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Post-exposure prophylaxis and possible breakthrough infections among human rabies case in China, 2019–2024: a nationwide retrospective surveillance study

Shouming Lyu
Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Xi Chen
National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Jinhui Zhang
National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Xiao Yuan
Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Danjian Zheng
Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Yanping Zhang
Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Di Mu
Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Canjun Zheng
zhengcj@chinacdc.cn

Division of Infectious Disease Management, Chinese Center for Disease Control and Prevention (Chinese Academy of Preventive Medicine)

Article

Keywords: Rabies, China, post-exposure prophylaxis, breakthrough infection, incubation period, One Health, surveillance

Posted Date: October 29th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10721720/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Rabies remains a uniformly fatal yet preventable zoonotic disease that continues to pose a public health threat in China, especially in rural populations. Although post-exposure prophylaxis (PEP) is highly effective when delivered promptly and correctly, deaths still occur, including rare infections that develop despite prophylaxis. This study characterized exposure patterns, PEP use, and possible breakthrough infections among human rabies deaths in China from 2019 to 2024.

Methods

We conducted a retrospective cross-sectional analysis of data from China's national rabies surveillance system. Clinically diagnosed and laboratory-confirmed human rabies cases reported between 1 January 2019 and 31 December 2024 were included. We analyzed demographic characteristics, exposure information, animal sources, wound sites, PEP measures, and incubation periods. Multivariable unconditional logistic regression identified factors associated with PEP receipt, while Cox proportional hazards models, Mann–Whitney *U* tests, and Kruskal–Wallis *H* tests were used to examine factors associated with the incubation period. Chi-square or Fisher's exact tests compared standard and non-standard PEP cases.

Results

Among 930 human rabies deaths, most patients were male, rural farmers, and middle-aged or older adults. Dogs caused 86.88% of exposures, yet only 1.83% of owned biting animals had documented rabies vaccination. PEP uptake was very low: 852 cases (91.62%) received no prophylaxis whatsoever, and only 51 cases (5.48%) received rabies vaccine. Non-category III exposure, wounds at lower-risk sites, injury by household animals, and single-victim incidents were associated with lower likelihood of receiving wound care, vaccination, or rabies immunoglobulin. Among 697 cases with a documented incubation period, the median was 70 days (IQR: 38–134.5). Head, face, or neck exposure and multiple-victim incidents were independently associated with shorter incubation periods. Seventy-eight patients developed rabies despite receiving at least one prophylaxis measure; 60 (76.92%) had clearly non-standard PEP, whereas 18 (23.08%) had no identifiable procedural failure. These possible breakthrough infections accounted for 1.94% of all cases and were characterized by category III exposure, head, face, or neck injuries, stray-dog bites, and a short median incubation period of 16 days.

Conclusion

Most human rabies deaths in China resulted from a failure to initiate or complete PEP, reflecting preventable gaps in risk perception, access, affordability, and follow-up. Possible breakthrough infections

were rare but were concentrated in extremely high-risk exposures. Targeted health education, improved prophylaxis adherence, integrated bite case management, and strengthened dog vaccination under a One Health framework are essential to eliminate dog-mediated human rabies deaths.

Background

Rabies is an acute, progressive, and almost invariably fatal zoonotic encephalitis caused by viruses of the genus Lyssavirus, most commonly rabies virus [1]. Despite the availability of effective human and animal vaccines, rabies remains responsible for an estimated 59,000 human deaths annually, with approximately 95% occurring in Asia and Africa [2]. The disease disproportionately affects rural and socioeconomically disadvantaged populations, reflecting persistent gaps in dog vaccination, community awareness, access to post-exposure prophylaxis (PEP), and integrated human–animal health systems [2–4].

PEP is widely accepted as the key way to prevent rabies. Standard PEP comprises three components: immediate and thorough wound washing, timely administration of rabies vaccine, and passive immunization for severe exposures [5–6]. When delivered promptly and correctly, PEP is highly effective. Accordingly, most human rabies deaths worldwide are attributed to failure to seek care, incomplete vaccination, the absence of passive immunization when indicated, or delayed treatment [6–8]. Nonetheless, fatal rabies following receipt of PEP has occasionally been reported. A 2023 global systematic review found that, among 122 reported fatal cases that had received PEP, about 44% had no identifiable error in treatment [9]. This finding suggests that PEP failure does not always stem from substandard practice. It may also reflect biological factors such as exposure severity, viral load, and the host immune response, producing what are called breakthrough infections. Such cases temper the long-held view that PEP is almost invariably protective.

In China, rabies is a notifiable Class B infectious disease. It peaked in the 1980s and again around 2007, after which reported cases declined markedly following strengthened surveillance, expansion of rabies exposure clinics, updated prophylaxis guidelines, and public health interventions [10–13]. National guidelines have been periodically updated to align with global evidence and WHO guidance. The latest 2023 guidelines require proper wound care and vaccination for category II and III exposures (using either the Zagreb 2-1-1 or the five-dose Essen regimen), plus passive immunization for category III and selected high-risk category II exposures [14]. China's definition of standard PEP is stricter than that of the WHO, which centers on wound care plus vaccination. Nevertheless, rabies continues to occur, particularly in rural regions, and recent surveillance has raised concern about a renewed increase in reported cases [11].

Understanding why fatal cases continue to occur is essential for guiding elimination strategies. Previous studies have described the demographic and epidemiological features of human rabies in China [11–13], while other work has highlighted the importance of laboratory diagnosis, national surveillance, and improved case detection [15]. However, few studies have examined the full post-exposure pathway at the case level, including whether exposed individuals sought care, whether prophylaxis was completed, and whether rare possible breakthrough infections occurred despite apparently standard care. This distinction is critical because deaths caused by failure to initiate PEP call for different interventions from deaths

associated with extremely high-risk exposures that may progress before vaccine-induced immunity develops.

Using national rabies surveillance data from 2019 to 2024, this study aimed to: (1) describe the demographic and exposure characteristics of human rabies cases in China; (2) identify factors associated with PEP receipt and with incubation period; (3) compare standard and non-standard post-PEP onset cases to explore possible features of breakthrough infection. The findings provide evidence for improving prophylaxis uptake and adherence, strengthening risk stratification at exposure clinics, and advancing dog-mediated rabies elimination through a One Health approach.

Methods

Study Design and Data Sources

This retrospective, cross-sectional study used China's national rabies surveillance system and analyzed cases reported from January 1, 2019, to December 31, 2024. Data came from two sources: the National Notifiable Infectious Disease Reporting Information System (NIDRIS) and the individual case investigations collected under the National Rabies Surveillance Program (2005 edition).

Under China's Law on the Prevention and Treatment of Infectious Diseases, all clinically diagnosed and laboratory-confirmed rabies cases on the mainland (excluding Hong Kong, Macao, and Taiwan) must be reported through NIDRIS. The system records basic demographic and administrative data. During the study period, NIDRIS logged 1,073 rabies cases, which formed the source population.

To obtain more detailed information on exposure and PEP, we added data from individual case investigations. Following the 2005 surveillance program, trained staff at district and county Centers for Disease Control and Prevention conducted face-to-face interviews with patients' family members after each case was reported. A standardized questionnaire captured key variables, including how the exposure occurred, details of the biting animal, and the PEP received.

Because these investigations form part of enhanced surveillance and are not mandatory nationwide, they cover only a subset of NIDRIS cases. We retained 930 cases with reasonably complete investigation data (86.7% of the source population) as the final analytical dataset, which was comparable to the source population in demographic composition and temporal distribution.

Ethics statement

Data for this study were derived from continual public health monitoring of a designated notifiable infectious disease. The National Health and Family Planning Commission of China classified the investigation of human rabies incidents as a perpetual public health surveillance effort, exempting it from institutional ethical review board evaluation. Similarly, this project was recognized as a standard public health surveillance activity, aligning with the human subjects' protection protocols of the United States

CDC (CGH #2015–238). This retrospective study used routinely collected surveillance data without intervention or direct interaction with patients. All analyzed data were anonymized and contained no personally identifiable information. The requirement for informed consent was also waived by the Ethics Committee of the Chinese Center for Disease Control and Prevention. All methods were performed in accordance with relevant guidelines and regulations.

Case Definition and Classification

Cases were defined using China's national standard Diagnostic Criteria for Rabies (WS281–2008). We included clinically diagnosed and laboratory-confirmed cases and excluded suspected cases.

To study post-PEP onset, we classified cases as follows. (1) Post-PEP onset case: a patient who received at least one PEP measure after exposure — wound care, rabies vaccine, or passive immunization — but subsequently developed rabies. (2) Standard-PEP case: a post-PEP onset case that met both of the following criteria: no evidence of a clear delay in seeking care after exposure; and PEP from the first visit until onset that fully complied with the disposal requirements of the Work Standard for Rabies Exposure Prophylaxis and Disposal (2023 edition) for that exposure category. (3) Non-standard-PEP case: a post-PEP onset case with at least one major procedural deficiency, including absence of appropriate wound irrigation and disinfection, incomplete vaccination, or failure to receive passive immunization when indicated.

Because surveillance data could not fully capture technical details such as vaccine cold-chain integrity, the adequacy of wound irrigation, or the completeness of rabies immunoglobulin infiltration around the wound, cases classified as standard-PEP were interpreted as possible breakthrough infections rather than definitive biological prophylaxis failures.

Study Variables

Variables analyzed included sex, age, occupation, residence, animal species, animal source, exposure route, exposure reason, exposure category, wound site, whether the same animal injured multiple people, wound management, rabies vaccination, passive immunization, incubation period, interval from exposure to vaccination, interval from vaccination to onset, and interval from onset to death.

The incubation period was defined as the interval in days between exposure and symptom onset. Exposure categories were classified according to national rabies exposure prophylaxis guidelines. Category III exposures included transdermal bites or scratches, contamination of mucous membranes or broken skin with saliva, or direct contact with bats. Category II exposures included minor scratches or abrasions without bleeding. Records confirming a bite or scratch but lacking sufficient detail to distinguish category II from category III were coded as "category II or III". Records with unclear exposure routes were coded as "unknown".

For analysis of wound site, head, face, and neck exposures were considered high-risk sites because of abundant innervation and proximity to the central nervous system. Other anatomical sites were considered general-risk sites.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Continuous variables with skewed distributions were summarized as medians and interquartile ranges.

Multivariable unconditional logistic regression was used to assess factors associated with receipt of post-exposure prophylaxis measures, including wound management, vaccination, and passive immunization. Results were reported as odds ratios with 95% confidence intervals.

For incubation-period analysis, Mann–Whitney *U* tests were used for binary variables and Kruskal–Wallis *H* tests for variables with more than two categories. Variables with $P < 0.05$ in univariable analysis were entered into a multivariable Cox proportional hazards model to identify independent predictors of shorter or longer incubation periods. Results were reported as hazard ratios with 95% confidence intervals.

Chi-square tests or Fisher's exact tests were used to compare characteristics between standard- and non-standard-prophylaxis cases. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Data were managed using Microsoft Excel 2016 and analyzed using SPSS version 26.0.

Results

Demographic characteristics

Among the 930 human rabies cases included in the analysis, males outnumbered females, with a male-to-female ratio of 2.18:1. The median age was 59.0 years, with an interquartile range (IQR) of 45.0–69.0 years. Cases were concentrated among middle-aged and older adults. Patients aged 65 years and above accounted for 38.60%, followed by those aged 55–64 years and 45–54 years. Children younger than 15 years accounted for 10.32%.

Farmers were the predominant occupational group, accounting for 78.28% of all cases. Students and preschool children accounted for 11.08%. Together, these two groups accounted for nearly 90% of all reported cases, indicating that rabies deaths remained concentrated among rural and socioeconomically vulnerable populations.

Exposure characteristics

Dogs caused most injuries (86.88%), followed by cats (3.66%), and biting was the most common type of exposure (70.65%). The biting animals were mainly household-owned (45.05%) or stray (28.06%). Notably, only 11 of the domestic animals (2.11%) had been vaccinated against rabies (9 dogs and 2 cats). The leading circumstance of exposure was an unprovoked attack by the animal (42.47%), followed by playing

with the animal (19.14%), suggesting that a substantial share of exposures involved deliberate human–animal contact.

For exposure category, the original records listed 53 category I exposures and 110 with no recorded category. After the exposure route was verified and reclassified, 65 of these were confirmed bites or scratches but could not be separated into category II or III because of incomplete information; they were labeled “category II or III”. The remaining 98 were classified as “unknown” due to missing or unclear data. Overall, category III predominated (58.60%), followed by category II (23.87%), “category II or III” (6.99%), and unknown (10.54%). Injuries most often involved nerve-rich areas, including the upper limbs (43.23%), the head, face, and neck (5.27%), and multiple sites involving the head, face, or neck (1.08%) (Table 1).

Table 1
Exposure characteristics of human rabies cases in China, 2019–2024.

Characteristics	No. of human rabies cases	Proportion (%)
Animal vector		
Canine	808	86.88
Cat	34	3.66
Wild animal	3	0.32
Other	85	9.14
Source of attacking animal		
Domesticated animal from own home	419	45.05
Domesticated animal from the neighborhood	103	11.08
Free-roaming animal	261	28.06
Wild animal	3	0.32
Other	144	15.48
Exposure reason		
Active attack by the vector	395	42.47
Defensive attack by the vector	129	13.87
Playing with the vector	178	19.14
Other	228	24.52
Exposure category		
II	222	23.87
III	545	58.60
II or III[a]	65	6.99
Unknown[b]	98	10.54
Exposure site		
Upper limb	402	43.23
Lower limb	169	18.17
Head/face/neck	49	5.27
Trunk	5	0.54
Multiple wounds (including head/face/neck)	10	1.08

Characteristics	No. of human rabies cases	Proportion (%)
Animal vector		
Multiple wounds (excluding head/face/neck)	14	1.51
Unknown	281	30.22
Incubation period		
≤ 30 days	128	13.76
31–60 days	174	18.71
61–90 days	126	13.55
91–120 days	78	8.39
121–150 days	36	3.87
151–180 days	18	1.94
181–365 days	72	7.74
> 1 year	65	6.99
Unknown[c]	233	25.05

[a] Exposure caused by an animal bite or scratch but classified as category I by medical staff, or with an unknown exposure level.

[b] The exposure level was not classified and the exposure route was unknown.

[c] There is no complete record of the exposure or onset time.

Incubation Period

Among 697 cases with a known incubation period, the distribution was right-skewed (skewness = 4.447, kurtosis = 21.787). The median was 70 days (IQR 38–134.5). The most common interval was 31–60 days (24.96%), followed by 30 days or less (18.36%); overall, 61.41% of cases had an incubation period under 3 months. Extreme values also occurred: 65 cases (9.33%) exceeded 1 year and 21 (3.01%) were under 1 week. The longest recorded period was 7 years, although this exposure history relied on family recall and is uncertain.

We first performed univariable analyses. Seven factors were significantly associated with incubation-period length: age, bite site, exposure category, type of wound care, whether the same animal injured multiple people, whether rabies vaccine was given, and whether rabies immunoglobulin (RIG) was used (all $P < 0.05$; Supplementary Table 1). These variables were then entered into a Cox proportional hazards model. Three remained independent predictors: bite site, vaccination, and whether one animal injured multiple people (Table 2). Compared with upper-limb exposure, head/face/neck exposure was associated

with a shorter incubation period (*HR* = 2.085, 95% *CI* = 1.495–2.910), and lower-limb exposure with a longer one (*HR* = 0.786, 95% *CI* = 0.639–0.967). Cases in which one animal injured several people also had shorter periods (*HR* = 1.450, 95% *CI* = 1.133–1.857). Notably, patients who received at least one vaccine dose had a shorter incubation period than those who received none (*HR* = 1.528, 95% *CI* = 1.005–2.324).

Table 2
Cox regression analysis of factors associated with the incubation period of human rabies.

Variables	***β***	**S.E.**	**Wald**	**df**	***P***	***HR* (95% *CI*)**
Exposure site						
Lower limb vs Upper limb	-0.240	0.106	5.170	1	0.023	0.786 (0.639–0.967)
Head/face/neck vs Upper limb	0.735	0.170	18.705	1	< 0.001	2.085 (1.495–2.910)
Received PEP vaccination						
Yes vs No	0.424	0.214	3.925	1	0.048	1.528 (1.005–2.324)
Animal injured multiple people						
Yes vs No	0.372	0.126	8.681	1	0.003	1.450 (1.133–1.857)

Post-Exposure Prophylaxis

PEP coverage was very low. Only 65 of the 930 cases (6.99%) received proper wound care (irrigation and disinfection) at a medical facility, whereas 594 (63.87%) had no wound care at all. Vaccination was even lower: 51 cases (5.48%) received rabies vaccine (all on the five-dose Essen regimen), but only 6 (11.76%) completed all five doses, while the other 45 (88.24%) received just 1–4 doses. RIG use was also low—25 cases, all category III exposures. In total, 852 cases (91.62%) received no PEP, underscoring how rarely PEP was initiated (Table 3).

Table 3
Post-exposure prophylaxis (PEP) of human rabies cases in China, 2019–2024.

Variables	No. of human rabies cases	Proportion (%)
Type of wound treatment		
Untreated	594	63.87
Self-treated	271	29.14
Treated in a medical institution	65	6.99
Received PEP vaccination		
No	879	94.52
Incomplete regimen	45	4.84
Complete regimen	6	0.65
RIG injection		
Yes[a]	25	2.69
No	905	97.31
Time to PEP vaccination (days)[b]		
0	24	47.06
1–3	9	17.65
≥ 4	4	7.84
Unknown[c]	14	27.45

[a] All 25 cases that received RIG were category III exposures.

[b] Time to PEP vaccination is the interval between potential exposure and receiving the rabies vaccine.

[c] There is no complete record of the exposure or vaccination time.

Of the 930 cases, 78 (8.39%) started at least one PEP measure. The combinations were: wound care only, 27 cases (34.62%); vaccine only, 9 (11.54%), of which 1 completed the full course; wound care plus vaccine, 17 (21.79%), of which 2 completed the full course; vaccine plus RIG, 4 (5.13%), of which 1 completed the full course; wound care plus an incomplete vaccine course plus RIG, 21 (24.36%); and full standard PEP (proper wound care, full vaccine course, and RIG), only 2 (2.56%). Both of these last cases were category III exposures — one to the head/face and one to the hand — and both completed the recommended steps within 24 hours of exposure, yet still developed rabies (Supplementary Table 2). Thus, breakthrough infection occurred even among the few cases in which standard PEP was fully followed.

Factors Associated with PEP receipt

To identify factors affecting PEP, we used the receipt of wound care, vaccination, and RIG as outcomes, and entered sex, age, occupation, exposure type, exposure category, bite site, animal source, and whether one animal injured multiple people into unconditional logistic regression models (Table 4). Four factors stood out: exposure category, bite site, animal source, and whether one animal injured multiple people. Compared with category III exposures, non-category III cases were more likely to skip wound care (*OR* = 0.141, 95%*CI* = 0.050–0.395) and vaccination (*OR* = 0.263, 95%*CI* = 0.094–0.733), suggesting that people underestimate the risk of minor exposures and neglect PEP. Compared with high-risk sites (head, face, neck), exposures at lower-risk sites were more likely to go without wound care (*OR* = 0.059, 95%*CI* = 0.025–0.139), vaccine (*OR* = 0.039, 95%*CI* = 0.016–0.097), and RIG (*OR* = 0.026, 95%*CI* = 0.008–0.084). Compared with neighbor-owned or stray animals, household animals were more often linked to no wound care (*OR* = 0.117, 95%*CI* = 0.049–0.279; and *OR* = 0.262, 95%*CI* = 0.116–0.592), no vaccine (*OR* = 0.129, 95%*CI* = 0.044–0.380; and *OR* = 0.247, 95%*CI* = 0.091–0.675), and no RIG (*OR* = 0.028, 95%*CI* = 0.003–0.239; and *OR* = 0.040, 95%*CI* = 0.004–0.379), suggesting that familiarity with the animal lowers perceived risk. Single-victim incidents were also more likely than multi-victim ones to involve no wound care (*OR* = 0.413, 95%*CI* = 0.180–0.948) and no vaccine (*OR* = 0.281, 95%*CI* = 0.116–0.681), suggesting that incidents affecting several people heighten risk awareness and prompt PEP. In summary, a higher exposure category, a sensitive wound site, an unfamiliar biting animal, and multi-victim incidents were the principal factors that prompted timely PEP.

Table 4
Unconditional logistic regression of factors associated with post-exposure prophylaxis (PEP) in human rabies cases.

Outcome	Variable	*β*	S.E.	Wald	df	*OR* (95% *CI*)	*P*
Wound treatment	**Animal source**						
	Own vs Neighbor's	-2.147	0.445	23.289	1	0.117 (0.049–0.279)	< 0.001
	Own vs Stray	-1.339	0.415	10.393	1	0.262 (0.116–0.592)	0.001
	Animal injured multiple people						
	No vs Yes	-0.885	0.424	4.354	1	0.413 (0.180–0.948)	0.037
	Exposure site						
	General risk[a] vs High risk[b]	-2.833	0.438	41.912	1	0.059 (0.025–0.139)	< 0.001
	Exposure category						
	Non-category III vs Category III	-1.959	0.528	13.760	1	0.141 (0.050–0.395)	< 0.001
PEP vaccination	**Animal source**						
	Own vs Neighbor's	-2.049	0.552	13.754	1	0.129 (0.044–0.380)	< 0.001
	Own vs Stray	-1.397	0.512	7.432	1	0.247 (0.091–0.675)	0.006
	Animal injured multiple people						
	No vs Yes	-1.270	0.452	7.892	1	0.281 (0.116–0.681)	0.005
	Exposure site						
	General risk vs High risk	-3.232	0.458	49.805	1	0.039 (0.016–0.097)	< 0.001
	Exposure category						
	Non-category III[c] vs Category III	-1.335	0.522	6.534	1	0.263 (0.094–0.733)	0.011
RIG injection	**Animal source**						

Outcome	Variable	*β*	S.E.	Wald	df	*OR* (95% *CI*)	*P*
	Own vs Neighbor's	-3.575	1.233	8.414	1	0.028 (0.003–0.239)	0.004
	Own vs Stray	-3.218	1.147	7.875	1	0.040 (0.004–0.379)	0.005
	Exposure site						
	General risk vs High risk	-3.663	0.606	36.574	1	0.026 (0.008–0.084)	< 0.001

[a] General-risk sites are body parts excluding the head, face, and neck.

[b] High-risk sites have abundant nerve distribution, such as the head, face, and neck.

[c] Non-category III includes II, II or III, and Unknown.

Characteristics of post-PEP onset cases

The 78 cases (8.39%) that started at least one PEP measure met the definition of post-PEP onset. This group was mostly male (1.79:1) and largely aged 60 years or older (52.56%). Farmers predominated (74.36%), followed by children not in care and students (11.54%). Dogs caused most injuries (75 cases, 96.15%): 34 (45.33%) by strays, 19 (25.33%) by neighbors' animals, 18 (24.00%) by household animals, and 4 (5.33%) from other sources. Biting was the most common exposure (84.62%), most exposures were category III (80.77%), and the most common sites were the head/face/neck (38.46%) and the upper limbs (37.18%).

To track disease progression in post-PEP onset cases, we analyzed four intervals: exposure to first visit, incubation period, first vaccine dose to onset, and onset to death (Supplementary Table 3). Among 42 cases with clear exposure and visit records, 34 (80.95%) received their first dose within 24 hours of exposure. Among 71 cases with full incubation data, the median was 22 days (IQR 16–63); 40 (56.34%) were 28 days or less, 59 (83.10%) were 3 months or less, and 6 (8.45%) exceeded 1 year, with a maximum of 4.8 years. Among 48 cases with timing from first dose to onset, 38 (79.17%) fell ill within 28 days of the first dose. Among 68 cases with onset-to-death data, 58 (85.29%) died within 7 days of onset. These cases therefore tended to have short incubation periods, rapid progression, and early death.

Standard versus Non-Standard PEP Cases

Of the 78 post-PEP onset cases, 18 (23.08%) were standard and 60 (76.92%) were non-standard. All standard cases sought care within 24 hours of exposure and followed the recommended PEP steps before onset and death; their median incubation period was 16 days (IQR 14–22), and all fell ill within 28 days of the first dose. Compared with non-standard cases, standard cases had a higher proportion of head/face/neck exposures (94.44% vs. 23.21%, $P < 0.001$) and stray-dog injuries (77.78% vs. 37.50%, $P < 0.001$) (Table 5). Their median incubation period was also significantly shorter (16 vs. 31 days; Mann–

Whitney $U = 276.000$, $P = 0.024$). These findings suggest that, even under standard PEP, extremely high-risk exposures—to the head, face, or neck, or from stray dogs — can lead to rapid-onset breakthrough infection.

Table 5
Exposure characteristics of standard and non-standard PEP cases.

Variable	Category	Total cases	Proportion (%)	Non-standard PEP (N = 60)		Standard PEP (N = 18)		χ^2 / Fisher	*P*
				n	%	n	%		
Animal vector	Canine	75	96.15	57	95.00	18	100.00	0.726	1.000
	Cat	2	2.56	2	3.33	0	0.00		
	Wild animal	1	1.28	1	1.67	0	0.00		
Exposure route	Bite	66	84.62	51	91.07	15	83.33	2.632	0.271
	Scratch	7	8.97	4	7.14	3	16.67		
	Other	5	6.41	5	8.93	0	0.00		
Source of attacking animal	Household-owned	16	20.51	16	28.57	0	0.00	12.819	0.003
	Neighbor-owned	19	24.36	15	26.79	4	22.22		
	Stray	35	44.87	21	37.50	14	77.78		
	Other	8	10.26	8	14.29	0	0.00		
Animal injured multiple people	Yes	18	23.08	11	19.64	7	38.89	2.239*	0.135
	No	60	76.92	49	87.50	11	61.11		
Exposure site	Upper limb	29	37.18	28	50.00	1	5.56	30.366	< 0.001
	Lower limb	13	16.67	13	23.21	0	0.00		
	Head/face/neck	30	38.46	13	23.21	17	94.44		
	Trunk	6	7.69	6	10.71	0	0.00		
Exposure category	III	63	80.77	45	80.36	18	100.00	4.896	0.129
	II	9	11.54	9	16.07	0	0.00		
	II or III	5	6.41	5	8.93	0	0.00		

Variable	Category	Total cases	Proportion (%)	Non-standard PEP (N = 60)		Standard PEP (N = 18)		χ^2 / Fisher	*P*
				n	%	n	%		
	Unknown	1	1.28	1	1.79	0	0.00		

* Chi-square test; other comparisons used Fisher's exact test.

Discussion

This nationwide, surveillance-based study provides case-level evidence on why human rabies deaths continued to occur in China between 2019 and 2024. Three major findings emerged. First, most deaths occurred among individuals who did not receive any post-exposure prophylaxis. Second, among those who initiated prophylaxis, most received incomplete or non-standard care. Third, possible breakthrough infections were rare but were concentrated among patients with severe category III exposures involving the head, face, or neck, especially after stray-dog bites, and were associated with very short incubation periods.

Most deaths still occurred in people who received no PEP. In this study, 91.62% of cases had no PEP and 94.52% had no vaccine, consistent with Chinese surveillance over the past two decades [8, 12]. This indicates that the recent rebound reflects not a decline in the effectiveness of current PEP policy, but rather a failure of exposed individuals to receive PEP at all. Cases clustered in rural, middle-aged and older male farmers (farmers 78.28%; aged ≥ 65 years 38.60%), again matching earlier Chinese studies [11–13] and confirming that this group remains at high risk.

Analysis of what blocked PEP pointed to three main factors: non-category III exposure, injury by an owned animal, and single-victim incidents. Compared with category III cases, non-category III cases more often skipped wound care and vaccine, suggesting that the public underestimates the risk of minor exposures [16]. People may not understand how the virus spreads and instead judge risk by visible cues such as bleeding. People bitten by their own animals were also less likely to start PEP, probably because they trusted the animal and chose not to seek care [17]. Since dog vaccination coverage in rural China is generally below the 70% herd-immunity threshold [18–20], this false sense of safety is one of the most insidious yet dangerous gaps. PEP was also started less often after single-victim incidents than after multi-victim ones. Because several provinces now actively trace and follow up people exposed in multi-victim incidents, this suggests that social risk signals help drive protective behavior [21]. Given the profile of Chinese rabies cases, raising PEP uptake in high-risk groups will require health education that directly targets these misconceptions, along with subsidies and stronger grassroots services to make rural patients more willing to seek care.

Among the few who did start PEP, most received substandard care. Of the 78 post-PEP onset cases, 60 (76.92%) had a clear failure: inadequate wound irrigation, an incomplete vaccine course, or no passive

immunization. Likely reasons include not understanding why the full course matters (for example, thinking that finishing is unnecessary if no illness appears), high cost (especially for passive immunization), and the time needed to travel and attend visits. These are preventable failures. Beyond improving access, programs should improve affordability and outpatient follow-up to raise adherence. Reducing these failures could, in theory, markedly lower the rabies death toll.

In 18 cases (1.94% of all cases and 23.08% of post-PEP onset cases), the available investigation data showed no clear failure in the PEP process, meeting the operational definition of a possible breakthrough infection. These cases were strikingly similar: 94.44% involved the head, face, or neck, all were category III, 77.78% were caused by stray dogs, and the median incubation period was just 16 days.

The incubation analysis helps explain these findings. The Cox model identified head/face/neck exposure (*HR* = 2.085) and one animal injuring several people (*HR* = 1.450) as independent predictors of a shorter incubation period, with lower-limb exposure predicting a longer one (*HR* = 0.786). The head, face, and neck are nerve-rich and close to the central nervous system, allowing the virus to reach it quickly; an animal that injures several people is often in the late stage of disease with a high viral load. When these two factors coincide, the virus may reach the central nervous system faster than the current PEP regimen can elicit protective immunity, which typically requires 7–14 days [22–24]. This matches the breakthrough cases in the systematic review by Whitehouse et al [9]. The observation that vaccinated patients had shorter incubation periods than unvaccinated patients should not be interpreted as the vaccine shortening the incubation period [25]. It more plausibly reflects selection bias: individuals with more severe, conspicuous injuries were more likely to seek care and receive PEP, and their inherently shorter incubation periods produced this association [19].

It must be stressed that possible breakthrough infections were a very small share of all deaths (1.94%) and should not be read as PEP failing in general. The main challenge remains raising PEP uptake and ensuring it is done correctly. Any proposal for a "category IV" exposure tier or intensified treatment must first exclude substandard care, so that a rare phenomenon is not used to justify broad policy change or misapplied [26].

Clinically, our results support the WHO concept of Integrated Bite Case Management (IBCM). Current exposure grading is based mainly on wound appearance, yet the incubation period depends heavily on bite site and severity. We suggest piloting joint medical–veterinary teams in high-incidence areas, these teams would weigh the patient's comorbidities, bite site, the biting animal's status, and local epidemiology, and provide more aggressive treatment and closer follow-up for high-risk patients (for example, category III head/face/neck exposures, stray-dog bites, or serious comorbidities) [27–28]. Such clinics could also serve as education hubs to improve public understanding of rabies.

Rabies in dogs remains the root cause of the human rebound. In this study, vaccination coverage among owned animals was only 1.83%, far below the 70% herd-immunity threshold. Strengthening dog management and raising vaccination coverage remains the fundamental route to controlling, and ultimately eliminating, dog-mediated human rabies deaths [29–30].

This study has several limitations. First, the study was retrospective, and some exposure and prophylaxis information was obtained from family interviews, which may be subject to recall bias. Second, individual case investigations were not available for all reported cases, although the included dataset covered most cases and was broadly comparable to the source population. Third, technical details of prophylaxis were difficult to verify, including wound washing quality, vaccine cold-chain integrity, exact timing and site of immunoglobulin infiltration, and host immune status. Misclassification of standard and non-standard prophylaxis is therefore possible. Fourth, animal vaccination status was often based on family report rather than veterinary records and may have been underreported or uncertain. Finally, because all included individuals developed rabies, this study identified factors associated with PEP receipt among fatal cases but could not estimate PEP effectiveness in the wider exposed population.

Conclusion

This nationwide, surveillance-based study shows that most human rabies deaths in China between 2019 and 2024 were associated with a failure to initiate PEP, particularly among rural, middle-aged and older farmers. Risk underestimation after minor-appearing exposures, injuries caused by household animals, wounds at lower-risk sites, and single-victim incidents contributed to low prophylaxis uptake. Among patients who initiated prophylaxis, most received incomplete or non-standard care, indicating preventable gaps in wound management, vaccination completion, and passive immunization.

Possible breakthrough infections were rare but occurred mainly after severe category III exposures involving the head, face, or neck, especially from stray dogs, and were characterized by very short incubation periods. These cases highlight the need for better risk stratification and close follow-up of extremely high-risk exposures, while reinforcing that standard post-exposure prophylaxis remains highly effective when delivered promptly and correctly.

To reduce human rabies deaths, China should strengthen targeted health education, improve access and adherence to prophylaxis, subsidize passive immunization for severe exposures, implement integrated bite case management, and accelerate dog vaccination and dog population management under a One Health framework.

Abbreviations

PEP
Post-exposure prophylaxis
RIG
Rabies immunoglobulin
CI
Confidence interval
HR
Hazard ratio
OR

Odds ratio
WHO
World Health Organization

Declarations

Animal Ethics and Consent to Participate declarations

Not applicable.

Clinical trial

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This work research was supported by the Emergency Response Mechanism Operation Program (102393220020010000017) and the Comprehensive Prevention and Control of Diseases Program (102393260020011000011).

Author Contribution

Di Mu and Canjun Zheng conceived and designed the study. Shouming Lyu, Xi Cheng, Jinhui Zhang, Xiao Yuan and Danjian Zheng collected and verified the surveillance data. Shouming Lyu performed the statistical analysis. Shouming Lyu and Di Mu drafted the manuscript. Canjun Zheng and Yanping Zhang interpreted the findings and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgement

We thank the staff of provincial, prefectural, and county Centers for Disease Control and Prevention for their contributions to rabies case investigation and surveillance data collection.

Data Availability

The data supporting the findings of this study are available from China CDC, and relevant data may be obtained from the corresponding author upon reasonable request and with permission of China CDC.

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