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RESEARCH

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Epidemiological characteristics of human rabies cases reported by sites in China from 2006 to 2022

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Abstract

Background Rabies is an incessant public health threat in China. The Ministry of Health implemented the Central Payment for Rabies Prevention and Control Project to assist with rabies prevention and control in a few representative provinces in 2006.

Methods Data on human rabies cases reported by the National Infectious Disease Reporting Information Management System and national surveillance sites from 2006 to 2022 were collected, and statistical and multivariate analyses were then used to assess the effectiveness of current prevention and control efforts.

Results During 2006–2022, a total of 2025 human rabies cases were collected by the national surveillance sites, with incidence rates far above the national average, but the incidence rate was consistent with the national trend. Human rabies cases demonstrated a dual peak distribution in terms of exposure and onset dates, with the peak exposure dates falling mostly in the spring and summer and the peak onset dates occurring mostly in the summer and autumn. Three danger categories are shown by the geographical distribution: high, medium and low. Dogs had a high infection rate (86.93%), with own domesticated dogs accounting for the majority of infections. The rates of post-exposure prophylaxis are not constant. The median incubation period was 71 days.

Conclusions Various measures and policies implemented by the government have played a key role in reducing the incidence of rabies. To effectively prevent and control the resurgence of epidemics and halt the spread of the virus among host animals, it is imperative to prioritize and implement a robust dog management system, accelerate research and development of animal vaccines and improve the level of post-exposure prophylaxis.

Keywords Rabies, Epidemiologic characteristics, Post-exposure prophylaxis, Influencing factor

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Background

Rabies, one of the oldest zoonotic diseases worldwide, is caused by rabies virus and rabies-related lyssaviruses, which are members of the genus *Lyssavirus* of the family *Rhabdoviridae* [1]. Dog- mediated rabies is an incessant public health threat in China due to intra- and interspecific rabies virus infection among dogs, humans, domestic animals, and wildlife [2]. To assist with rabies prevention and control in a few representative provinces, the Ministry of Health implemented the Central Payment for Rabies Prevention and Control Project (also known as the "Rabies Transfer Project") in 2006 [3]. In China, rabies-related fatalities continue to decrease annually from 3,300 cases in 2007 to 133 in 2022. In this study, case data were collected from national surveillance sites spanning from 2006 to 2022 to systematically analyze the epidemiological characteristics of rabies at these sites, identify factors that influence the incidence of rabies in China, and assess the effectiveness of current prevention and control efforts to avoid the recurrence of a rabies outbreak and achieve zero human fatalities from rabies by 2030.

Methods

Data collection

All demographic data were obtained from the National Bureau of Statistics of China (http://www.stats.gov.cn/), while human rabies data from 2006 to 2022 were obtained from the National Infectious Disease Reporting Information Management System and the Disease Prevention and Control Centers of the provinces and autonomous areas where the national surveillance sites are situated. The national surveillance sites encompass various regions in China, including Guangxi Zhuang Autonomous Region (Guilin City, Yulin City, Qinzhou City, and Guigang City), Hunan Province (Shaoyang City, Yongzhou City, and Hengyang City), Guizhou Province (Anlong County, Suiyang County, and Dushan County), Anhui Province (Fuyang City, Mengcheng County, and Lujiang County), Jiangsu Province (Yancheng County), and Shandong Province (Linyi City). The data were classified as clinically diagnosed or laboratory confirmed cases that occurred between January 1, 2006 and December 31, 2022. In total, 2,025 human rabies cases were included for analysis after eliminating duplicate cases and those with missing data. These included 1,948 clinically diagnosed and 77 laboratory confirmed case. There was no data pertaining to human rabies cases during the years 2013 and 2014.

Case definition

Human rabies cases were classified as probable or confirmed in accordance with the diagnostic criteria established by the National Health Commission of the People's Republic of China. In accordance with criteria of the World Health Organization, a probable case was defined as a patient with symptoms (e.g., hyperactivity, hallucinations, paralysis, and coma) and reported being licked, bitten, or scratched by a dog, cat, or other mammal, while a confirmed case was defined as a patient with confirmation of rabies by laboratory tests (e.g., direct fluorescent antibody test, reverse-transcriptase polymerase chain reaction, or virus isolation of clinical specimens) [4].

Exposure category

Rabies exposure is classified into three levels according to the type of exposure and degree of exposure. Category I touching or feeding animals, animal licks on intact skin (no exposure). Category II nibbling of uncovered skin, minor scratches or abrasions without bleeding(exposure). Category III single or multiple transdermal bites or scratches, contamination of mucus membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure) [5].

Data analyses

Statistical indicators and corresponding statistical charts were generated using Excel 2019 software (Microsoft Corporation, Redmond, WA, USA). The distribution of geographic information was mapped using the Spatial Mapping application of ArcGIS software version 10.3.1 (Ersi, Redlands, CA, USA). Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 25.0. (IBM Corporation, Armonk, NY, USA). The epidemiological characteristics of human rabies cases included demographic characteristics, history of exposure, and post-exposure prophylaxis (PEP). An unconditional logistic regression method was used to identify factors influencing PEP, while Cox proportional hazard regression analysis was used to identify factors influencing the incubation period. The odds ratio and 95% confidence interval were calculated.

Results

Epidemiology situation at national surveillance sites

From 2006 to 2022, the overall incidence and mortality rates of human rabies in China were 0.094/100,000, and 100%, respectively. The annual incidence rate of human rabies in China has continuously decreased from the highest rate in 2007 of 0.250/100,000 to the lowest rate in 2022 of 0.009/100,000. Within the same timeframe, 2025 human rabies cases were recorded by the national surveillance sites with incidence and mortality rates of 0.170/100,000 and 100%, respectively. Notably, the incidence rate was much higher than the national average, and the decreasing trend of incidence was consistent with the national trend (Fig. 1).

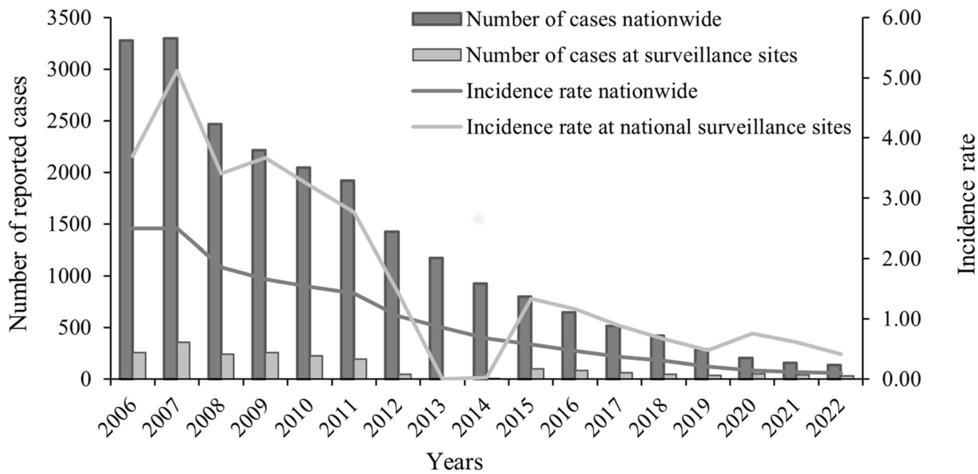

Fig. 1 Incidence of human rabies reported by the national surveillance sites from 2006 to 2022

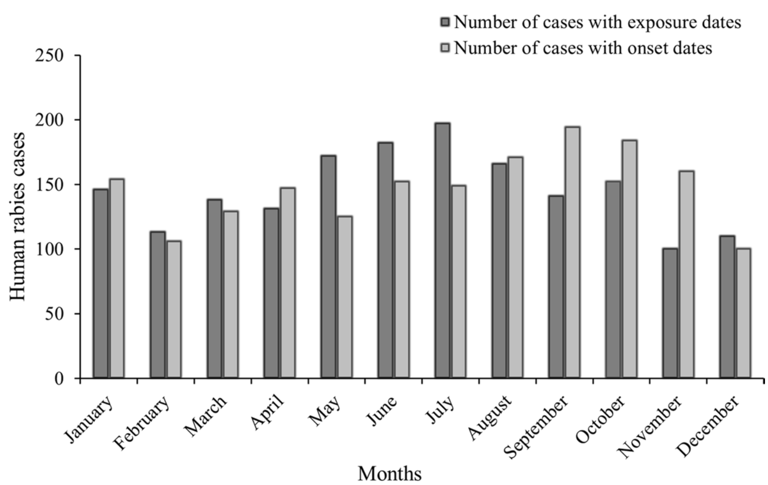

Fig. 2 Temporal distribution of human rabies reported by the national surveillance sites from 2006 to 2022

Temporal distribution

Human rabies cases were reported each month by the national surveillance sites between 2006 and 2022. Cases demonstrated a dual peak distribution in terms of exposure and onset dates, with the peak exposure dates falling mostly in the spring and summer. The highest and lowest number of cases were reported in July and November, respectively. The highest concentration of onset dates occurred in the summer and autumn, with September and December having the most and least, respectively (Fig. 2).

Geographical distribution

From 2006 to 2022, the distribution of human rabies cases across 15 national surveillance sites significantly varied. According to the cluster analysis of human rabies cases in each national surveillance site, the rabies epidemic areas were divided into 3 categories: high, medium, and low. A high-risk area was defined as having more than 200 cases, a medium risk area as 100–200 cases, and a low-risk area as <100 cases. Yongzhou City and Shaoyang City in Hunan Province in addition to Yulin City, Guigang City, Guilin City, and Qinzhou City in Guangxi Zhuang Autonomous Region were classified as high-risk areas. Linyi City in Shandong Province was classified as a medium risk area. Hengyang City in Hunan Province, Anlong County, Suiyang County, and Dushan County in Guizhou Province, Fuyang City, Mengcheng County, and Lujiang County in Anhui Province, and Yancheng City in Jiangsu Province were classified as low risk areas (Fig. 3).

Regions with >200 cases were mainly distributed in Hunan Province and Guangxi Zhuang Autonomous Region, which included Yongzhou City (301 cases), Shaoyang City (278 cases), Yulin City (272 cases), Guigang City (270 cases), Guilin City (255 cases), and Qinzhou City (217 cases), accounting for 78.67% (1,593/2,025) of all cases reported by the national surveillance sites. In Linyi City, Shandong Province, 104 cases were reported. The other national surveillance sites had <100 cases each.

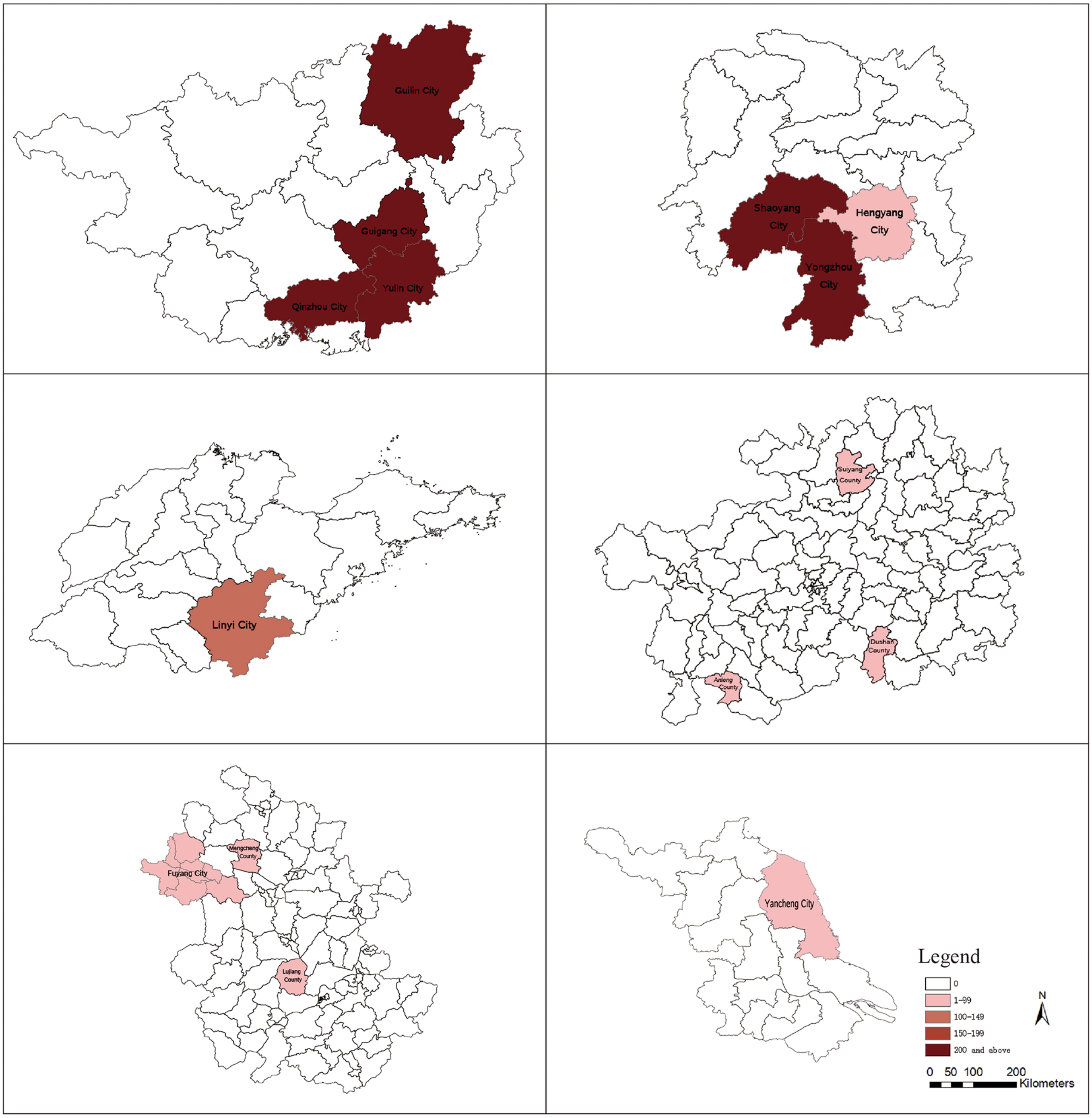

Fig. 3 Geographical distribution of human rabies reported by the national surveillance sites from 2006 to 2022

Among them, Lujiang County, Anhui province, had the lowest number of cases, with just 6 (Fig. 4).

Demographic distribution

The cases of national surveillance sites were analyzed, including 1396 male cases and 629 female cases, with a male to female ratio of 2.22:1. The majority of cases were over 45 years old, with 1140 cases, representing 56.35% of the total. In terms of occupation, there were 1,457 cases among farmers, making up 71.95% of the total. Most of the cases were bitten by infected animals, 1,568 cases, accounting for 78.36% of the total. And most of the cases involved category III exposure, with 1,131 cases, representing 57.79% of all cases. Exposure to infected dogs was the most frequent route of exposure, with 1,742 cases of canine infection, accounting for 86.93%. Among the diseased animals, a majority were own domesticated animals, totaling 1,275 cases. This included 1,184 dogs and 83 cats. Additionally, 432 were stray animals, with 406 being dogs and 24 being cats. And 20 were wild animals, which could be traced back to 1 bat, 1 marmot and 4 mice.

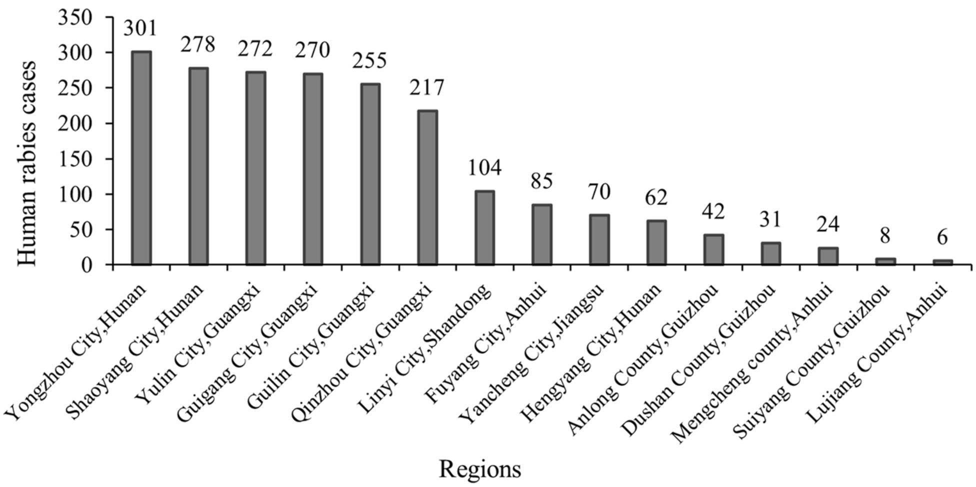

Fig. 4 Number of human rabies cases reported by the national surveillance sites from 2006 to 2022

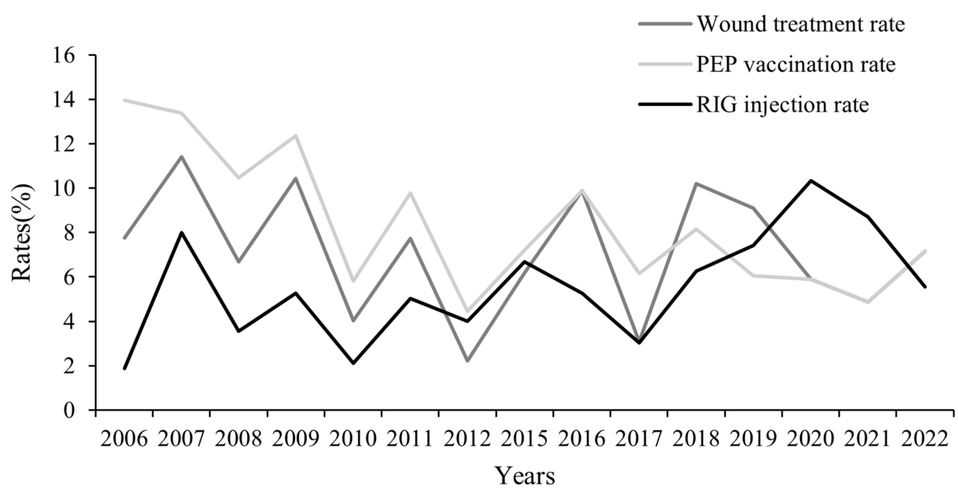

Fig. 5 Trends in PEP rates for human rabies at national surveillance sites from 2006 to 2022. [1]The wound treatment rate is the proportion of cases reported by the national surveillance sites each year that were treated after exposure in medical institutions; [2]The PEP vaccination rate is the proportion of vaccinated cases reported annually by the national surveillance sites; [3]The RIG injection rate is the proportion of rabies immunoglobulin injected into third level exposed cases at the national surveillance sites every year

PEP overall statistics at national surveillance sites

The incidence of human rabies cases has continued to decrease in recent years, with the implementation of more robust PEP as a significant contributing factor [6, 7]. Among all cases reported by the national surveillance sites from 2006 to 2022, 154 cases with clear bites or scratches were erroneously classified as category I exposure, without receiving PEP vaccination or rabies immunoglobulin (RIG) injection. Of these, 116 were caused by own domesticated animals, and 27 by stray animals. Eight cases classified as category II exposure received RIG injections, of which three cases received only RIG injection without the PEP vaccination. The PEP vaccination rates fluctuated widely and was significantly higher than the wound treatment rates and RIG injection rates before 2018. Beyond 2020, the PEP vaccination rates and wound treatment rates overlapped and continued to rise. Prior to 2018, the RIG injection rates remained relatively low, followed by an increasing and then declining trend, and was higher than other rates in 2020 and 2021. Before 2012, there was a significant difference across the three rates, but there was some degree of overlap and the discrepancy diminished subsequent to 2012 (Fig. 5).

Identification of influencing factors

Factors influencing the PEP

From 2006 to 2022, only 8.08% (160/1,979) of cases reported by the national surveillance sites received treatment in medical institutions. The rate of vaccine coverage was only 10.41% (207/1,988) and the rate of RIG injection of cases classified as category III exposure was only 5.04% (57/1,131). Sex, age, occupation, exposure mode, exposure category, exposure position, and other factors were included as independent variables in an unconditional logistic regression model to identify factors influencing the PEP rate of human rabies cases. The findings indicated that the factors influencing wound treatment and PEP vaccination after rabies exposure included exposure category, exposure position and animal source and animal injury reason. The rate of wound treatment (P=0.001) and PEP vaccination (P<0.001) was significantly higher in the cases with category III exposure than in those with category I exposure. The rate of wound treatment (P<0.001) and PEP vaccination (P<0.001) was markedly higher in the cases with high-risk exposure than general-risk exposure. The rate of wound treatment (P=0.003, P=0.001) and PEP vaccination (P<0.001, P=0.003) was substantially greater in the cases who were injured by neighbor's domesticated or stray animals than those who were injured by own domesticated animals. The rate of wound treatment (P=0.007) and PEP vaccination (P=0.004) was significantly higher in the cases who were attacked by animals actively than other cases. The factors influencing RIG injection after rabies exposure included exposure position and animal source and animal injury reason. The rate of RIG injection (P=0.001) was apparently higher in the cases with high-risk exposure than general-risk exposure. The rate of RIG (P=0.005, P<0.001) injection was significantly higher in the cases who were injured by neighbor's domesticated or stray animals than those who were injured by own domesticated animals. The rate of RIG injection (P=0.036) was obviously higher in the cases who were attacked by animals actively than other cases. (Table 1).

Factors influencing the incubation period

The median incubation period of human rabies reported by the national surveillance sites range was 71 (range, 1–34,818) days. The incidence rate within 1 year was 73.59% (1,435/1,950). The incubation period of human rabies cases was positively skewed with skewness and kurtosis values of 8.460 and 102.299, respectively. Cox regression analysis revealed that the incubation period was shorter for females than males and the risk of onset was 1.171-fold higher. The incubation period of category III exposures was shorter than that of category I exposures and the risk of onset was 1.315-fold higher. Bites in areas with rich nerve distribution, such as the head, face, neck, and hands, had shorter incubation periods as compared to other wounds, and the risk of onset was 1.368-fold higher. The incubation period of cases that were not fully vaccinated was shorter than those that were not

Table 1 An unconditional logistic regression model of factors influencing PEP of human rabies cases

Y	X	β	S.E.	Wald	df	P	OR(95%CI)
Wound Treatment	Exposure Category						
	III vs I	1.913	0.6	10.164	1	0.001	6.772(2.089 ~ 21.948)
	Exposure Position						
	High risk[a] vs General risk[b]	0.684	0.195	12.317	1	< 0.001	1.981(1.352 ~ 2.903)
	Animal Source						
	Neighbor's vs Own	0.732	0.243	9.051	1	0.003	2.079(1.291 ~ 3.350)
	Stray vs Own	0.744	0.231	10.355	1	0.001	2.105(1.338 ~ 3.311)
	Animal Injury Reason						
	Active assault vs Other	1.059	0.391	7.338	1	0.007	2.882(1.340 ~ 6.200)
PEP Vaccination	Exposure Category						
	II vs I	1.204	0.492	5.994	1	0.014	3.333(1.271 ~ 8.736)
	III vs I	1.654	0.473	12.2	1	< 0.001	5.226(2.066 ~ 13.219)
	Exposure Position						
	High risk[a] vs General risk[b]	0.838	0.176	22.672	1	< 0.001	2.313(1.638 ~ 3.266)
	Animal Source						
	Neighbor's vs Own	0.803	0.211	14.449	1	< 0.001	2.232(1.475 ~ 3.377)
	Stray vs Own	0.613	0.206	8.84	1	0.003	1.846(1.232 ~ 2.765)
	Animal Injury Reason						
	Active assault vs Other	0.956	0.328	8.491	1	0.004	2.600(1.367 ~ 4.945)
RIG Injection	Exposure Position						
	High risk[a] vs General risk[b]	1.055	0.329	10.276	1	0.001	2.873(1.507 ~ 5.478)
	Animal Source						
	Neighbor's vs Own	1.275	0.458	7.743	1	0.005	3.578(1.458 ~ 8.784)
	Stray vs Own	1.593	0.425	14.031	1	< 0.001	4.917(2.137 ~ 11.313)
	Other vs Own	1.404	0.671	4.378	1	0.036	4.073(1.093 ~ 15.177)
	Animal Injury Reason						
	Active assault vs Other	2.235	1.033	4.682	1	0.03	9.348(1.234 ~ 70.792)

Note (a) High risk positions have abundant nerve distribution, such as the head, face, neck, and hand; (b) General risk positions are body parts other than above vaccinated and the risk of onset was 1.888-fold higher. Similarly, the incubation period of cases injected with RIG was shorter than those that were not injected and the risk of onset was 2.424-fold higher (Table 2).

Discussion

Rabies is an acute infectious and vaccine-preventable disease with a mortality rate of approximately 100% [8]. From 2007 to 2022, the annual incidence and mortality rates of human rabies in China consistently decreased and the incidence trend reported by the national surveillance sites was consistent with the national incidence trend. This significant achievement is closely related to the heightened focus of the Chinese government on rabies prevention and control in the 21st century [9]. The Chinese government has implemented various prevention and control measures and strategies, which include surveillance, detection, vaccination, various laws and regulations, and cooperation among various ministries [10, 11].

Human rabies has clear seasonal patterns but can occur at any time of the year. The peak incidence of rabies is concentrated in summer and autumn, while the risk of exposure peaks in spring and summer. The increase in exposure may be related to dog activity and skin exposure in spring and summer [12, 13]. Therefore, it is necessary to strengthen prevention and control measures as well as publicity efforts in spring and summer to reduce seasonal exposure of high-risk populations, especially male farmers who have higher occupational exposure risks. There was an uneven distribution of cases among the regional surveillance sites. A high risk region may be strongly correlated with the density of dogs, as a high density of dogs will increase the incidence of rabies in residents with incomplete vaccination [14]. In China, the animal surveillance system is still far from ideal because of several economic and other factors [15]. Thus, further efforts are needed to monitor dog circulation and density, and improve animal management systems.

Almost all mammals can be infected with the rabies virus and many wild animals are natural sources [16, 17]. The WHO position paper indicates that rabies infection in rodents is extremely rare and belongs to the accidental event of terminal overflow of rabies virus infection [5]. Research confirmed that rodents can be infected with rabies virus [18]. In this study, four cases were exposed to mice, but it cannot be proven directly caused by rodents due to lack of laboratory testing. Rabies epidemics of humans and dogs cannot be prevented unless the host is considered [19, 20]. Dog-mediated infection is the main source of human rabies infection in China [21], and domestic and stray dogs are the main sources of infection, indicating that the immune effect and immunity coverage in dogs must be improved. The experience of many countries also showed that eradication of rabies depends on control of the number of dogs and the formation of an immune barrier [22]. In the final stage of rabies elimination in China, improving the immunization coverage of dogs and establishing a sustained herd immunity level among dogs are important measures to achieve the elimination of rabies in dogs by 2030. In contrast to mass dog vaccination, reliance on PEP to reduce the burden of human rabies is costly and ineffective to prevent rabies transmission from dogs to humans and other susceptible animals [2] Therefore, increasing dog immunity can reduce the economic burden caused by PEP and the disease burden caused by rabies. In recent years, although widespread immunization and management of dogs has reduced the number of rabies cases, dog immunization and management are challenged by the large number of dogs and the low registration rate. In China, dog management is still locally regulated and limited to urban dogs [3], thus dog management in rural regions must be improved. Canine rabies immunization coverage is far below 70% as recommended by the World Health Organization, especially in rural areas where rabies is highly prevalent, with only 2.8% canine rabies immunization coverage [23–25]. Improving surveillance measures for rural dogs, stray dogs, and wild animals, enhancing the efficacy of animal vaccines, strengthening research and development of oral animal vaccines, reducing circular transmission of viruses among host animals, promoting

Table 2 Cox regression model analysis of factors influencing the incubation period of human rabies cases

X	β	S.E.	Wald	df	*P*	OR (95%CI)
Sex						
Female vs. Male	0.158	0.054	8.487	1	0.004	1.171(1.053 ~ 1.302)
Exposure Category						
III vs. I	0.274	0.09	9.258	1	0.002	1.315(1.103 ~ 1.569)
Exposure Position						
High risk vs. General risk	0.313	0.052	36.024	1	< 0.001	1.368(1.235 ~ 1.515)
PEP vaccination						
Yes vs. No	0.635	0.089	50.729	1	< 0.001	1.888(1.585 ~ 2.249)
RIG Injection						
Yes vs. No	0.885	0.154	33.258	1	< 0.001	2.424(1.794 ~ 3.274)

public awareness of legal and civilized dog care, and preventing resurgence of the epidemic remain crucial objectives.

In China, pre-exposure immunization of the entire population is not a feasible strategy to prevent rabies [26], which mainly relies on PEP. The findings indicated that the proportion of wound treatment and PEP vaccination in medical institutions was low at 8.08% and 10.41%, respectively, and only 5.04% of category III exposures received an RIG injection. Therefore, it is recommended to enhance policy support and health education efforts, and increase compliance with whole PEP vaccination and RIG injection of category III exposures. According to the position document of the World Health Organization and the Guidelines for Prevention and Treatment of Rabies after Exposure in China, category I exposure does not cause rabies [27, 28]. However, there were still 154 cases with clear bites or scratches that were mistakenly classified as category I exposure due to the absence of post-exposure treatment, which resulted in fatalities. Only three cases of category II exposure received an RIG injection but not PEP vaccination. Therefore, standardized training and evaluation of outpatient treatment after exposure must be enhanced, especially in rural and remote areas. Human rabies poses a high risk of transmission and disease burden in rural areas [29]. The level of PEP of cases reported by the national surveillance sites continues to fluctuate, indicating that PEP does not totally prevent vulnerability. Optimization of the PEP vaccination strategy is crucial to avoid missing links and reduce the occurrence of failed cases. At the same time, in the context of regional and occupational differences in the incidence, it is also possible to consider the development of new efficient, low-cost and acceptable measures to control the occurrence of the epidemic [30].

One of the reasons for the low level of PEP vaccination is the lack of knowledge among residents to prevent rabies. Health education intervention can effectively improve the timely vaccination rate of rabies-exposed individuals, awareness of rabies-related knowledge, and the levels of knowledge, belief, and practice [31]. Hence, clinical application can effectively improve health education models, while improving knowledge and PEP compliance.

Other studies conducted abroad have reported rabies incubation periods of 1 to 2 months and 3 weeks to 3 months [32, 33]. The median incubation period of rabies in this study was 71 days and the length of the incubation period was related to sex, which may be related to sex-based differences in immunity to the rabies virus. Thus, further research is needed to determine the specific impact [34, 35]. The wound of category III exposure is large and deep, and a high viral load may lead to a shortened incubation period. Due to neuroticism of the rabies virus, bites on the head, face, neck, and hands, which have abundant nerve distribution, can reduce the distance of viral invasion of extension nerves, resulting in a shortened incubation period [36]. The incubation period was shorter for vaccinated than unvaccinated cases, and the incubation period of injected passive immune agents was shorter than unvaccinated cases, similar to the results of relevant domestic research. The phenomenon of individuals with immune failure having a shorter incubation period than those without vaccination is called the "premature death" phenomenon. Studies of animal models have confirmed that this phenomenon may be due to insufficient neutralizing antibodies against the virus to form infectious complexes with antigens, and the Fc segment of the antibody can enhance the complexes with susceptible cell surface Fc receptors, thereby promoting infection [20]. Research indicates that after exposure to rabies, timely and standardized PEP should be carried out, and risk assessment should be optimized, especially for wounds near the central nervous system, which have a shorter incubation period and require more timely, standardized, and strict PEP. It is recommended to optimize the PEP standards for high-risk exposure to avoid immunization failure and reduce the risk of rabies in the exposed population.

Some limitations of this study should be mentioned. Firstly, the majority of cases are based on clinical diagnoses without corroborative laboratory evidence. It is recommended to promote laboratory diagnosis and improve the laboratory confirmation rate. Secondly, all rabies cases resulted in death, and the details were recalled by the patients' relatives during the investigation. Some cases were exposed for too long, resulting in recall bias.

Conclusion

In recent years, the prevalence of rabies has remained relatively low in China. To effectively prevent and control the resurgence of epidemics and halt the spread of the virus among host animals, it is imperative to prioritize and implement a robust dog management system, while increasing financial investments to accelerate research and development of animal vaccines, and improve access to healthcare professionals, in addition to strengthening intervention capabilities, surveillance efforts, and laboratory testing of host animals, especially dogs and wild animals. Management efforts can be improved by implementation of joint prevention and control measures among various departments, in addition to intensifying public education and consciousness about prevention.

Abbreviations

PEP Post-exposure prophylaxis
RIG Rabies immunoglobulin

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Author contributions
T conceived of and designed this study. L and Z drafted the manuscript, T and Z revised the manuscript in detail. D and K made significant contributions to this work by providing assistance and helped in the data manipulation and analysis. All authors read and approved the final manuscript.

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None.

Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Committee of the National Institute of Viral Disease Control and Prevention, China CDC. Informed consent was obtained by the relatives of all the cases. Participants were unable to provide consent once a rabies infection was suspected due to their medical condition.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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