constantly intensified and the number of outpatients after exposure of rabies has been constantly increased, showing that the prevention has been enhanced to exactly reduce the number of cases. However, if the radical prevention is not made from the immunity of dogs, the economic and medical burden of individuals and society will still be increased in the long run.

In summary, the epidemic situation of national human rabies from 2016 to 2020 decreased year by year and the number of PLADs in incidence gradually reduced. In 2020, the number of cases was near a record low and sporadic. With the elimination of

human rabies in China, we have reached the last critical stages towards elimination. However, in order to further reduce cases, we should enhance the management of dogs. All PLADs should, considering local conditions, speed up the introduction of specific measures for dog epidemic prevention and management, identify the collection and management units of dogs and stray dogs in rural areas, improve the immunization rate of dogs, and control the epidemic from the source. Local governments should launch new monitoring schemes as soon as possible and strengthen the joint cooperation of multiple departments to realize the entire coverage of monitoring all the reported cases, accurate prevention and control, and to reduce the occurrence of human rabies, achieving the target of zero death of human rabies by 2030.

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## Preplanned Studies

# Epidemiological Study of Outpatients in Rabies Post-Exposure Prophylaxis Clinics — Tianjin Municipality, China, 2020

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## Summary

### What is already known on this topic?

Rabies remains a serious public health problem in China. The only way to prevent the fatal disease was through timely and adequate post-exposure prophylaxis (PEP).

### What is added by this report?

Among all the 126,133 cases visited Tianjin PEP clinics during 2020, more than 90% of the patients were injured by domestic dogs or cats, and about 70% of the animals received vaccination. Most outpatients have knowledge of rabies and show high compatibility with PEP.

### What are the implications for public health practice?

To better control rabies, we need to pay more attention to people who lack knowledge of rabies and help them gain awareness of PEP.

Rabies remains a serious public health problem in China. The disease is preventable through timely provision of adequate post-exposure prophylaxis (PEP), and designated PEP clinics exist in China to provide PEP treatment. This study aimed to understand the characteristics of outpatients in rabies PEP clinics to provide a basis for follow-up work. Data in this study was from an electronic, PEP clinic-based case registration system, including case information, exposure history, PEP recommendations, and vaccination status, which covered all 91 clinics in Tianjin Municipality from January 1 to December 31, 2020. Among all the 126,133 first-visit cases, more than 90% of the patients washed the wound by themselves and went to PEP clinics within 24 hours after exposure; 97.04% of the outpatients received the first dose of the rabies vaccine; and 94.64% of the outpatients completed the whole schedule of doses (5-doses/2-1-1 regimen). The result showed that most of the outpatients have knowledge of rabies. To better control rabies, we need to pay more attention to people who do not know about rabies and help them establish

awareness of PEP.

A total of 126,133 first-visit cases sought a consultation to PEP clinics in Tianjin Municipality from January 1 to December 31, 2020. The reported exposure rate was 909.66/100,000 population. Among all the cases, 50.97% were female (n=64,291). The mean age was 36.3 years (range: 3 months to 99 years). The major exposure animal was dogs (56.06%) and cats (40.78%); most of the animals were domesticated with identified owners (92.20%), and 69.47% of them had rabies vaccination history. Among total exposures, 50.38% (n=63,381) were classified as category III (single or multiple transdermal bites or scratches, etc.). Hands (56.56%, n=65,032) and legs (21.09%, n=26,000) were the most common sites for exposures. More than 90% of patients washed their wounds before arriving to PEP clinics and 57.98% of the cases finished wound-washing in the PEP clinics; 89.40% of the cases went to the PEP clinics within 24 hours after exposure (Table 1).

Among the 106,769 persons with category II or III exposure who had no history of prior rabies vaccination (or re-exposure >3 years), 96.68% (n=103,221) received the first dose of rabies vaccination. Nearly 95% of the cases completed the whole schedule of doses. Adherence to rabies is shown in Table 2. Only 25.21% (n=15,979) of the cases with category III received the rabies immunoglobulin (RIG).

## DISCUSSION

Tianjin was one of the four municipalities of China, has a population of nearly 14 million people. This study shows that the annual incidence of rabies exposure was 909.66/100,000 population. But the actual incidence may be much higher than our data since almost none of the reported rabies patients went to see a doctor after they got rabies exposure (1–2).

The standard PEP treatment comprises of wound treatment, rabies vaccine, and RIG if warranted (3). The fear of acquiring rabies and knowledge of the

TABLE 1. Characteristics of the patients visited post-exposure prophylaxis clinics in Tianjin Municipality, China, 2020.

Characteristics	No. of reported exposures	Percent (%)
Sex		
Male	61,842	49.03
Female	64,291	50.97
Exposure category		
I	2,859	2.01
II	59,893	47.61
III	63,381	50.38
Exposure site		
Hands	65,032	51.56
Legs	26,600	21.09
Arms	16,244	12.88
Feet	7,900	6.26
Head/face/neck	5,372	4.26
Trunks	4,985	3.95
Multi-sites (more than one area)	2,668	2.12
Animal		
Dog	70,707	56.06
Cat	51,433	40.78
Other	3,993	3.16
Owner status		
Owned	116,292	92.2
Not owned	9,841	7.80
Animal vaccination history		
At least one	80,793	64.54
Never/unknown	45,340	35.46
Type of exposure		
Bite	77,417	61.38
Scratches	45,011	35.69
Others	3,705	2.93
Interval between exposure and medical attention		
2 hours	50,974	40.41
2–6 hours	21,828	17.31
24 hours	39,953	31.68
>24 hours	13,378	10.60
Wound washing		
By one's own	116,164	92.10
By the clinics	72,944	57.83
History of exposure and re-exposure		
Within 6 months	3,528	2.27
6 months to 1 year	4,785	3.79
1–3 years	8,192	6.49

TABLE 2. Adherence to rabies vaccination advice among persons who visited the post-exposure prophylaxis clinics in Tianjin Municipality, China, 2020.

Dose	No. of people actually vaccinated	No. of people should be vaccinated (5 doses/2-1-1 regimen)	Completion rate (%)
1	103,221	106,769	96.68
2	102,470	106,769	95.97
3	101,917	106,769	95.46
4	101,415	106,769	94.99
5	95,488	100,899	94.64

gravity of the disease, as well as the cost of PEP were main factors affecting PEP compliance (4).

Among all the exposures, more than 90% were caused by domestic dogs or cats, and the animal vaccination rate was much higher than that in the other studies (1,5–6). Almost 10% of the patients were re-exposed. The high proportion of outpatients who cleaned the wound after exposure, visited PEP clinics within 24 hours (h) after exposure, and adhered to rabies vaccination showed that the majority of outpatients in the PEP clinics understood the risks of rabies.

The adherence to rabies vaccination was very high in Tianjin. The completed inoculation rate was close to 95%, which was much higher than the results in other studies (6). However, it should also be noted that there were still a small number of patients who had not been vaccinated, the causes of which needs to be further explored. Taking a 60 kg person as an example, the cost of RIG is about 5 times of the rabies vaccine. The high price may be a barrier to practical use.

Almost all rabies cases were not treated with regular PEP (1–2). We can find that many of the outpatients in our study were not at high risk to rabies exposure (injured by immunized domestic animals, exposure sites were not on the face or the head, etc.). This is a reminder to prioritize providing education on rabies knowledge to the high-risk groups, e.g., populations in rural areas with large populations of dogs, low animal immunization rates, and little knowledge of rabies — so they would be more aware of the harm of the disease.

The study was subject to at least two limitations. First, the data comes from PEP clinic-based case registration system. There may be duplicate cases in our study because the ID numbers were not required for entry into the system. Second, data only covered information in Tianjin Municipality; if a patient went to another province for vaccination after the first



consultation, this could not be reflected in the data.

In conclusion, to better control rabies, we need to pay more attention to people who lack knowledge of rabies and help them gain awareness of PEP. Meanwhile, we should also continue to manage PEP clinics to ensure the standardization and effectiveness of the treatment.

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## Commentary

## Progress in the Development of Animal Rabies Vaccines in China

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Rabies is caused by neurotropic viruses of the genus *Lyssavirus* in the family Rhabdoviridae, of the order Mononegavirales and can be transmitted to all mammals (1–2). Rabies will infect humans who are bitten or scratched by rabies-infected animals, including dogs, cats, bats, foxes, wolves, rats, weasels, badgers, raccoon dogs, etc. (3–5). At present, there are no effective cures for the disease, and the fatality rate is almost 100%.

Rabies cases have been recorded in China since ancient times as there were recorded in “Huainan Zi”, telling the story of the rabies dog biting Ziyang, which led to his death and was likely the first recorded case of rabies in Chinese history. Even at present, China is still seriously affected by rabies with more than 200 cases of rabies morbidity and death reported every year (6–7). Infected dogs and cats are the main sources of rabies infections. Strict management of dogs and cats and active immunization are active and effective methods to control rabies transmission among humans. Rabies vaccine development has gone through different stages, including nerve tissue vaccine, avian embryo tissue vaccine, cell culture-derived live virus vaccine, cell culture-derived inactivated virus vaccine, attenuated virus vaccine with reverse genetic manipulation research, nucleic acid vaccine, and recombinant genetic engineering subunit vaccine and live vector vaccine (8).

### ANIMAL NERVE TISSUE VACCINE

In the 1950s, Chinese veterinary scientists developed an attenuated vaccine from sheep brain tissue. Although the vaccine could protect animals' immunity, its residual virulence was still pathogenic to some animals. By the 1960s, China had also used sheep brain tissue to prepare inactivated vaccines. The vaccine was not pathogenic to animals and was safer. However, this vaccine could cause paralysis-like symptoms to animals for the components of goat or sheep tissue. Nevertheless, the vaccine was proved to be effective by using experiment dogs to carry out immunity efficacy tests. The use of the neural tissue inactivated seedlings on early animal rabies prevention

and control played an important role. The nerve tissue vaccine had been replaced by other vaccines due to the encephalitis factor related to the myelin in brain tissue, which could trigger allergic encephalomyelitis and cause death, lifelong paralysis, paraplegia, and other adverse consequences.

### ATTENUATED VACCINES FOR POULTRY EMBRYO CULTURE

Avian embryo attenuated vaccine can be prepared by using a virus to infect avian embryos. Flury low egg passage (LEP) virus and Kelev were the main strains for the production of this vaccine. Virus strains were inoculated into Specific Pathogen Free (SPF) chicken embryos, and the allantoic fluid was harvested and lyophilized after virus proliferation. This vaccine was recommended for muscular immunity in dogs, cats, and cattle for a one-year duration of immunity. The most widely used strain of chicken embryo vaccine was the Flury strain. The strain was isolated from human brain tissue from patients who died of rabies in 1940 and was passed in the brain of one-day-old chickens for 138 generations, and then passed through chicken embryos for 40–50 generations. After passing through chicken embryos for more than 178 generations, the pathogenicity to animals was greatly reduced, but it was still pathogenic to inoculate in the brain of suckling mice and monkeys. The chicken embryo vaccine was used to inoculate rabies virus with chicken embryo, which was easier to operate than the brain tissue vaccine and had no neurological side effects compared to the brain tissue vaccine.

### LIVE ATTENUATED VACCINE IN CELL CULTURES

The LEP strain, Evelyn-Rokitnicki-Abelseth (ERA) strain, CTN-1 strain, and their modified strains were used to produce live attenuated vaccine in cell culture. In China, live rabies vaccine was first used in 1980. In 1977, China Institute of Veterinary Drug Control

(IVDC) adapted rabies LEP to proliferate in the BHK21 cell line. Results showed that virus growth was stable and the virus content per 0.03 mL was above  $10^{4.0}$ LD<sub>50</sub>. There were no adverse reactions after intramuscular injection of the lyophilized vaccine in 3-month-old dogs and rabbits. Once an intramuscular injection is made on domestic dogs, the immunity period is more than 1 year. The vaccine has been approved for production and put into use since 1980 (9).

In 1983, IVDC introduced the ERA strain of rabies virus from abroad. BHK-21 cells and primary porcine kidney cells were used to replicate the virus, and the biological characteristics were identified. The strain had good immunogenicity and no adverse reactions were observed in dogs, cattle, sheep and other animals. After propagation and passage on BHK-21 cells, the virus content was more than  $10^{5.0}$ LD<sub>50</sub>/0.03 mL. The lyophilized vaccine was made from BHK-21 cells and immunized dogs, horses, cattle and sheep with different doses. The immunization period was more than one year. The vaccine had been tested in 13 provinces, with no adverse reactions. Compared with LEP strain, ERA strain was safer and more suitable for target animals.

At the same time, IVDC had also carried out oral immunization tests with the vaccine in a large number of dogs. Domestic dogs were immunized with different doses of vaccine and feeding methods, which increased the level of safety. Samples were collected at different periods after immunization to detect serum neutralizing antibodies against rabies. The antibody positive conversion rate (1:8) was 40%–50%.

In the following years, IVDC cooperated with a number of biological products manufacturers to develop a live primary cell vaccine of ERA strain for rabies, using gophers, donkeys, sheep, pigs, cattle, and other animals of different origin for the primary cells. The results showed that bovine testis primary cells inoculated with ERA strain had the best adaptability, high yield, and stable virulence. Furthermore, ERA/BT cell adaptive strain of the rabies virus was developed. Bovine testis primary cells were used to produce the vaccine successfully.

However, the attenuated live vaccine also had some potential safety hazards, because the virus may cause disease due to the regurgitated mutation in vivo or it may cause gene rearrangement with the naturally infected epidemic strains producing strains. Therefore, commonly used vaccines were mainly inactivated vaccines rather than attenuated vaccines. China

stopped manufacturing and using live rabies vaccine on June 30, 2018 (10).

## INACTIVATED VACCINE IN CELL CULTURES

At present, beta-Propiolactone (BPL) is commonly used to inactivate rabies virus at 4 °C in China, and formaldehyde is no longer used as the inactivated agent. BPL can destroy viral nucleic acid but does not change the structure of viral protein or affect the antigenicity of rabies virus. The inactivated antigen can be completely hydrolyzed in the vaccine liquid, with no inactivated agent residue in the finished vaccine (10). Therefore, the usage of BPL can avoid the reduction of virus immunogenicity and toxic substances or irritants residue. Virus strains used in the preparation of inactivated vaccines usually include the SAD strain, ERA strain, LEP strain, CVS-11 strain, PM strain, PV strain, etc. Stromal cells were used in the preparation of attenuated vaccines generally with BHK-21, MDCK, Vero, etc. Many kinds of inactivated rabies vaccines were produced and used in China, including the inactivated rabies vaccine (LEP strain) developed by IVDC, the inactivated rabies vaccine (PV2061 strain) developed by Liaoning Cheng Da Animal Pharmaceutical Co., Ltd., the inactivated rabies vaccine (LEP strain) developed by Liaoning Yikang Biological Co., Ltd., the inactivated rabies vaccine developed by PLA Academy of Military Medical Sciences (CVS-11 strains), the inactivated rabies vaccine developed by Tangshan Yian Biological Engineering Co., Ltd. (CTN-1 strains), the inactivated rabies vaccine developed by Changzhou Tongtai Biological Pharmaceutical Technology Co., Ltd. (SAD strains), the inactivated rabies vaccine (DG strain) developed by South China Agricultural University, and the inactivated rabies vaccine (R3G strain) developed by Shandong Huahong Biological Engineering Co., Ltd.

## AN ATTENUATED VACCINE DEVELOPED BY REVERSE GENETIC TECHNIQUE

Reverse genetic technology is cloned by molecular biology technology on the basis of the full genome sequence, through the modification of target genes and mutations to assemble a new individual virus. This platform as the research basis can be used to study the

influence of gene changes on the phenotype of the organism. Therefore, the development of reverse genetics technology is of great significance to the study of life sciences.

With the application and development of reverse genetics technology, many achievements have been made in the research of live rabies vaccine. To establish the rabies virus reverse genetic operation, the expression of antisense RNA genome expression plasmid (genome plasmid) and three kinds of expressions of virus nucleoprotein protein (N), phosphorus (P), and large transcription protein (L) of plasmid (auxiliary plasmid) should to be established. With cells expressing T7RNA polymerase transfection, the antisense genomic RNA and these N, P, and L proteins form an antisense genomic ribonucleoprotein complex (RNP). The antisense genomic RNP complex has the same biological activity as the RNP complex produced in rabies virus-infected cells. Therefore, genomic RNA can be synthesized using antisense genomic RNP as a template, and then mRNA can be synthesized from genomic RNP and expressed viral proteins. Infectious recombinant rabies virus was produced after the assembly of genomic RNP, membrane protein (M), and glycoprotein (G). The mutation of arginine or lysine 333 on G protein plays a decisive role in the pathogenicity of rabies virus. According to the analysis of G protein epitope of rabies virus, the recombinant virus of G gene from different strains of rabies virus will be derived. The results show that the substitution of this amino acid residue can effectively weaken the virus strain. By inserting another 2 or 3 G genes to construct recombinant virus G protein stability and expressing them using the original manufacturer's mass traditional methods of G protein that had similar stability, Chinese scientists have successfully constructed the dG and r3G strains virus containing two or three G proteins (11).

In conclusion, the characteristics of the attenuated live vaccine constructed by reverse genetic manipulation are low production cost and simple production procedure. Due to the characteristics of the attenuated live vaccine, the most concerning issue is the safety of the vaccine. The reason is that after the recombinant virus immunized the animal, once the animal is recessive, the wild strain and the recombinant virus may be recombined, and the original missing genes can be restored through recombination and the original virulence can be regained. In the future, it may be mainly used for oral vaccine immunization in wild animals.

## GENETICALLY ENGINEERED RECOMBINANT LIVE VECTOR VACCINE

Recombination live vector vaccine is prepared by using gene engineering technology to construct virus or bacteria into a vector and insert foreign genes into it to express the constructed live vector. The live vector vaccine has the advantages of both the conventional attenuated live vaccine and the inactivated vaccine. It has the advantages of high immunity efficacy and low cost of the attenuated live vaccine and good safety of the inactivated vaccine.

In rabies live vector vaccine research, poxvirus and adenovirus are researched and used comprehensively as carriers. In 1992, the rabies virus G gene of CVS-11 strain were inserted into a recombinant poxvirus vector to construct recombinant poxvirus through subcutaneous immunization in mice and rabbits and guinea pigs were immunized through oral immunization (12). Immunization with the recombinant poxvirus subcutaneously and in the muscle could induce neutralizing antibodies with high titer, but no positive antibodies were observed by oral immunization. In 1993, Zhao WG et al. also adopted the recombinant poxvirus expression system, and successively constructed the recombinant poxvirus expressing the N protein of rabies virus and the recombinant virus Tiantan strain of vaccinia virus co-expressing the G protein and N protein of CVS-11 strain of rabies virus (13). The immunization of mice showed that the neutralizing antibodies could be produced after immunization, and could resist attack by rabies virus. In 2001, Li WH et al. constructed a recombinant adenovirus expressing the G protein replication defect of rabies virus (14). After immunizing mice with this virus, the mice were attacked with a lethal amount of rabies virus, and the protection rate of immunized mice reached 87.5%–100%. Immunization of target dogs could induce a high level of protective rabies virus specific neutralizing antibody. In 2006, Zhang SF et al. constructed canine adenovirus serotype 2 vector vaccine expressing rabies virus glycoprotein, and the experimental results showed that it could resist the virulent rabies virus challenge with an immune effect similar to that of conventional inactivated vaccine (15). Furthermore, the protective neutralizing antibody remained in immunized dogs for several months, showing the potential to replace the existing vaccine. The results showed that about 87.5% of the

immunized dogs produced neutralizing antibodies, which can be detected 2 to 3 weeks after injection, peaking at 5 to 6 weeks later. The serum neutralizing antibody level of 90.8% dogs was more than 24 months, and the antibody titer was higher than 0.5 IU/mL, showing a gradual but slow decline (16). The recombinant vaccine could be taken orally with a good immunity effect on dogs. Recombinant human adenovirus type 5 expressing G protein of attenuated SRV9 strain of rabies virus was constructed in 2011. The complete open reading frame of G gene of SRV9 strain of rabies virus was cloned into the shuttle plasmid polyclonal site of adenovirus expression system. Overall, 293 AD cells were co-transfected with linearized skeletal plasmid and recombinant shuttle plasmid mediated by Roche's transfection solution. After 14 days, anti-rabies neutralizing antibody was produced, and the effective protection rate reached 90% (16).

## NUCLEIC ACID VACCINE

Nucleic acid vaccine prepared by gene recombination technology will have a certain immune active antigen gene promoter downstream of restructuring in eukaryotic expression system and constructing the recombinant expression vector, after a large number of extraction of plasmid DNA is injected into animals by subcutaneous, intramuscular injection, or gene gun methods. By the transcription of host cell synthesis, the DNA vaccine stimulates the host's immune system to produce immune response to the protein. The nucleic acid vaccine is characterized by easy operability and construction. In addition, the nucleic acid vaccine can induce immune animals to produce humoral and cellular immune responses. Because the nucleic acid vaccine only produces the corresponding immune response to the designated antigen, but not for other unrelated antigens, it does not affect the use of other vaccines.

In the rabies virus nucleic acid vaccine research, the cDNA of rabies virus G protein was placed downstream of the SV40 promoter, then the constructed plasmid DNA was directly injected into the gastrocnemius muscle of mice and serially immunized 3 times, each time with an interval of 2 to 3 weeks. Anti-rabies virus neutralizing antibody and cellular immune response were produced in mice after immunization. Xiang ZQ et al. combined immunizing mice with murine granulocyte-phage colony-stimulating factor and rabies virus DNA vaccine could significantly improve the level of humoral immunity

and cellular immune response (17).

The nucleic acid vaccine has a lot of advantages; for example, it is easy to construct and preserve without cold chain transportation, which can make up for the traditional inactivated or attenuated vaccine shortages. However, there are also disadvantages to this kind of vaccine, mainly plasmid DNA in the body for a long time, causing gene mutations or leading to cancer and other potential harm. Given the safety concerns of nucleic acid vaccines, which have yet to be resolved, nucleic acid vaccines cannot replace the vaccines currently in use.

## GENETICALLY ENGINEERED SUBUNIT VACCINES

The genetically engineered subunit vaccine refers to the use of recombinant DNA technology, the coding of pathogenic microorganism protective antigen gene fragments into the prokaryotic or eukaryotic expression vectors, so that the virus protein can be highly expressed, the protective antigen can be extracted and then added to the adjuvant emulsification to prepare the genetic engineering subunit vaccine. The vaccine contains only one or more antigen epitopes of the pathogen, but no other genetic information of the pathogen, and can be used to inoculate animals with these vaccines to obtain protective immunity. Because the subunit vaccine does not contain infectious components, it does not need to be inactivated, nor does it have pathogenicity, so the prepared vaccine has high safety.

G and N proteins of rabies virus are the main antigens that induce humoral and cellular immune responses. Therefore, G protein and N protein are mainly proteins in the research of rabies subunit vaccine. In 1983, the G gene of CVS-11 strain of rabies virus was inserted into the bacterial expression plasmid, and then transformed into *Escherichia coli* and successfully expressed G protein. However, due to the lack of glycosylation function in the prokaryotic expression system, the immune effect of the expressed protein was very poor. The G gene of rabies virus SAD strains was inserted into the yeast expression system, with a high protein expressing quantity. However, the main problems existing in the system are that the expression of the type of G protein glycosylation and the location of the glycosylation are different from the original strain, as there is no correct G protein glycosylation. Therefore, the immune effect of G protein is affected. At present, the G protein of the



rabies virus was successfully expressed in SF9 cells using baculovirus expression system, and purified it to prepare vaccine to immunize animals. The results showed that the protein could induce the production of protective neutralizing antibodies and resist the lethal dose of the virus after oral immunization (18).

## RESEARCH PROGRESS OF ADJUVANT FOR RABIES VACCINE

Adjuvants can improve the immunogenicity of subunit vaccines, thus reducing the amount of vaccine needed, the cost of vaccine production, and the number of immunization failures. Inactivated vaccines currently in use include either no adjuvant or aluminum adjuvant. Aluminum adjuvant can enhance Th2 response in mice and induce IgG1 antibody production. Tests have shown that the inactivated vaccine containing Al(OH)<sub>3</sub> can immunize dogs and cats for up to 3 years. In recent years, scientists have gained a deeper understanding of the basic immune pathways that enhance the immune response and have known that the activation of the innate immune response is the most critical step in the acquired immune response. Cell signaling involved in the activation of innate immune response cells has been well identified, such as Toll-like receptors and NOD-like receptors. Therefore, many new adjuvants are developed to replace aluminum adjuvants, such as the new adjuvant CpG oligo deoxynucleotide, which can bind to TLR-9 to activate the innate immune response. The research team prepared inactivated rabies vaccine with aluminum adjuvant and CpG adjuvant respectively in mice and carried out a comparative test. The antibody level of CpG immunized for 3 times was similar to that of aluminum adjuvant immunized for 5 times. In recent years, many new adjuvants have emerged or have been studied in preclinical trials. Their modes of action have been described in detail in the literature, and it is necessary to develop a second generation of rabies vaccine adjuvants based on these theories.

## QUALITY CONTROL OF INACTIVATED RABIES VACCINE FOR ANIMAL USE IN CHINA

As of December 2020, the Ministry of Agriculture and Rural Affairs of China had approved the new veterinary drug certificate of 9 inactivated rabies vaccines for animals. All live rabies vaccines (including

related combined vaccines) have been stopped for animal immunization since June 30, 2018. The quality standard control indexes of inactivated rabies vaccine for animal use in China are not completely consistent, but mainly including the following indexes. The physical properties of the vaccine should conform to the labeling requirements of the product; vaccines should be pure and are usually tested for sterility according to the current edition of the Chinese Veterinary Pharmacopoeia. The inactivation test of the vaccine was usually the number of mice (weight, age, and quantity varied according to different products) inoculated in the brain, 0.03 mL for each, and observed for 21 days. Some products should be subcutaneously inoculated into mice, 0.5 mL for each, and observed for 7–14 days. All the above test mice should be healthy, and subcutaneously inoculated mice should not show any reaction at the injection site. The safety test of the vaccine requires intramuscular injection of at least 2 healthy susceptible dogs (usually beagles) with negative antibodies to rabies virus, and subcutaneous inoculation of 1 or 2 doses of vaccine in mice and guinea pigs for 21–28 days. All of test animals should be healthy and alive. The most commonly used test for vaccine efficacy is the National Institutes of Health (NIH) method derived from the NIH, but the specific procedures for the NIH method vary widely from different products. The method is to use the same dose of rabies virus (such as CVS-24 strain), challenge two (or one) intraperitoneal injection of different dilution of the vaccine to be tested and international standard (reference) vaccine. According to the PD<sub>50</sub> value of each group, the number of international units of the vaccine to be tested relative to the international standard (reference) vaccine should be calculated. The standard of inactivated rabies vaccine in China is that each dose of vaccine should be ≥2 international units (IU). In the Chinese Veterinary Pharmacopoeia (2020 edition, the third volume appendix 3407), a unified method for testing the efficacy of inactivated rabies vaccine for veterinary has been developed, which reduces the errors of National Institutes of Health test results in different laboratories to a certain extent.

At present, rabies inactivated vaccine is mainly for dogs and cats over 3 months of age. The immunization period is generally 12 months, and the initial immunization is generally 30–60 days, followed by one strengthening immunization after 28 days. Inactivated vaccine free of adjuvants is for intramuscular injection; however, vaccines containing adjuvants should be injected subcutaneously. The injection dose shall be

subject to the manufacturers' instructions for the product.

## CURRENT SITUATION OF THE USE OF VETERINARY RABIES VACCINE IN CHINA

At present, the animal rabies vaccine is an inactivated vaccine, which is mainly used for pet dogs and cats in urban and rural domestic situations. However, there is no commercial vaccine for cattle, sheep, foxes, and raccoon dogs that are wild animals. The oral vaccine is expected to be used for wildlife and stray animals in the future, which has been developed by many institutes.

In the past three years, China issued about twenty-five million doses of domestic inactivated rabies vaccine and twelve million doses of imported inactivated rabies vaccine each year, with a total of about thirty-seven million doses. According to preliminary estimates, there are about 110 million dogs and cats in China that means the annual coverage rate of rabies vaccine for dogs and cats in China is only about one-third. In order to effectively control the occurrence of human rabies in China, the animal rabies (especially pet dogs and cats) immunization rate should reach more than 70%; therefore, China needs a large quantity of animal rabies vaccines. At the same time, we should strengthen the development of vaccines suitable for urban and rural stray dogs and cats, as well as foxes, wolves, raccoon dogs and other wild animals, including oral live vaccines and recombinant live vector vaccines and formulate corresponding scientific immunization procedures and application areas. It is suggested that the health, urban management, agriculture, forestry and other related departments in our country cooperate to actively enhance public awareness of rabies and improve the rabies vaccine immunization rate of animals.

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## Commentary

## Progress and Prospects of Dog-Mediated Rabies Elimination in China

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### CURRENT STATUS OF RABIES IN CHINA

Through concerted stakeholder effort, rabies prevention and control in China has achieved remarkable results. The reported incidence of human rabies continues to decline at a rate of approximately 20% each year. In 2020, a total of 202 human rabies cases were reported countrywide, a decrease of 94% when compared with the most recent peak in 2007 (3,300 human cases). Likewise, rabies was reported only in 143 counties and districts, a decrease of 86% when compared to 984 counties and districts in 2007. More than 20 provincial-level administration divisions (PLADs) reported a drop in the number of cases to zero or single digits, demonstrating a sporadic trend in rabies occurrence. China has more than 2,800 counties and districts, and dog-mediated rabies may have been eliminated in some areas, which is a solid foundation for achieving the goal of eliminating dog-mediated rabies nationwide (1–3).

Human rabies cases in China present the characteristics of “Tri-more,” i.e., 1) there are more cases in rural areas and peasants account for over 65% of the total number of cases; 2) the number of male cases approximately doubles that of female cases; and 3) most of the cases are observed in children under 15 and people over 50 years of age.

Dogs are the major source of human rabies in China (3), accounting for approximately 95% of all cases, followed by cats (approximately 5% of all cases). Foxes, raccoon dogs, badgers, and wolves are the main rabies hosts of wild animals, but less than 1% of human rabies were transmitted by wild animals.

Despite remarkable achievements in the past decade, rabies remains a serious health threat in China. In recent years, the number of deaths from rabies ranked among the top five reported notable infectious diseases in China, posing a huge threat to people’s lives. The number of people who have to seek post-exposure prophylaxis (PEP) due to animal injury has been estimated to be as high as 8–10 million annually in

China. It is estimated that the cost of human rabies vaccination, immunoglobulin, and wound medical treatment may exceed 7 billion CNY per year. The rabies epidemic not only seriously threatens people’s lives, but also poses a heavy economic burden and has serious psychological impacts.

### STRATEGIES AND MEASURES FOR RABIES CONTROL IN CHINA

The Chinese government established a government-led, multisectoral-coordinated, “whole-society participation” mechanism under the concept of One Health in order to combat rabies. This approach entailed the following: 1) prioritizing elimination of dog rabies, including dog population control, registration, vaccination, quarantine, and movement management as dog vaccination remains the most cost-effective way to prevent human rabies; 2) ensuring the availability, accessibility, and quality of PEP services to establish a second line of defense against rabies, while providing pre-exposure immunizations to high-risk groups, such as veterinarians and laboratory staff; 3) integrating human and animal health surveillance systems and implementing a containment strategy based on a One Health approach, once any human or dog cases are reported; and 4) promoting the welfare of dogs through advocacy, risk communication, and social mobilization.

The strategies and measures for rabies control are detailed as follows:

Active advocacy for the elimination of dog-mediated human rabies by 2030 as recommended by World Health Organization (WHO), a goal that has been highly prioritized by the Chinese government. The National Health and Family Planning Commission (NHFP) [(currently National Health Commission (NHC)], Ministry of Public Security (MoPS), Ministry of Agriculture (MOA) [(currently Ministry of Agriculture and Rural Affairs (MARA)], and State Food and Drug Administration (SFDA) jointly issued the Current Status of Rabies Control in China in

September 2009 (4). This document further defines the responsibilities of multiple sectors, establishing a multisectoral rabies prevention and control strategy, promoting close cooperation between various sectors, and actively carrying out prevention and control programs. It also defines major responsibilities for local governments, such as establishing grassroots organizations and strengthening dog management in rural areas.

Formulation and implementation of rabies prevention and control programs in China. The General Office of the State Council issued the National Medium and Long-Term Animal Epidemic Prevention Planning (2012–2020) on May 25, 2012 (5), which listed rabies as a zoonosis with priority in prevention and control and set a goal of achieving the control standard by 2020. To implement the national plan, relevant departments have implemented their own prevention and control programs.

- The MOA has strengthened the prevention and control programs for animal rabies. The MOA issued and implemented the National Animal Rabies Prevention and Control Plan (2017–2020) (NYF [2017] No. 18) to strengthen rabies surveillance and response as well as dog immunization on June 2, 2017 (6). The MOA conducted large-scale dog immunization campaigns based on the “red collar” project. The MOA strengthened the core role of veterinarians and their sectors in rabies prevention and control and implemented compulsory rabies immunization regulations countrywide. The MOA further strengthened the countrywide dog surveillance and immunization system, especially in rural areas, to ensure the effective implementation of dog immunization measures in both rural and urban areas. As a result, the dog immunization rate has improved dramatically and the incidence of rabies in dogs has decreased, both of which led to the minimization of large-scale dog culling.

- Since 2005, the NHFPC has continued to implement the Central Government Transfer Payment National Rabies Surveillance Program in order to effectively conduct rabies surveillance, strengthen the epidemiological investigation of human rabies cases, and to improve multisectoral cooperation such as the sharing of surveillance information and promoting rabies responses. The NHFPC issued the Rabies Post-Exposure Prophylaxis Regulation in 2006 (7) and Technical Guidelines for Human Rabies Prevention and Control in 2016 (8) to standardize rabies PEP. Specifications for the Treatment Clinic Setting of Rabies Post-exposure Prophylaxis (T/CADERM

3010–2019) (9) were issued by Chinese Medical Rescue Association to strengthen the disposal clinic management of rabies PEP. Public health sectors have continuously strengthened training and conducted widespread professional rabies PEP training for grassroots outpatient doctors in various forms, including annual rabies meetings, online training, and standardized training courses for outpatient doctors at local injury clinics, and rabies awareness programs through official accounts and doctor groups on WeChat. Furthermore, the NHFPC promoted the incorporation of rabies vaccination and immunization into medical insurance in PLADs with high incidence of rabies to improve the accessibility and affordability of PEP services.

- The MoPS has continued to improve the registration and management of urban dogs.
- The SFDA has continued to strengthen the supervision of the quality and circulation of the human rabies vaccines and rabies immunoglobulins in order to supply high quality human rabies vaccines, and the supply of animal rabies vaccines is now sufficient to ensure the needs of prevention and control programs.

Strengthening rabies surveillance and utilizing integrated surveillance information. Based on case reports and post-exposure monitoring, surveillance of situations in which one dog bites multiple people has been emphasized in recent years. China CDC holds rabies laboratory testing training workshops every year to strengthen the construction of laboratory networks. Laboratory testing showed that the virus positive rate of one dog biting multiple people exceeded 80%. The strengthening of epidemiological investigation, with the aim at achieving a case investigation rate of 100% as well as increasing investigation and responses, have been conducted.

Implementing surveillance, containment, and epidemic point and source elimination strategies. Rabies is a reemerging disease or imported infectious disease in most areas, and emergency response strategies should be implemented. All localities are supposed to strengthen joint prevention and control mechanisms and closely monitor and strengthen information sharing. Once a human or animal epidemic or “One dog biting multiple people” scenario emerges, a report must be submitted promptly to initiate the emergency response. Under the guidance of the government and multiple sectors including agricultural, health, and public security, among others, should cooperate closely, strengthen the implementation of various prevention and control measures in epidemic areas, and ensure the elimination



of hidden dangers of epidemic spread in accordance with Technical Specification for Prevention and Control of Rabies. This includes the identification of epidemic areas and threatened areas, the culling of infected animals and other animals bitten by infected animals, the isolation of stray dogs, an emergency rabies immunization of all dogs and cats and restriction of their movement, and risk communication with the public.

Promoting the introduction of national laws and regulations related to rabies prevention and control as well as managing dogs according to law. Before 2021, there were no national, unified dog management regulations; moreover, local dog management regulations were only instituted in some regions. The Animal Epidemic Prevention Law of the People's Republic of China was revised and implemented on May 1, 2021 (10). It defined the main responsibilities of local governments in dog management and stipulated that dog owners should register and vaccinate dogs against rabies. When walking their dogs out of their houses, dog owners should ensure that their dogs have tags and adhere to necessary measures, such as tying dog leashes in accordance with the related regulations to prevent the dog from hurting people and spreading rabies.

Wide publicity, mass mobilization, active advocacy for civilized dog breeding and consolidation of the popular support. Mass media can actively facilitate the publicity of rabies prevention and control knowledge, which would enhance the public understanding of public health. Some non-governmental organizations can participate in the publicity and shelter of stray dogs.

## DIFFICULTIES AND CHALLENGES

Currently, management of dogs is not yet optimal, and the registration rate is low particularly in rural areas. It is estimated that there are approximately 80–100 million dogs in China. The scattered breeding of dogs and cats is common, and this results in increasing danger to animals and human due to the spreading of rabies among animals and resulting transmission to humans. The supervision of dog breeding in rural areas is not well organized. It is not easy to implement immunization measures for rabies in dogs. Moreover, shelter for stray dogs should be expanded (11–13).

- The rate of vaccination in dogs is low in rural areas, posing difficulty in achieving 70% coverage in order to contain rabies transmission.

- People's awareness of civilized dog breeding needs to be improved. There are many phenomena, such as scattered breeding, absent registration, absent immunization, and random abandonment. Public understanding and involvement are key.

- The rabies epidemic is relatively serious in poor, marginal areas.

- The surveillance capacity is insufficient. Surveillance data for livestock and wild animals are insufficient. Furthermore, the rate of laboratory diagnosis in the reported cases of human rabies is low.

- The population of wild carnivores has increased recently; the spatial distribution has been restored or expanded; and small carnivores, such as weasels and raccoon dogs, have been increasing in cities. Thus, the risk of wild animal rabies has become increasingly prominent. Field surveillance demonstrates that foxes have become the main source of rabies infection from wild animals in China.

## KEY SUGGESTIONS ON RABIES PREVENTION AND CONTROL IN THE NEXT STAGE

WHO and the World Organisation for Animal Health (OIE) jointly held the International Conference on Rabies Elimination in Geneva on December 10 and 11, 2015, to adopt an action plan and program framework for eliminating dog-mediated human rabies worldwide by 2030 (14–15).

The rabies epidemic has been effectively controlled in China but yet far away from elimination. China has complete public health and veterinary service systems, possesses the technologies for rabies prevention and control, and potentially produces and supplies animal and human rabies vaccines that meet international standards. China revised the Animal Epidemic Prevention Law of the People's Republic of China in 2021, which stipulates the requirement for dog owners to vaccinate dogs against rabies and perform civilized dog breeding. This law provides a national legal guarantee for the elimination of dog-mediated human rabies in China. Therefore, it is completely feasible for China to achieve the goal of “dog-mediated human rabies” in 2030, as proposed by the WHO. China should actively respond to the international call and action plan and commit to eliminating dog-mediated human rabies by 2030.

Rabies elimination has entered the final stage. We should strive to eliminate dog-mediated human rabies and contribute to the health of China. China should



continuously improve rabies surveillance, containment, and epidemic point and source elimination strategies as well as continue to exercise prevention and control measures, such as dog immunization and PEP.

Further attention is required. China should make an overall plan to eliminate rabies countrywide, increase investment, and strengthen the surveillance system. China should also strengthen animal rabies surveillance, including that of wild animals, improve the rate of laboratory diagnosis in reported cases, and continue to conduct surveillance data analysis and risk assessment of rabies.

Animal rabies prevention and control should be prioritized. China should continue routine dog management and immunization. The surveillance of rabies in wild animals is of paramount importance. In surrounding areas with wild-animal rabies foci, an immune barrier should be established to prevent the spread and spillover of wild-animal rabies to the dog population. Rabies risk in various places should be evaluated, with emphasis on the fact that the rate of dog immunization in high-risk areas must exceed 70%.

PEP services should be provided continuously and service quality should be improved. China should update PEP specification, publicize, and implement PEP outpatient specifications, and introduce “integrated bite case management” with veterinary cooperation to ensure a more targeted use of PEP on the basis of risk assessments and diagnostic input and subsequently reduce administration of PEP for low-risk exposure.

The control of infectious sources should be increasingly emphasized and a rabies epidemic preparedness plan should be prepared. Various prevention and control measures, including the coordination of sector responsibilities; detection of rabies epidemics; initiation of the joint prevention and control mechanism; and cooperation with public security, agriculture, and other sectors, should be taken to eliminate the epidemic.

The Animal Epidemic Prevention Law of the People's Republic of China should be emphasized, civilized dog breeding should be promoted in accordance with the law, and the stray dog shelter system should be improved.

Multisectoral cooperation by NHC, MARA and other departments should be promoted in the certification of dog-mediated human rabies elimination in domestic areas and preparation for the countrywide elimination of dog-mediated human rabies.

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