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Epidemiological Characteristics and Spatial Clustering of Single-Dog-Induced Multiple Human Exposure Events — Chongqing, China, 2016–2025

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ABSTRACT

Introduction: Single-dog-induced multiple human exposure events can result in multiple potential rabies exposures within a short period, with substantial public health and economic costs. In China, these events are managed under nationally standardized procedures and require a coordinated public health and animal health response. This study analyzed the epidemiological characteristics, post-exposure prophylaxis (PEP), and response gaps associated with these events in Chongqing from 2016 to 2025.

Methods: Data on events, offending dogs, and exposed persons were collected from investigation reports submitted by district and county CDCs. Human rabies surveillance data for Chongqing were obtained from the China CDC Information System. Spearman correlation analysis was used to assess the association between annual event counts and the number of human rabies cases reported, and cross-correlation function (CCF) analysis was used to assess the temporally lagged association. Joinpoint regression was used to evaluate temporal trends, and global and local Moran's *I* statistics were used to assess spatial clustering. Statistical significance was defined as $P < 0.05$.

Results: A total of 124 events involving 649 exposed persons were reported, including 3 human rabies deaths. Annual event counts were positively correlated with the number of human rabies cases reported during the same period ($r = 0.782$, $P < 0.01$), and CCF analysis showed positive correlations across all lag months, with the correlation being strongest with a 2-month lag ($r = 0.426$, 95% CI: 0.355, 0.629, $P < 0.001$). The annual number of events declined during the study period (average annual percent change = -19.0% , $P < 0.01$), with a rapid decline between 2016 and 2022 and a nonsignificant increase between 2022 and 2025. Most events (74.2%)

occurred in rural areas. Spatial clustering was detected in 2016–2017, 2018–2019, and 2024–2025. Category III exposures accounted for 82.7% of exposed persons. Rabies vaccine coverage was 98.9%, and rabies immunoglobulin was administered to 87.5% of persons with Category III exposure. No deaths occurred among those who received standard PEP, whereas mortality was 2.6% among those who did not ($P < 0.01$). Stray dogs accounted for 66.9% of offending dogs. Only 7 canine specimens were tested from the 124 offending dogs (5.6%), and all were positive for rabies virus antigen by direct fluorescent antibody test using brain tissue.

Conclusions: From 2016 to 2025, single-dog-induced multiple human rabies exposure events in Chongqing declined overall and showed localized clustering. Most events occurred in rural areas, with Category III exposures predominating. In this group, no deaths occurred among standardized PEP recipients, whereas 3 deaths occurred among individuals who did not receive standardized PEP. To reduce human rabies, event monitoring and standardized PEP should be strengthened.

Rabies is an acute zoonotic disease caused by rabies virus infection and is almost invariably fatal once clinical symptoms develop (1–2). Globally, approximately 59,000 people die from rabies each year, primarily in Asia and Africa (1). Dogs are the primary source of human rabies, accounting for approximately 99% of human rabies cases worldwide (2–3). Although the incidence of human rabies in China has decreased substantially, sporadic cases, localized re-emergence, and spatial clustering persist in some regions (4–5).

In China, surveillance of single-dog-induced multiple human exposure events is a specialized component of rabies prevention and control,

implemented under nationally standardized procedures (6–8). Such events constitute a statutory trigger for initiating an animal epidemic emergency response, including epidemiological investigations and delineation and management of affected areas, when required. Government-coordinated, multisectoral action involving health, agriculture and rural affairs, public security, community-level organizations, and other relevant sectors is required to ensure timely management of exposed persons and offending dogs. Previous studies have reported that more than 80% of tested offending dogs involved in such events were positive for rabies virus (9–11), indicating a high risk of rabies transmission.

Chongqing has complex terrain and marked urban-rural differences, and dog management is challenging in rural and peri-urban areas. Historically, Chongqing has been a high-risk area for human rabies in China (5). This study used Chongqing as a case study to examine the local implementation of surveillance, human exposure management, animal health investigation, and multi-sectoral coordination, to provide evidence to inform wider implementation of national prevention and control strategies.

METHODS

Data Sources and Collection

Data on single-dog-induced multiple human exposure events in Chongqing from January 1, 2016, to December 31, 2025, were obtained from investigation reports submitted by district and county CDCs. For each reported event, standardized investigation forms were used to collect information on the event date and location, source and disposition of the offending dog, demographic characteristics of the exposed persons, exposure route, exposure site, exposure category, wound management, rabies vaccination, rabies immunoglobulin (RIG) administration, and outcomes. Field investigators categorized the gaps in prevention, control, and response based on investigation forms, response records, and interview information. Rabies surveillance data for Chongqing were obtained from the China CDC Information System. Brain tissue specimens from offending dogs were submitted to the Chongqing Animal Disease Control Center when available. Rabies virus antigen was detected by direct fluorescent antibody (DFA) testing. Township- and subdistrict-level administrative boundary data were obtained from

the map service website of the Chongqing Planning and Natural Resources Bureau.

Definitions and Classifications

A single-dog-induced multiple human exposure event was defined as one in which the same dog bit or scratched two or more persons within one week (11–12). Rabies exposure classification and post-exposure prophylaxis (PEP) recommendations followed national technical guidelines (8). Standardized PEP was defined as timely care after exposure and completion of wound management, rabies vaccination, and RIG administration according to national recommendations for the corresponding exposure category. Non-standardized PEP was defined as non-standardized wound management, failure to receive rabies vaccination according to the schedule, or failure or substantial delay in RIG administration when indicated. For fatal cases, the classification was based on treatment received before disease onset to avoid misclassification due to inability to complete vaccination after rabies onset. Urban and rural areas were classified according to the urban-rural classification codes issued by the National Bureau of Statistics of China, based on the township or subdistrict where each event occurred.

Statistical Methods

Descriptive epidemiological methods were used to analyze the temporal and geographic distribution of events, characteristics of exposed persons, PEP management, and offending dog characteristics. Spearman correlation analysis was used to assess the association between annual event counts and reported human rabies cases. Cross-correlation function (CCF) analysis was then applied to the monthly event counts and reported human rabies cases to examine the temporally lagged association (maximum lag, 12 months). Confidence intervals for CCF coefficients were estimated via block bootstrapping with 1,000 resamples to account for temporal autocorrelation. Joinpoint regression was used to estimate annual percentage change (APC) and average APC (AAPC). The township or subdistrict was used as the geographic unit for spatial analysis. Global Moran's I was used to evaluate spatial autocorrelation. When global Moran's I was statistically significant, local indicators of spatial association (LISA) were used to identify local clusters, with emphasis on high-high clusters (hotspots). Fisher's exact test was used to compare mortality

between standardized and non-standardized PEP groups. All tests were two-sided, with $\alpha=0.05$. Excel 2016 (Microsoft Corp., Redmond, WA, USA) and R 4.4.3 (R Foundation, Vienna, Austria) were used for data management and analysis.

RESULTS

Epidemiological Overview and Temporal Trends

From 2016 to 2025, 124 single-dog-induced multiple human exposure events, involving 649 exposed persons, were reported in Chongqing, with a median of 4 exposed persons per event [interquartile range (IQR): 2–6], with a maximum of 23 persons. During the study period, 89 human rabies cases were reported in Chongqing. Among the 649 exposed persons in these events, 3 died of rabies.

Annual event counts were positively correlated with reported human rabies cases ($r=0.782$, $P<0.01$) (Figure 1). CCF analysis revealed that monthly event counts were positively correlated with reported human rabies cases across all lag months, with a 2-month lag having the strongest correlation [$r=0.426$, 95% confidence interval (CI): 0.355, 0.629, $P<0.001$].

Joinpoint regression showed that event counts declined overall between 2016 and 2025 (AAPC=-19%, $P<0.01$). A rapid decline occurred between 2016 and 2022 (APC=-27%, $P<0.05$), followed by a nonsignificant increase during 2022–2025 (APC=17%). Events were reported throughout the year, with 94 of 124 events (75.8%)

reported between March and September, with a peak in August (20/124, 16.1%) (Supplementary Figure S1, available at <https://weekly.chinacdc.cn/>).

Geographic Distribution and LISA Clustering

From 2016 to 2025, events were reported in 93 townships or subdistricts across 22 districts or counties in Chongqing. The three districts or counties with the highest numbers of reported events were Liangping District (22 events, 17.7%), Jiangjin District (20 events, 16.1%), and Zhong County (18 events, 14.5%). Most events (92/124, 74.2%) occurred in rural areas with 92 events and only 32 events (25.8%) occurred in urban areas. Five townships or subdistricts reported three or more events: Lishi Town (6 events) and Youxi Town (3 events) in Jiangjin District; Liangshan Subdistrict (5 events) and Wenhua Town (3 events) in Liangping District; and Shuanggui Town (4 events) in Zhong County (Supplementary Table S1, available at <https://weekly.chinacdc.cn/>).

Global spatial autocorrelation analysis showed significant positive spatial clustering during 2016–2017, 2018–2019, and 2024–2025. Local spatial autocorrelation analysis showed that hotspots varied by period. In 2016–2017, hotspots were located mainly in Jinjie, Maguan, Bashan, and Yongfeng towns in Zhong County; Shuanggui Subdistrict and Tiemen Township in Liangping District; and Xihu Town in Jiangjin District. In 2018–2019, hotspots were located in Youxi Town, Xihu Town, and Degan Subdistrict in Jiangjin District and Jukui Town in Liangping

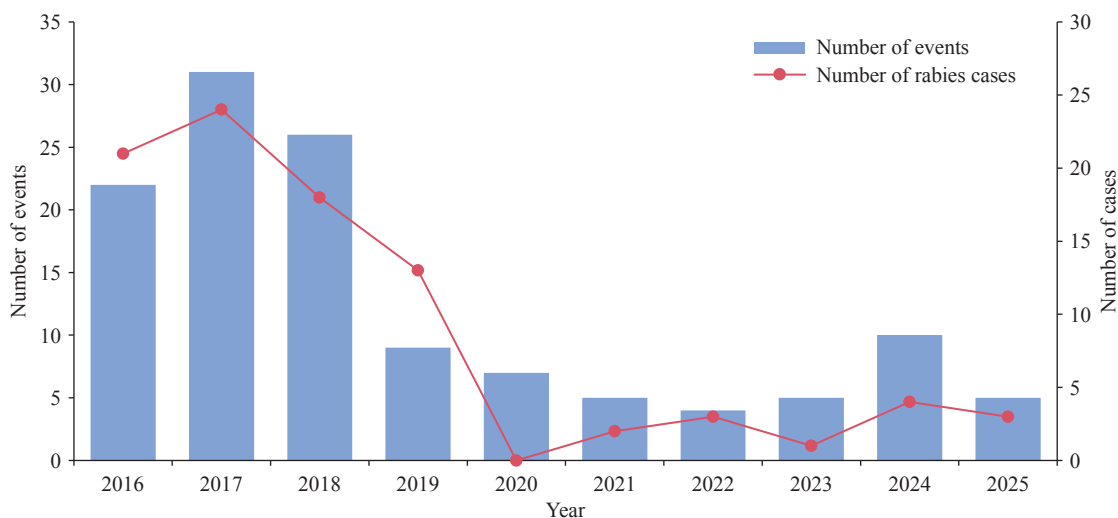


FIGURE 1. Number of single-dog-induced multiple human exposure events and the number of reported human rabies cases in Chongqing, China, 2016–2025.

TABLE 1. Spatial autocorrelation analysis of single-dog-induced multiple human exposure events in Chongqing, China, 2016–2025.

Period	Global spatial autocorrelation		Local spatial autocorrelation			
	Moran's <i>I</i>	<i>P</i>	High-highclusters	High-lowclusters	Low-highclusters	Low-lowclusters
2016–2017	0.105	<0.01	7	17	122	8
2018–2019	0.044	<0.05	4	19	117	15
2020–2021*	0.014	>0.05	NA	NA	NA	NA
2022–2023*	0.031	>0.05	NA	NA	NA	NA
2024–2025	0.082	<0.01	3	11	69	109

Abbreviation: NA=not applicable.

* Spatial autocorrelation analysis revealed no significant spatial clustering.

District. In 2024–2025, hotspots were located in Huaxing Town, Weilong Town, and Damiao Town in Tongliang District (Table 1).

Offending Dogs

Among the 124 offending dogs, 83 (66.9%) were strays, 37 (29.8%) were household pets, and 4 (3.2%) were of unknown origin. Based on descriptions from witnesses and exposed persons, 71 dogs (57.3%) had suspected rabies manifestations, including agitation, salivation, abnormal vocalization, or unprovoked biting. After the events, 98 dogs (79.0%) were killed and incinerated or safely disposed of, 17 (13.7%) were tethered or restricted, and 9 (7.3%) escaped. Only 7 offending dogs (5.6%; 6 strays and 1 household pet) had brain tissue specimens available for testing, and all were positive for rabies virus antigen by DFA.

Characteristics of Exposures and Exposed Persons

Dog bites accounted for 626 of 649 exposures (96.5%). The most common exposure site was the legs (429/649, 66.1%). Of the 649 exposures, 537 (82.7%) were Category III and 93 (14.3%) were Category II.

The median age of exposed persons was 50 years (IQR: 13–65 years), and the majority (368/649, 56.7%) were aged 45 years or older. Of the 649 exposed persons, 339 (52.2%) were male. Farmers (46.8%) and students or kindergarten-age children (29.0%) were the most common occupational groups (Supplementary Table S2, available at <https://weekly.chinacdc.cn/>).

PEP and Mortality

Among the 649 exposed persons, 600 (92.4%) received clinical wound management, including washing, disinfection, or debridement; 642 (98.9%)

received rabies vaccination; and 492 (75.8%) received RIG. Among the 537 persons with Category III exposures, 510 (95.0%) received clinical wound management within 24 hours, 528 (98.3%) completed rabies vaccination, and 470 (87.5%) received RIG.

Nineteen individuals with Category I or unknown exposure were excluded from the PEP standardization and mortality analyses. Among 630 individuals with Category II or III exposure, 513 received standardized PEP, with no deaths reported. Three deaths occurred among the 117 individuals who received non-standardized PEP (case fatality rate: 2.6%). The difference in mortality between the two groups was statistically significant ($P<0.01$, Fisher's exact test). The estimated relative risk of death in the standardized PEP group compared with the non-standardized PEP group was 0.033 (95% CI: 0.002, 0.668) after Haldane–Anscombe correction.

The three fatal cases occurred in three separate events. Case 1 was a 6-year-old child bitten on the leg by a household dog. No wound management was performed and neither rabies vaccination nor RIG was administered. The child died approximately 4 months after exposure. Case 2 was a 9-year-old child bitten on the head and face by a stray dog. The child received wound management at a medical institution and completed 3 doses of rabies vaccination; however, RIG was administered 2 days after exposure. The child died 36 days after exposure. Case 3 was a 74-year-old adult bitten on the head, face, and arm by a stray dog. No wound management was performed. The individual completed 4 doses of rabies vaccination (Essen regimen) but did not receive RIG and died 29 days after exposure. The key PEP deficiencies identified in these three cases included absence of wound management, incomplete rabies vaccination, and delay or absence of RIG administration. Each fatal case had at least one key PEP deficiency.

Gaps in Prevention, Control, and Response

Field investigations identified several gaps in prevention, control, and response, including inadequate dog management systems (79 events, 63.7%), gaps in standardized PEP (61 events, 49.2%), limited surveillance sensitivity and public reporting awareness (45 events, 36.3%), insufficient public knowledge regarding rabies prevention (36 events, 29.0%), and limited RIG availability (15 events, 12.1%). Multiple gaps were sometimes identified in the same event (Table 2).

DISCUSSION

This 10-year regional analysis provides several unique insights. It characterizes the long-term trend of single-dog-induced multiple human exposure events in Chongqing, quantifies their exploratory lagged association with reported human rabies cases, documents the temporal shift of reported-event spatial clusters, evaluates PEP standardization in relation to fatal outcomes, and documents gaps in grassroots response to these events identified in the field. These findings extend previous short-term or local studies and provide regional evidence that can be used to inform national rabies control strategies.

The annual event counts were positively correlated with the number of human rabies cases reported annually, and CCF analysis showed the strongest correlation after a 2-month lag. However, this is an ecological association based on surveillance data and cannot establish causality. The exposure event served as a statutory trigger for an immediate field emergency response (6–7). Using event counts to forecast future

human rabies cases remains a candidate supplementary early warning approach (10–11), and its predictive performance, thresholds, and external validation have not been established. Its practical value lies mainly in providing a window for case finding, standardized PEP, offending-dog control, and specimen testing (6–8), rather than replacing integrated human and animal rabies surveillance. Events were reported year-round but the number of events reported was higher between March and September, peaking in August, consistent with other regions in China (10–13). This may be related to increased dog activity, more frequent human-dog contact, more outdoor activities, and use of lighter clothing during warmer months (14).

Spatial analysis showed significant clustering, with the event hotspots shifting. These findings indicate that the distribution of hotspots was not geographically fixed but showed temporal and spatial heterogeneity. However, LISA high-high clusters should be interpreted as clusters of reported events rather than as true hotspots of rabies virus transmission among dogs. Changes in hotspots may be associated with dog density, dog vaccination coverage, stray dog management, public reporting awareness, primary healthcare recognition capacity, and dog movement across areas (12,15). Therefore, spatial clustering should be interpreted together with animal rabies surveillance, clinical data on dog bites, and dog vaccination coverage, and should not be used alone for resource allocation.

The PEP findings are programmatically important. Category III exposures accounted for 82.7% of exposed persons, and vaccine and RIG coverage were high, exceeding previously reported levels among human rabies cases in China (16). According to WHO

TABLE 2. Gaps in prevention, control, and response to single-dog-induced multiple human exposure events in Chongqing, China, 2016–2025.

Gap	Summary	No. of events, n (%) (N=124)
Inadequate dog management systems	Insufficient dog registration and tethering in rural and peri-urban areas; inadequate stray dog sheltering and control; insufficient owner responsibility.	79 (63.7)
Gaps in standardized PEP	Delayed healthcare seeking or non-standard wound management; refusal of RIG or delayed RIG administration among Category III exposures; incomplete vaccination.	61 (49.2)
Limited surveillance sensitivity and public reporting awareness	Insufficient early recognition by primary healthcare facilities; delayed reporting; limited public awareness of active reporting.	45 (36.3)
Insufficient public knowledge of rabies prevention	Limited awareness of rabies fatality and the importance of wound management, vaccination, and RIG.	36 (29.0)
Limited RIG availability	Some primary dog bite clinics did not routinely stock RIG; cross-area referral caused delayed or forgone RIG administration.	15 (12.1)

Note: Multiple gaps could be identified in the same event.
Abbreviation: PEP=post-exposure prophylaxis; RIG=rabies immunoglobulin.

recommendations and Chinese technical guidelines, persons with Category III exposure should immediately receive wound management, rabies vaccination, and RIG (2,8). In this series, no deaths were observed among persons who received standardized PEP, whereas all 3 deaths occurred among persons who received non-standardized PEP, each with deficiencies in at least one key component. However, only 3 deaths occurred, and PEP deficiencies overlapped; the independent effect of individual components could not be distinguished. Standardized PEP is highly effective but the protection is not absolute, and fatal breakthrough infections have been reported (17). In China, many exposed individuals receive insufficient PEP (16); therefore, timely and complete PEP is essential. Most exposed persons were middle-aged or older farmers, and most events occurred in rural areas; however, 2 of the 3 fatal cases were in children. Previous studies have shown that human rabies in China is closely related to dog management in rural areas, insufficient dog vaccination coverage, and delayed or incomplete PEP (15–16), highlighting rural areas and children as priority groups for early care-seeking and exposure management.

A distinctive finding of this study is the low level of testing of offending dogs. Although stray dogs accounted for the majority of offending dogs and more than half showed suspected rabies-related signs, only 7 dogs were tested for rabies, and all were positive. Previous studies have reported that more than 80% of offending dogs involved in such events test positive for rabies virus (9–11). Owing to the low testing proportion and probable selection bias, our positivity rate cannot be extrapolated to all offending dogs. Nevertheless, this reveals a critical gap in the response chain regarding animal management. Under China's standardized procedures, such events should trigger a defined emergency workflow with clear multi-sectoral roles (6–7); however, challenges remain in capture and control of offending dogs, standardized specimen collection, cold-chain transport, laboratory testing, and timely feedback of results. A closed-loop management system for offending dogs — mandatory capture or isolation, standardized sampling, testing, and result feedback — is needed, particularly for stray dogs, dogs with abnormal behavior, and events involving multiple severe exposures.

Field investigations also identified gaps in dog management, standardized PEP administration, surveillance sensitivity, public reporting, rabies

prevention knowledge, and RIG availability. These findings indicate the need for a time-bound multisectoral response (6–8); however, the key implication of this study is that event reporting, exposed-person management, offending-dog control, animal testing, and feedback of results must be linked in a closed loop.

This study has several limitations. First, the data were based on passive surveillance and field records, so underreporting, delayed reporting, incomplete PEP information, and exposure classification bias may have occurred, and spatial clusters represent reported-event clusters rather than true transmission hotspots. Second, no comparison group of single-person dog-bite exposures was included, and only 7 offending dogs were tested, limiting the assessment of exposure severity, PEP quality, rabies risk, and animal rabies circulation. Third, township-level data on dog vaccination, stray dog management, and PEP resources were unavailable, limiting the interpretation of shifts in hotspots and the assessment of future risk.

In conclusion, single-dog-induced multiple human exposure events declined overall in Chongqing during 2016–2025 and showed localized clustering. Counts of such events could be used as a candidate supplementary early-warning indicator of human rabies risk. Strengthening event monitoring and standardized PEP is needed to reduce the risk of rabies in humans.

Conflicts of interest: No conflicts of interest.

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Ethical statement: This study used de-identified data from routine public health surveillance and field investigations. According to relevant national regulations and institutional requirements, ethical review was waived.

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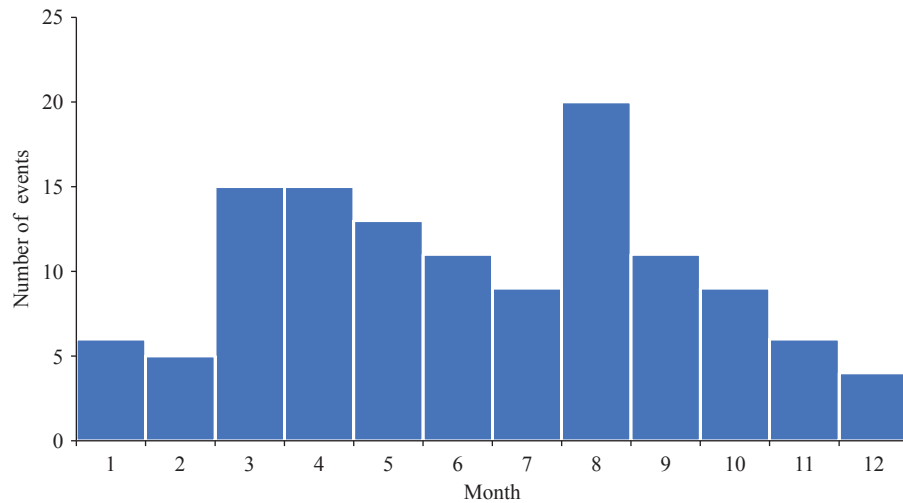
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SUPPLEMENTARY MATERIALS



SUPPLEMENTARY FIGURE S1. Number of single-dog-induced multiple human exposure events reported in Chongqing, China by month, 2016–2025.

SUPPLEMENTARY TABLE S1. Distribution of single-dog-induced multiple human exposure events by district/county and township/subdistrict in Chongqing, China, 2016–2025.

Administrative division	Number of reported events, <i>n</i> (%) (<i>N</i> =124)	Number of involved townships (sub-districts)
Liangping District	22 (17.7)	13
Jiangjin District	20 (16.1)	11
Zhong County	18 (14.5)	10
Beibei District	10 (8.1)	8
Tongliang District	7 (5.6)	7
Shapingba District	6 (4.8)	6
Nanchuan District	6 (4.8)	4
Dianjiang County	6 (4.8)	5
Wuxi County	5 (4.0)	5
Youyang Tujia and Miao Autonomous County	4 (3.2)	4
Changshou District	3 (2.4)	3
Pengshui Miao and Tujia Autonomous County	3 (2.4)	3
Qijiang District	2 (1.6)	2
Dazu District	2 (1.6)	2
Kaizhou District	2 (1.6)	2
Wushan County	2 (1.6)	2
Wanzhou District	1 (0.8)	1
Yuzhong District	1 (0.8)	1
Jiulongpo District	1 (0.8)	1
Rongchang District	1 (0.8)	1
Wulong District	1 (0.8)	1
Xiushan Tujia and Miao Autonomous County	1 (0.8)	1

Note: The remaining 16 districts/counties that reported no single-dog-induced multiple human exposure events are not included in the table.

SUPPLEMENTARY TABLE S2. Demographic characteristics of persons exposed to single-dog-induced multiple human exposure events in Chongqing, China, 2016–2025.

Characteristic	Number of cases (N=649)	Percentage (%)
Age group (years)		
0–4	34	5.2
5–9	84	12.9
10–14	52	8.0
15–24	31	4.8
25–34	31	4.8
35–44	49	7.6
45–54	102	15.7
55–64	97	14.9
65–74	97	14.9
75–86	72	11.1
Sex		
Male	339	52.2
Female	310	47.8
Occupation		
Farmer	304	46.8
Students or kindergarten children*	188	29.0
Housewife or Retiree	25	3.9
Worker	23	3.5
Preschool children†	13	2.0
Others‡	96	14.8

* Students or kindergarten children include individuals attending kindergarten, primary school, middle school, high school, college, or university.

† Preschool children refer to children younger than 3 years who were cared for at home and did not attend childcare institutions.

‡ Others include teachers, laborers, self-employed persons, unemployed persons, food industry workers, and government or institutional staff.

Preplanned Studies

The Epidemiological Characteristics of 55 Multiple-Victim Incidents Involving Bites from a Single Dog — Shandong Province, China, 2025

Yufang Xing^{1,✉}; Tao Liu^{2,✉}; Zengqiang Kou¹; Xinlei Guo³; Wenguo Jiang⁴; Shujun Ding¹; Xiaomei Zhang^{1,✉}

Summary

What is already known about this topic?

Rabies is a zoonotic infectious disease caused by rabies virus infection and was classified as a Class B notifiable infectious disease in China. Events involving multiple victims bitten by a single dog represent a distinct category in rabies epidemiological surveillance and risk assessment. These incidents indicate high-probability point-source exposure to potentially rabid animals and thus pose urgent public health threats.

What is added by this report?

This study analyzed the epidemiological characteristics of events involving multiple victims bitten by a single dog in Shandong Province in 2025 and evaluated the effectiveness of post-exposure prophylaxis (PEP) implementation.

What are the implications for public health practice?

This study highlights the severity of events involving multiple victims bitten by a single dog in Shandong Province and validates the effectiveness of post-exposure prophylaxis (PEP) strategies, providing robust evidence for the formulation of rabies prevention and control strategies.

(20.00%, 11/55). A total of 191 patients were classified as Category II or Category III exposure, and 181 (90.95%) received standard post-exposure prophylaxis (PEP) treatment. The overall rabies vaccination rate was 98.43% (188/191). Two individuals developed rabies.

Conclusions and Implications for Public Health Practice: These findings may provide evidence for canine vaccination efforts in rural areas, optimization of PEP strategies, and health education initiatives.

Rabies is a zoonotic infectious disease caused by the rabies virus and is classified as a Class B notifiable infectious disease in China (1–2). Its main clinical manifestations include hydrophobia, pharyngospasm, and progressive paralysis, and the disease has an almost 100% mortality rate. A resurgence of human rabies cases was observed nationwide in China in 2024 (3).

Almost all rabies cases are caused by bites from infected dogs (4). In Hunan Province, the positivity rate for rabies virus among dogs involved in such incidents reached 90%, substantially higher than that among dogs involved in general single-bite incidents (3.61%) (5). A systematic review of dog-bite incidents found that 80% involved multiple victims bitten by a single dog (6).

Shandong Province has a large population, with a substantial proportion residing in rural agricultural areas. In this study, we analyzed the epidemiological characteristics of incidents in which multiple individuals were bitten by a single dog in Shandong Province in 2025 and evaluated the effectiveness of post-exposure prophylaxis (PEP) implementation.

Multiple-victims incidents involving a single dog are defined as incidents in which two or more individuals are exposed (bite, scratch, or contamination) to the same dog within 48 hours.

The exposure categorization and PEP were

ABSTRACT

Introduction: This study aimed to analyze the epidemiological characteristics of multiple-victim incidents involving bites from a single dog in Shandong Province in 2025 and provide robust evidence to support rabies prevention and control.

Methods: Data on incidents of multiple victims being bitten by a single dog in 2025 were collected and analyzed using descriptive epidemiological methods.

Results: A total of 55 incidents were reported in Shandong Province in 2025, involving 199 exposed individuals. The majority of cases were concentrated in Heze City (61.82%, 34/55), followed by Jining City

administered according to the *Guidelines for Rabies Exposure Prevention and Treatment (2023 Edition)*.

The surveillance data from January 1 to December 31, 2025, were obtained from the Public Health Emergency Management Information System and China Information System for Disease Control and Prevention.

The rabies virus nucleic acid was detected in brain tissue specimens of the dogs using a real-time PCR diagnostic kit (XABT, Beijing, China).

Descriptive epidemiological methods were used to analyze the epidemiological characteristics of multiple-victims bitten by a single dog. Epidata (version 3.1, Epidata Association, Denmark) and SPSS version 18.0 (SPSS Inc. Chicago, IL, USA) were used for all statistical analyses. $P < 0.05$ was considered statistically significant.

A total of 55 such incidents were reported in 2025, 11 times more than in 2024 (5 incidents) and 5-fold higher than that of 2020–2024 (11 incidents). Most incidents occurred from May to September (63.64%, 35/55) and September had the highest monthly incidence (18.18%, 10/55) (Figure 1). The number of incidents was the highest in Heze City (34 incidents, 61.82%, 34/55), followed by Jining City (11 incidents, 20.00%, 11/55), and Liaocheng City (7 incidents, 12.73%).

As shown in Table 1, 199 individuals were involved in these incidents. Among them, 117 (58.79%) were males and 82 (41.21%) were females. The median age was 53 years [interquartile range (IQR)=24 years, Q1=37 years, Q3=61 years], and agricultural workers constituted the majority (80.40%, 160/199).

As shown in Table 2, most of the exposed individuals lived in rural villages (45/55, 83.64%). The majority of exposures were Category III (87.94%,

175/199), followed by Category II (8.04%, 16/199). Stray dogs were identified as the leading source of rabies exposure, accounting for 61.82% (34/55) of incidents and affecting 63.82% (127/199) of exposed individuals. Domestic dogs were responsible for 34.55% (19/55) of incidents, involving 66 exposed individuals (33.17%). The predominant exposure mode was biting (95.48%, 190/199), followed by scratching (2.51%, 5/199) and contact during culling of sick dogs (1.01%, 2/199). The lower limbs were the most common exposure site (76.88%, 153/199), followed by the upper limbs (12.06%, 24/199).

Among the 199 exposed individuals, 8 with Category I exposure did not require wound treatment. Among the other 191 individuals with Category II or III exposure, 189 (98.95%) completed standardized wound treatment after exposure, while two declined wound treatment; in terms of PEP, 188 (98.43%, 188/191) received rabies vaccination, one exposed person failed to finish the full vaccination schedule, and two people declined vaccination. Among the 175 individuals with Category III exposure, 161 (92.00%) received rabies immunoglobulin (RIG) administration, 4 had a prior history of rabies vaccination and therefore did not require it, and the remaining 10 refused RIG after repeated risk communication.

As shown in Table 3, among the 55 incidents, Chinese native rural dogs were the main bite source (27.27%, 15/55), followed by Chinese greyhounds (9.09%, 5/55). None of the dogs had a history of rabies vaccination. Among these dogs, 46 (83.64%, 46/55) were culled, 7 (12.73%, 7/55) escaped, 1 (1.82%, 1/55) died naturally, and 1 (1.82%, 1/55) remained in captivity. Before inflicting bite injuries, 20 (36.36%, 20/55) dogs had exhibited abnormal behaviors, including abnormal vocalization and

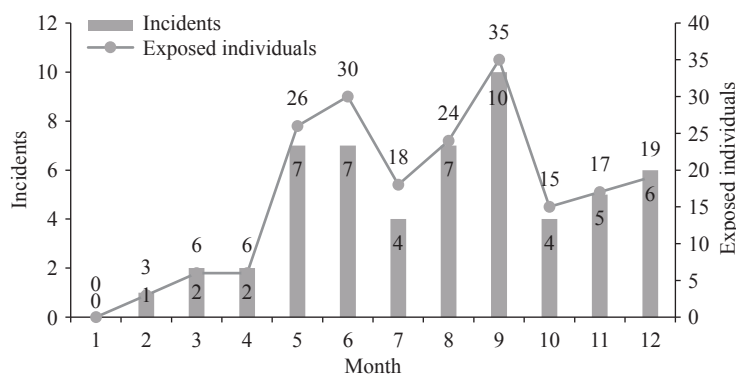


FIGURE 1. The temporal distribution of 55 incidents involving multiple-victims bitten by a single dog and human rabies cases in Shandong Province in 2025.

TABLE 1. The demographic characteristics of exposed individuals.

Exposure characteristics	Number of people	Proportion (%)
Gender		
Male	117	58.79
Female	82	41.21
Age group (years)		
<14	27	13.57
15–29	8	4.02
30–44	32	16.08
45–59	63	31.66
≥60	69	34.67
Occupation		
Farmers	160	80.4
Students	17	8.54
Preschool children	6	3.02
Others	16	8.04

anorexia. Brain tissue specimens were collected from 46 of the dogs. Rabies virus nucleic acid was detected in 38 samples, corresponding to an overall positivity rate of 82.61% (38/46). The positivity rate was 88.24% (15/17) among domestic dogs, 81.48% (22/27) among stray dogs, and 50% (1/2) among suspected ownerless dogs. The positivity rate was 75.00% (9/12) among incidents involving 2 exposed persons (15 total incidents, 12 samples), 92.86% (13/14) for those involving 3 exposed persons (16 total incidents, 14 tissue samples), and 80.00% (16/20) for those involving ≥4 exposed persons (24 total incidents, 20 tissue samples). Statistical analysis showed no significant difference in the nucleic acid positivity rate across the three subgroups ($\chi^2=1.636$, $P=0.492$).

Two exposed individuals among the 199 exposed individuals developed rabies and subsequently died. The first incident involved a 62-year-old female with Category III exposure who was bitten on her left calf by a stray dog at the door while grocery shopping. She rinsed the wound 24 hours after exposure and received the rabies vaccine but did not receive RIG. Unfortunately, she developed rabies 17 days after completing the vaccination course. Another exposed individual was classified as having Category II exposure and received standardized PEP. This individual did not develop rabies. The offending stray dog fled the scene, and no biological specimens were collected. The second incident involved a 49-year-old male index case with Category III exposure. He sustained an ankle bite from a stray dog while returning home from farmland.

TABLE 2. The exposure characteristics of exposed individuals.

Exposure characteristics	Number of people	Proportion (%)
Exposure level		
I	8	4.02
II	16	8.04
III	175	87.94
Animal source		
Stray dog	34	61.82
Domestic dog	19	34.55
Resembling a domestic dog	2	3.64
Exposure mode		
Bite	190	95.48
Scratch	5	2.51
Culling of sick dogs	2	1.01
Veterinary contact	1	0.5
Daily feeding contact	1	0.5
Exposure site		
Lower limbs	153	76.88
Upper limb	24	12.06
Multiple sites combined	11	5.53
Trunk	4	2.01
Head and neck	1	0.50
Others	6	3.02

He only rinsed the wound without receiving any other treatment. He developed rabies one month later. The other co-exposed individual in the same village received both RIG and vaccine at an exposure prevention clinic. In this incident, the dog died and was buried. A dog brain specimen was collected 50 days later and tested positive for rabies virus by nucleic acid testing.

DISCUSSION

The number of incidents in which multiple individuals were bitten by or exposed to a single dog was 5 times as high as the total number reported during 2020–2024. These findings highlight the severity of the current resurgence. Moreover, substandard PEP remains a prominent deficiency in current clinical intervention practices.

In this study, the high-incidence areas where multiple individuals were bitten by or exposed to a single dog were concentrated in southwestern Shandong Province, including Heze City, Jining City, and Liaocheng City, which was consistent with the

TABLE 3. Canine characteristics of multiple-victims bitten by a single dog incidents.

Exposure characteristics	Number of people	Proportion (%)
Dog breeds		
Chinese rural dogs	15	27.27
Chinese greyhounds	5	9.09
Pugs	4	7.27
Other dogs	10	18.18
Unknown breeds	21	38.18
Dog ending		
Killed by owners or villagers	34	61.82
Killed by police	11	20.00
Killed by security personnel	1	1.82
Escaped	7	12.73
Kept in captivity	1	1.82
Died naturally	1	1.82
Brain sample test results		
Domestic dog	15	39.47
Stray dog	22	57.89
Suspected to be an ownerless domestic dog	1	2.64
Brain sample test results in different exposures		
2	9	23.68
3	13	34.21
≥4	16	42.11

past 10-year incidents (7). The reported peak of events was during the summer and autumn periods, which correlated with increased outdoor human activity and heightened animal irritability. This seasonal characteristic is consistent with the national epidemic pattern of human rabies in China, with nationwide cases predominantly clustered between July and November (8). Notably, rabies reemerged in Jinan and Tai'an cities that had reported no cases for many years, suggesting a possible trend of renewed circulation of rabies virus and posing challenges to existing rabies prevention and control systems in Shandong Province.

The exposed individuals were predominantly farmers aged over 45 years (66.33%), which is highly consistent with long-term rabies surveillance data from nationwide studies (8). These high-risk groups usually have frequent contact with dogs during agricultural production activities. In addition, limited knowledge of rabies and delayed or inadequate medical care may increase the risk of rabies following exposure. No significant difference was observed in the rabies virus nucleic acid positivity rate among dogs that exposed two, three, four, or more individuals ($\chi^2=1.636$, $P=0.492$). Consequently, incidents involving multiple

individuals exposed to the same dog should be given equal attention and monitored daily.

Standardized management of infectious sources is key to rabies prevention and control. All exposure events in this study were canine-derived, among which stray dogs accounted for 61.82%. The rabies virus nucleic acid detection rate in brain tissues of the involved dogs was 82.61%, which was consistent with the results (80.2%) of Ye et al., indicating a highly active infection reservoir (9). Such a high viral positivity rate can be primarily attributed to insufficient canine vaccination coverage and attributed primarily to insufficient dog management in rural areas. As reported by Hu et al., the immunization coverage of rural domestic dogs was merely 2.8% (10). Low herd immunity among rural household dogs, combined with their frequent contact with stray dogs and wild animals, substantially elevates their susceptibility to rabies virus infection (5). Priority measures should include enforcing compulsory vaccination and registration of rural dogs and improving the systematic sheltering and harmless disposal of stray dogs.

In our study, approximately 80% of exposed

individuals received PEP within 2 hours of exposure, and 98% ultimately received standardized PEP. Two exposed individuals developed rabies and died because of irregular PEP measures. Nevertheless, some elderly individuals refused passive immune agents even after repeated counseling, primarily due to financial constraints and limited awareness of proper exposure management. Furthermore, integrating rabies prevention and treatment costs into the healthcare security system may help reduce the economic burden on the public and improve adherence to standardized PEP.

This study has several limitations. First, all analytical data were derived from a passive surveillance system, which may have led to underreporting of incidents. Second, serological testing was not performed to evaluate the immunogenicity of rabies vaccination among exposed individuals. Third, full-genome sequencing of the virus strains was ongoing.

In conclusion, we have described the epidemiological characteristics of incidents in which multiple individuals were bitten by or exposed to a single dog in Shandong Province during 2025 and evaluated the effectiveness of PEP measures. Our study may provide suggestions for rural dog management, PEP strategies, and public health education.

Conflicts of interest: No conflicts of interest.

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Reviews

Two mRNA Platforms for Canine Rabies Vaccines: Advances, Limitations, and Field Application Prospects

Xi Wang¹; Shaozong Guo¹; Youheng Jiang¹; Suhui Wang¹; Yuzhu Gong¹; Jige Du¹; Chunsheng Yin^{1,*}

ABSTRACT

Canine rabies control in rural China faces logistical barriers such as multi-dose schedules, cold-chain requirements, and the recapture of free-roaming dogs, which impede progress toward 70% vaccination coverage. Although inactivated vaccines remain the cornerstone of rabies control, mRNA platforms offer both manufacturing and immunological advantages. This review compares non-replicating mRNA (nr-mRNA) and self-amplifying mRNA (saRNA) platforms. It also examines oral and vectored vaccines as comparators for free-roaming dogs beyond the reach of injectable products. LVRNA001 and ABO1005 are nr-mRNA candidates that provide complete protection in canine challenge models using two-dose regimens; neutralizing antibody geometric mean titers (GMTs) exceed the World Health Organization (WHO) 0.5 IU/mL threshold through day 125, with the LVRNA001 50- μ g group reaching approximately 100 IU/mL versus approximately 16 IU/mL for the inactivated vaccine ($P < 0.05$). Both elicited Th1-biased cellular and cross-neutralizing antibody responses; lyophilized ABO1005 was stable at 2–8 °C for 12 months. For saRNA, single-dose protection has been shown only in mice and no canine data exist; dose extrapolation and excessive innate immune activation remain unresolved. Licensure requires compliance with China's 2026 draft guideline for animal mRNA products. Evidence derives from human candidates in beagles; prospects are most immediate for owned or accessible dogs; translation remains contingent on target-animal safety data, delivery innovation, regulatory approval, and operational feasibility.

Rabies is a fatal zoonotic disease caused by the rabies virus (RABV), with a case fatality rate approaching 100% (1–2). Globally, rabies causes approximately 59,000 human deaths annually, more than 99% of

which are attributable to dog-mediated transmission (3–5). In China, annual human rabies cases declined for 16 consecutive years following comprehensive control measures implemented in 2006, reaching a historic low of 122 in 2023 (6–7).

Maintaining canine vaccination coverage at or above 70% is recognized as the threshold required to interrupt dog-to-dog transmission (7–11). In China, rural canine vaccination coverage remains substantially below this threshold; a 2021 household survey in rural Guangxi reported that only 19.1% of dog owners had vaccinated their dogs (12). Although post-exposure prophylaxis (PEP) is life-saving for exposed individuals, it cannot interrupt the canine transmission cycle at the source (9). Three persistent barriers have impeded progress: poorly enumerated free-roaming and stray dog populations with unknown vaccination status (13); multi-dose schedules and cold-chain constraints, which compound the difficulty of recapturing free-roaming dogs (14–17); and limited financial resources and veterinary personnel shortages in endemic settings (18–19).

mRNA vaccine platforms have been the focus of intensive vaccine research (20–21). Several mRNA rabies vaccine candidates have been evaluated in animal models, including dogs (22–23). Two principal modalities have emerged: non-replicating mRNA (nr-mRNA) delivers a conventional transcript encoding the rabies glycoprotein, while self-amplifying mRNA (saRNA) encodes a viral replicase that amplifies the transcript intracellularly, permitting substantially lower input doses (20,24). This review compares the protective efficacy, manufacturing characteristics, immunogenicity, and safety profiles of these two modalities, particularly focusing on human vaccine candidates evaluated in canine models. This review also examines their implications for the development of veterinary mRNA rabies vaccines in China. Delivery, not immunogenicity, is the binding constraint for free-roaming dogs; oral and vectored platforms are therefore considered as comparators.

FEATURES OF mRNA PLATFORMS

Protective Efficacy

LVRNA001, an nr-mRNA candidate encoding the CTN-1 strain RABV glycoprotein (RABV-G), has been evaluated in a canine model. Two intramuscular doses of 10 or 50 µg (days 0 and 7) conferred 100% protection against lethal challenge with 50 × LD₅₀ of the BD06 street virus strain on day 35. Neutralizing antibody geometric mean titers (GMTs) exceeded the World Health Organization (WHO) protective threshold of 0.5 IU/mL by day 7 in all vaccinated groups. By day 125, the titer in the 50-µg group had risen to its peak, whereas the titer in the inactivated group declined to approximately 16 IU/mL ($P<0.05$) (25). In a canine post-exposure prophylaxis (PEP) model, lyophilized ABO1005 (15 µg, two-dose) achieved a virus neutralizing antibody GMT of 67.0 IU/mL at day 60, compared with 45.2 IU/mL for the five-dose inactivated vaccine regimen (26). Time-course GMT values are summarized in Table 1.

Manufacturing

Conventional inactivated rabies vaccine production requires the large-scale propagation of live viruses, typically under BSL-3 containment. Meanwhile, mRNA vaccines are manufactured through cell-free in vitro transcription, eliminating live-virus handling and reducing biosafety requirements (22,25–26). As this process is independent of the encoded antigen, the same facility can rapidly adapt to new targets (31). Lyophilized mRNA–lipid nanoparticles (LNP) formulations can remain stable in 2–8 °C storage (26), overcoming the ultra-cold requirements of earlier

liquid mRNA vaccines. Per-dose costs currently exceed those of inactivated vaccines owing to proprietary LNP components and limited manufacturing scale; however, domestic supply chain development is expected to reduce costs over time (32).

Regulatory Landscape for Veterinary mRNA Vaccines

Translation from laboratory proof-of-concept to licensed veterinary products requires compliance with species-specific regulatory frameworks. In 2026, China Institute of Veterinary Drug Control issued the Technical Requirements for Registration Application of Animal mRNA Products (Draft for Comments) (33), specifying comprehensive data requirements including pharmaceutical characterization, target-animal safety (single-dose, repeated-dose, and reproductive toxicity), challenge-protection studies with at least three product batches, stability testing, and biosafety assessment. saRNA products are classified as genetically engineered veterinary biologics requiring an additional biosafety approval certificate — a requirement not applied to nr-mRNA products. EMA and WOHAI have also established quality guidelines for veterinary mRNA vaccines and rabies biologics (34–35). Notably, all three frameworks require target-animal data, multi-batch consistency, and long-term stability. A complete dossier, including target-animal efficacy and safety data, is mandatory for acceptance.

Immunogenicity

In addition to challenge protection, mRNA rabies vaccines elicit immune responses that are not typically observed with inactivated vaccines. LVRNA001

TABLE 1. Comparative overview of three vaccine platforms for canine rabies control.

Dimension	Inactivated vaccine	nr-mRNA	saRNA
Schedule	2–3 doses + annual booster	2 doses (D0–7 or D0–21)	Single dose (mouse only)
Canine protection	Pre: 100%; PEP: 83–100% (25,26)	100% pre- & post-exposure (25,26,27)	No data
Immunogenicity	Humoral; limited cellular (25)	Th1-biased cellular + cross-NAb + plasma cells (25,27–29)	Mouse: humoral + cellular (30)
Canine evidence	Decades of field data	Beagle efficacy, safety, stability (25,26,27)	All key data absent
Canine GMT (IU/mL; doses in µg)	D7: approximately 4; D35: approximately 60 (peak); D125: approximately 16 IU/mL (25)	D7: 50 µg approximately 3, 10 µg approximately 1.5; D35: 50 µg approximately 78, 10 µg approximately 19; D125: 50 µg approximately 100* (peak), 10 µg approximately 75; ABO1005: 67.0 (PEP D60) (25,26)	No canine GMT data

Abbreviation: nr-mRNA=non-replicating mRNA; saRNA=self-amplifying mRNA; GMT=geometric mean titer; NAb=neutralizing antibody; PEP=post-exposure prophylaxis; Pre=pre-exposure; D=day.

* $P<0.05$ versus inactivated vaccine.

induced a pronounced Th1-biased cellular response in mice, with increased frequencies of interferon-gamma (IFN- γ)-secreting splenocytes and RABV-G-specific CD4⁺ T cells (25,27). In cynomolgus macaques, two-dose LVRNA001 generated high-titer neutralizing antibodies within 7 days of the first dose and sustained RABV-G-specific bone marrow plasma cell responses (25). CureVac unmodified mRNA-LNP vaccines induced cross-neutralizing antibodies against heterologous lyssavirus strains lasting for at least 1 year in non-human primates (28–29). However, these features were observed exclusively in laboratory beagles and inbred mouse strains. Whether Th1 bias or cross-neutralizing breadth confers protection against heterologous street-virus exposure in genetically diverse free-roaming dogs remains to be established.

Reactogenicity

Repeated-dose toxicity studies of LVRNA001 in cynomolgus macaques reported transient elevations in fibrinogen and C-reactive protein levels with a decreased albumin-to-globulin ratio, all of which resolved after a 4-week recovery period; injection-site reactions were mild and self-limiting (25). A reproductive toxicity study in rats revealed no adverse effects on fertility or embryofetal development (25). These findings align with the known innate immune activation profile of LNPs, in which dose-dependent inflammatory responses are common (36). The reactogenicity of nr-mRNA vaccines is formulation- and dose-dependent: CV7202, another nr-mRNA rabies candidate, was discontinued at the 5- μ g dose in its Phase I trial owing to unacceptable reactogenicity, whereas 1- and 2- μ g doses were well tolerated (37). When developing veterinary mRNA products, injection site reactogenicity must be assessed in target animal studies, as owner acceptability under field conditions may be affected (38–39).

TARGET-SPECIES EVIDENCE: DATA AND GAPS

nr-mRNA Platform

nr-mRNA has generated more extensive canine evidence than saRNA. LVRNA001 has been evaluated in mice, dogs, and cynomolgus macaques, with two-dose regimens providing complete protection in both pre- and post-exposure canine challenge models (25). Lyophilized ABO1005 has demonstrated 12-month storage stability at 2–8 °C (26). SYS6008 has

demonstrated cross-clade protection against China I–VII RABV strains in murine post-exposure models (40). Studies in non-human primates have confirmed durable cross-neutralizing antibody responses and bone marrow plasma cell induction (28–29), and Phase I data for CV7202 have established clinical proof of concept (37). Veterinary mRNA rabies vaccine candidates have recently entered early development; however, peer-reviewed data from these programs are not yet available.

saRNA Platform

Two saRNA candidates have provided proof-of-concept evidence. JJ-saRNA-RABV001 demonstrated single-dose protection in murine models: a 0.1- μ g dose achieved 100% survival when administered 14 days before challenge (30). RBI-4000 has completed a Phase I human trial showing neutralizing antibody durability that matched or exceeded licensed inactivated rabies vaccines (41). Broader advances include protective efficacy against pseudorabies virus (42) and immunogenicity of a Rift Valley fever vaccine in mice (43). For canine rabies, however, no peer-reviewed study has reported neutralizing antibody GMTs, challenge protection, or repeated-dose safety in dogs for any saRNA construct. Dose extrapolation from rodents (approximately 20 g) to domestic dogs (5–40 kg) is unreliable because of differences in body mass, lymphatic drainage, and innate immune signaling (44–45). Canine saRNA studies, if undertaken, should prioritize species-specific dose determination and formal assessment of excessive innate immune activation risk in outbred populations, which requires specifically designed canine studies rather than extrapolation from existing murine data. The cross-species comparison is provided in Table 2.

Regulatory and Translational Barriers for saRNA

Beyond murine proof-of-concept, however, registration and field deployment in the short- to medium-term remain blocked by the absence of core target-animal data and by the additional biosafety approval required for genetically engineered veterinary biologics under China's current framework.

COMPARATOR APPROACHES AND FIELD DELIVERY

Oral administration offers an alternative route for

TABLE 2. Cross-species comparison of evidence for mRNA rabies vaccines.

Species	nr-mRNA key findings	saRNA key findings	Inactivated key findings	Data gaps	Peak neutralizing GMT
Mouse	2-dose: 100%; GMT > inact. (25,27)	0.1 µg single: 100% (D14) (30)	2–3 doses: 100%	saRNA: mouse-only, not extrapolable	nr-mRNA GMT > inact.; saRNA: mouse data only
Dog	LVRNA001: 100% pre-/post-exposure, ≥125 d (25); ABO1005: 12-mo 2–8°C (26)	GMT: N/A; Protection: N/A; Safety: N/A	Pre: 100% (25); PEP: ≥83% (26)	saRNA: all canine data missing	50 µg: approximately 100 IU/mL (D125)*; ABO1005: 67.0 (PEP D60); inact.: approximately 60 (D35) → approximately 16 (D125); saRNA: no data (25,26)
NHP	Cross-NAb ≥1 yr + plasma cells (28,29)	No data	Seroconversion	saRNA: no NHP data	nr-mRNA cross-NAb ≥1 yr (28,29); saRNA: no data
Human (Phase I)	CV7202: D43 100% seroconv.; 5 µg discontinued (37)	RBI-4000: durability ≥ inact. (41)	Seroconversion	–	CV7202: 100% D43 (37); RBI-4000 ≥ inact. (41)

Note: “–” means data not applicable.

Abbreviation: nr-mRNA=non-replicating mRNA; saRNA=self-amplifying mRNA; GMT=geometric mean titer; NAb=neutralizing antibody; PEP=post-exposure prophylaxis; NHP=non-human primate; inact.=inactivated vaccine; seroconv.=seroconversion; Pre=pre-exposure; D=day; mo=month; yr=year; N/A=not available.

* $P < 0.05$ versus inactivated vaccine.

dogs that cannot be captured. In wildlife reservoirs, baits containing recombinant vaccinia virus expressing RABV-G contributed to rabies elimination in Belgium, France, and Luxembourg (46). Both WHO and WOA position oral vaccination as complementary to parenteral vaccination for free-roaming populations that campaigns cannot reach (35,47–48). In a Chinese non-parenteral trial, a recombinant canine adenovirus type 2 vaccine expressing RABV-G, delivered in baits or as an intranasal solution, seroconverted 87.5% (119/136) of dogs; among seroconverted animals, 90.8% maintained virus-neutralizing antibodies above 0.5 IU/mL for 24 months, and all 10 dogs challenged with CVS-24 2 years after vaccination survived (49). Attenuated live rabies virus strains are an alternative oral candidate class, but require target-animal safety data and assessment of residual pathogenicity and non-target species exposure (47–48). These platforms therefore address delivery rather than immunogenicity, complementing injectable mRNA platforms rather than replacing them.

Injectable mRNA candidates, by contrast, require capture and, for nr-mRNA, two doses, and are therefore best suited to owned or accessible dogs presented at clinics or during centralized campaigns, when a second visit is feasible. Even a single-dose saRNA product would require parenteral administration; neither platform eliminates the need to recapture free-roaming dogs.

Vaccination alone is unlikely to eliminate rabies from free-roaming populations. The WOA Terrestrial Animal Health Code states that mass culling

of dogs is ineffective and may be counterproductive, and that dog population management contributes to rabies control by reducing population turnover and thereby sustaining the herd immunity established by vaccination (13,50). Under Article 30 of China's Animal Epidemic Prevention Law, owners are responsible for periodic vaccination and registration of their dogs, while local governments organize the control of free-roaming dogs and cats (51). mRNA vaccines are therefore best positioned as adjuncts to dog population management rather than as substitutes for it.

LIMITATIONS

This study has some limitations. First, the evidence base is both platform- and species-limited; no canine data are available for saRNA vaccines, and all available canine data are derived from controlled laboratory studies in beagles rather than from free-roaming dogs, which constitute the primary rabies reservoir in rural China. No veterinary mRNA rabies vaccine has been licensed, and no field delivery or effectiveness studies of mRNA rabies vaccines in dogs have been reported. Second, the immunogenicity follow-up for LVRNA001 did not extend beyond 125 days, and the 12-month stability of lyophilized ABO1005 was demonstrated only under constant-temperature conditions. Thus, long-term durability and performance under variable rural cold-chain logistics remain unverified. Third, no comparative cost-effectiveness or budget impact analyses of mRNA

versus inactivated canine rabies vaccines under Chinese field conditions are available. Finally, selection bias in literature inclusion cannot be excluded in this narrative review, and the 2026 draft guideline for veterinary mRNA products awaits formal promulgation.

CONCLUSIONS

In the short term, the nr-mRNA platform, which has accumulated canine efficacy data comparable to inactivated vaccines, can be developed for owned or accessible dogs, contingent on target-animal safety data, delivery feasibility, and regulatory approval. Remaining gaps include safety in juvenile, pregnant, and immunocompromised dogs, stability under variable rural cold-chain conditions, field trials clarifying vaccinator training and owner acceptability, and domestic LNP excipient development for cost compatibility with public immunization programs. In the medium term, bridging murine proof-of-concept to veterinary drug evaluation standards for saRNA requires systematic canine studies — dose escalation, repeated-dose safety, immunogenicity beyond one year, and biodistribution — together with empirical validation of cross-species dose extrapolation and formal assessment of excessive innate immune activation in outbred dogs. In the long term, products with superior thermostability, simplified dosing, and competitive cost could replace multi-dose inactivated vaccines in China's spring and autumn centralized campaigns. Such implementation, in alignment with the Zero by 30 strategic plan, will require coordinated investment in domestic mRNA supply chains and rigorous health-economic comparison. Therefore, contribution to the 2030 target depends on the availability of target animal safety data, delivery innovation for free-roaming dogs, regulatory approval under the 2026 draft framework, and operational feasibility in resource-limited rural settings.

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Outbreak Reports

Investigation and Response to a Single Cat Injuring Multiple People — Shandong Province, China, 2026

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Summary

What is already known about this topic?

Rabies is an almost universally fatal zoonosis; dogs remain China's main human exposure source. Cats are generally not persistent rabies reservoirs; most feline infections result from spillover from rabid dogs or wildlife. However, feline rabies has been documented worldwide.

What is added by this report?

This report describes a laboratory-confirmed incident in which one stray cat successively attacked two people in Shandong Province, China, in 2026. Rabies virus nucleic acid was detected in cat brain and saliva specimens; whole-genome sequencing showed extremely high homology with two canine-derived strains from Henan.

What are the implications for public health practice?

Large-scale canine vaccination and strengthened dog source management, including registration, confinement or tethering, and collection and sheltering of strays, should remain core interventions for blocking rabies spillover at its source. Cats should also be formally incorporated into rabies prevention and control systems.

tabby cat. One sustained a category III bite on the right foot; the other a category II scratch on the left foot with no visible wound. RABV nucleic acid was detected in the cat brain sample (cycle threshold [Ct] 16.8) and saliva sample (Ct 22.1). Both exposed individuals received rabies PEP and completed the full vaccination schedule; to date, neither has reported symptoms or adverse reactions. The complete rabies virus genome sequence, designated JN001542.1/M2026001, belonged to China lineage I. After the incident, local investigations identified 50 other people injured by animals during the previous 3 months, all of whom received standard PEP. Canine vaccination coverage in the involved township was 55.24% (1,512/2,737).

Conclusion: This incident confirms that cats can acquire RABV through spillover from dogs and transmit it to humans. Cats should not be overlooked as a potential rabies virus transmission source. Stray-cats traceability management should be strengthened, and rabies PEP clinics should improve awareness and emergency response capacity for cat-inflicted injuries.

On April 14, 2026, a district center for disease control and prevention (CDC) in Jining City, Shandong Province, received a report from a local township hospital describing an incident in which a single cat injured multiple people. After the cat was euthanized that day, Jining CDC staff performed laboratory testing on cat brain and saliva specimens, both of which tested positive for rabies virus (RABV) nucleic acid. To clarify the exposure characteristics, evaluate the effectiveness of rabies post-exposure prophylaxis (PEP), and trace the viral origin, provincial, prefectural, and district CDCs conducted a joint investigation.

ABSTRACT

Introduction: We analyzed the epidemiological characteristics, investigation, and response measures for an incident in which one cat injured multiple people in Shandong Province, China, in 2026, to improve rabies prevention and control.

Methods: Face-to-face epidemiological investigations collected information on exposure, rabies post-exposure prophylaxis (PEP), and characteristics of attacking animals. Rabies virus (RABV) nucleic acid was detected using real-time quantitative polymerase chain reaction. Saliva was sequenced for whole-genome analysis, and phylogenetic analysis was performed.

Results: Two women were attacked by a stray gray

At approximately 10:00 AM on April 14, 2026, a stray cat actively and consecutively attacked two people

INVESTIGATION AND RESULTS

beside a village convenience store. The first exposed individual was a woman who lived in the village and worked as a courier. She sustained a category III bite on her right foot. The second exposed individual was a woman from another county who worked as a delivery person. She sustained a category II scratch on her left foot, with no visible wound. CDC staff also screened for additional exposed people and animals associated with the incident, but none were identified.

The offending animal was a stray gray tabby cat weighing approximately 4 kg. Its age and vaccination history were unknown. The cat showed aggressive behavior and actively attacked people. It was humanely euthanized after the attack. After sample collection, village committee staff incinerated and deeply buried the carcass.

The first exposed individual drove herself to the PEP clinic for treatment on the day she was injured. In accordance with the 2023 guidelines issued by the National Health Commission of the People's Republic of China, clinic staff irrigated and disinfected her wounds and administered human rabies vaccine, tetanus vaccine, and rabies immunoglobulin. The second exposed individual, who had a category II exposure, visited a local PEP clinic for rabies vaccination on the day after the attack. Both exposed individuals completed the full vaccination schedule, and to date, neither has reported symptoms or adverse reactions.

On April 14, 2026, the prefecture CDC tested the collected cat brain and saliva specimens for viral nucleic acid using real-time quantitative polymerase chain reaction. The results were positive for RABV, with a cycle threshold (Ct) value of 16.8 for the cat brain specimen and 22.1 for the cat saliva specimen. The complete rabies virus genome sequence was obtained from the cat saliva sample using a Rabies virus Whole-Genome Capture Kit (Bioeye Corp., Hangzhou, China) and designated JN001542.1/M2026001. Whole-genome sequencing was performed on the Illumina NextSeq 2000 platform, and the sequence was assembled using CLC Genomics Workbench software (version 22.0; QIAGEN Corp., Hilden, Germany). Phylogenetic analysis of this sequence, together with 60 reference rabies virus sequences from GenBank (Figure 1), showed that the strain belonged to China lineage I, the predominant epidemic lineage of rabies virus in China. The sequence also showed extremely high homology with two canine-derived strains, PZ050825 and PZ050826, collected from Yongcheng City, Henan Province, and

submitted in 2026. These findings indicate an extremely close genetic relationship among the three strains, suggesting that they may have originated from the same transmission chain or from highly related variant branches.

PUBLIC HEALTH RESPONSE

CDC staff, together with personnel from the County Bureau of Animal Husbandry, the village committee, and the hospital, identified 50 additional people injured by dogs or cats during the previous 3 months; all had received standard PEP. To date, none has reported symptoms or adverse reactions. The local town government also conducted a baseline survey, which identified 2,250 dog-owning households with 2,737 dogs, of which 1,512 had been vaccinated, corresponding to canine vaccination coverage of 55.24%. The jurisdiction strengthened oversight of domestic animals and implemented centralized management of stray dogs and cats within a 5-km radius of the incident site. More than 10,000 rabies prevention leaflets were distributed to dog and cat owners, including more than 1,000 copies in the affected village.

DISCUSSION

In this incident, CDC staff implemented response measures based on the protocols for incidents in which a single dog injures multiple people. All exposed individuals received standardized PEP. After 3 months of follow-up, neither exposed individual reported symptoms or adverse reactions, indicating that standardized PEP after animal injury can effectively reduce the risk of rabies transmission.

Cats are generally not persistent reservoir hosts for rabies, and most infections result from viral spillover from rabid dogs or wildlife (1–2). Feline rabies has been documented in nearly all regions worldwide (1). In the United States, an average of 279 rabid cats were confirmed each year (3). In high-burden rabies regions, including Africa and Asia, the annual incidence of feline rabies exceeded 0.15% (2). Data from rabies surveillance sites in China from 2006 to 2022 showed that cats accounted for 8.39% of rabies-positive animals (4).

Cats have frequent contact with humans and can readily cause animal-related injuries. The proportion of rabies-exposed individuals injured by cats has increased

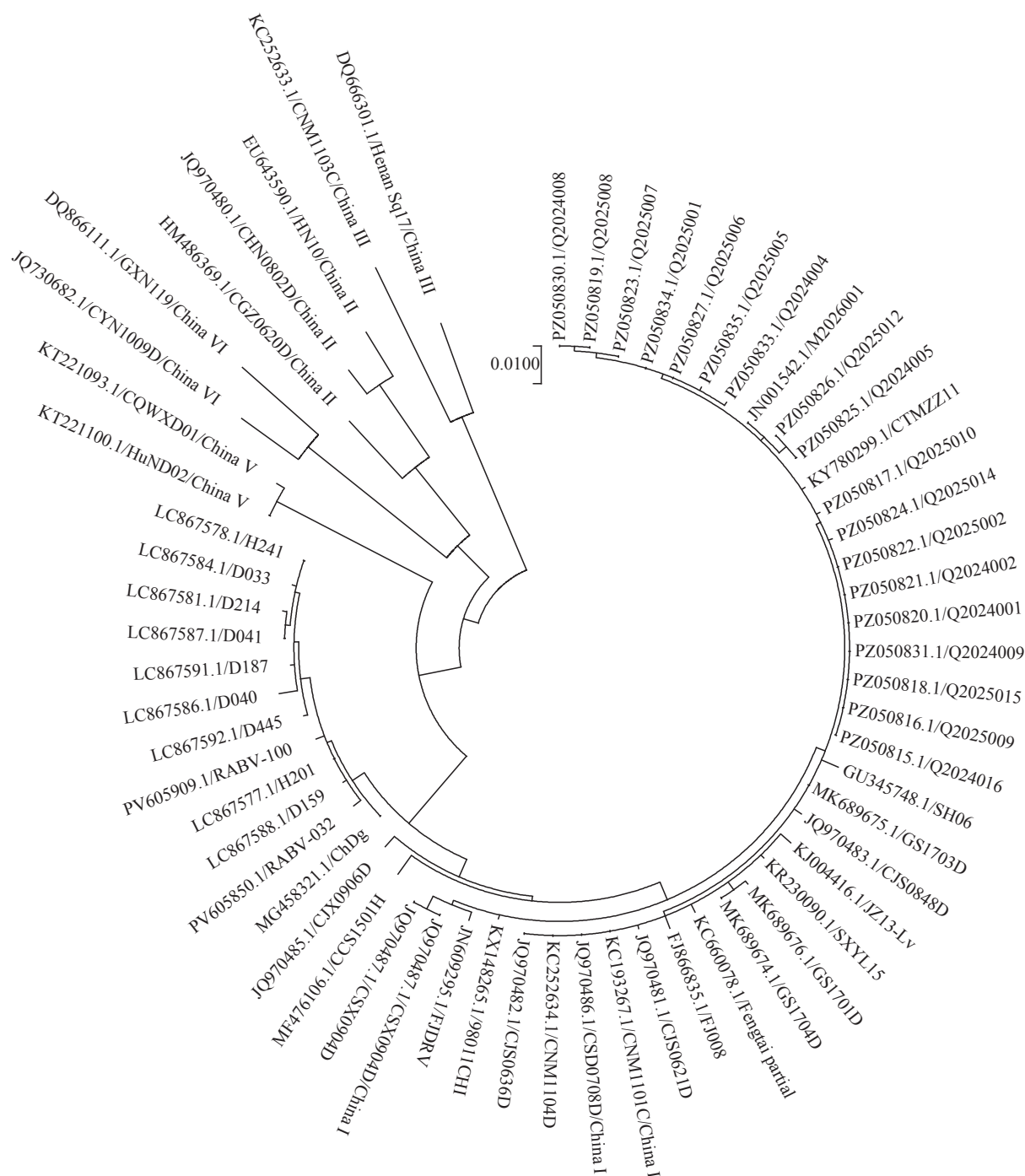


FIGURE 1. Phylogenetic tree of rabies virus N gene sequences.

Note: Reference sequences are named according to GenBank accession number/strain name/genotype. The highlighted strain is the isolate from this study.

Abbreviation: N=nucleoprotein.

in recent years. From 2019 to 2023, the proportion of rabies exposures caused by dogs in Shandong Province decreased from 65.36% to 51.67%, whereas the proportion caused by cats increased from 30.61% to 44.95% (5). Without timely and appropriate post-exposure management after cat-inflicted injuries, the

risk of rabies transmission remains. Human rabies cases caused by cat-inflicted injuries have been documented in multiple countries, including Argentina (6), Colombia (7), the United States (8), and Brazil (2). Approximately 5% of rabies cases in China have been attributed to cat-inflicted injuries (9). The role of cats

This incident represents a rare laboratory-confirmed case in China in which a cat attacked multiple people and tested positive for RABV nucleic acid. Although the incident was atypical, it directly confirmed the threat posed by cats as a source of rabies infection. Sequencing further showed that the viral sequence shared high homology with canine-derived strains from Henan Province, suggesting that the cat acquired the infection through viral spillover from dogs. This finding indicates that, although cats have become increasingly prominent in rabies transmission, canine vaccination and canine population management remain the core interventions for controlling infection sources and eliminating human rabies (10).

The continuously expanding cat population, coupled with low vaccination coverage, leaves cats highly susceptible to rabies (9). Cats also roam widely, increasing their likelihood of acquiring rabies virus infections through spillover from dogs or wildlife (1). In addition, vaccinating and centrally managing stray cats remain challenging. Difficulty controlling the stray-cat population (14) further increases the risk of cat-associated rabies transmission to humans. Surveillance of reservoir animals in China showed that rabies vaccination coverage among cats was substantially lower than that among dogs (15), suggesting that cats may become a reservoir that sustains rabies virus circulation and emergence. Current interventions focus primarily on dog-mediated rabies, whereas potential risks from other animals, including cats, are often underestimated (10). At present, China has not issued a specific management policy for rabies vaccination in cats (16).

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Perspectives

Signal-Oriented Framework for Early Identification of Imported Respiratory Infectious Disease Risk

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ABSTRACT

Increasing international travel and population mobility have made surveillance of imported infectious diseases more complex. However, current approaches still rely largely on confirmed epidemiological evidence and retrospective analyses of importation events. Their limited capacity to integrate heterogeneous information constrains early identification of emerging importation risks. Drawing on signal analysis theory, we developed a conceptual and operational framework for early identification of imported respiratory infectious disease risks involving human-to-human transmission. The framework conceptualizes imported disease risk as a dynamic process in which underlying risk factors generate observable surveillance indicators and event-based information that are progressively transformed into candidate risk signals, risk signals, and warning signals. We established an operational workflow comprising signal collection, integration, assessment, and escalation to organize heterogeneous evidence across the importation pathway. The framework incorporates four complementary domains: pathogen characteristics, overseas epidemic situation, cross-border importation risk, and post-entry transmission risk. These domains provide structured inputs for signal identification and assessment. Risk signals are evaluated according to signal characteristics, epidemiological stage, and consequence severity; they may be escalated to warning signals when predefined evidence and priority criteria are met. This framework provides an operational approach for integrating weak and heterogeneous information before importation events are fully confirmed, supporting earlier risk recognition and public health decision-making.

International travel, trade, and population mobility have increased the risk of cross-border infectious disease transmission. Concurrent outbreaks of

emerging and re-emerging pathogens have also complicated surveillance of imported infectious diseases. Early identification of importation risks is therefore essential to global public health preparedness. Current approaches rely mainly on confirmed case reports and retrospective analyses of importation events, making risk assessment largely reactive. Conventional systems also tend to analyze individual data streams separately, with limited capacity to integrate heterogeneous information such as international epidemic intelligence, population mobility, border surveillance, and public information, reducing their ability to detect early signals before importation is confirmed. Signal analysis offers an intelligence-driven approach for identifying weak, unverified information under uncertainty; by integrating multisource information and continuously evaluating signal evolution, it supports earlier recognition of potential public health threats and dynamic risk assessment, making it well suited to imported infectious disease surveillance. Building on signal analysis theory, this study proposes a conceptual framework for identifying risk signals of imported respiratory infectious diseases that integrates multisource information across the full importation pathway, defines the key components of risk signal generation and assessment, and describes an operational workflow supporting early warning and public health decision-making.

CONCEPTUALIZATION OF IMPORTED RESPIRATORY INFECTIOUS DISEASE RISK SIGNALS

Signal analysis has evolved from detecting abnormal surveillance indicators into an intelligence-driven approach for recognizing emerging public health threats under uncertainty (1–2). For imported infectious diseases, it supports identification of weak and incomplete evidence before importation is confirmed, enabling earlier situational awareness and

more proactive responses (3). Imported infectious disease risk does not arise from a single event but develops progressively through interactions among pathogen characteristics, international transmission, human mobility, and public health interventions; it should therefore be conceptualized as a dynamic rather than static process. Within this process, underlying epidemiological conditions generate observable surveillance indicators and event-based information (4). As evidence accumulates and converges across sources, these observations may evolve into risk signals indicating a preliminary increase in importation risk (5). After further verification and expert assessment, sufficiently credible risk signals become warning signals providing the basis for public health intervention (6). These relationships form the theoretical foundation of the proposed framework (Supplementary Table S1, available at <https://weekly.chinacdc.cn/>).

RISK FORMATION PATHWAY AND INFORMATION FOUNDATIONS FOR SIGNAL IDENTIFICATION

Imported infectious disease risk develops progressively along the importation pathway (7). We conceptualized this pathway as five sequential stages: overseas outbreak, cross-border movement, border screening, post-entry management, and local transmission. Each stage is a distinct epidemiological context with specific risk drivers, intervention opportunities, and sources of observable information. Risk may be attenuated or amplified along the pathway, depending on pathogen characteristics, international mobility, detection and control capacity, and opportunities for post-entry transmission (8–11). Information generated at different stages may initially constitute candidate risk signals, which can then be integrated across time, space, epidemiological context, and information sources to identify emerging risk patterns. Supplementary Table S2 (available at <https://weekly.chinacdc.cn/>) summarizes the major information sources, observable information, and risk drivers across the five stages, which together provide the information foundation for signal integration, assessment, and escalation.

OPERATIONAL FRAMEWORK AND APPLICATION

Epidemiological risk alone cannot directly support

public health action. To become actionable, heterogeneous observations must be collected, interpreted, integrated, and assessed by their temporal, spatial, epidemiological, and contextual characteristics. Building on the conceptual distinctions in Section 1 and the pathway in Section 2, the proposed framework provides an operational process for transforming observable risk information into candidate risk signals, risk signals, and ultimately warning signals supporting public health decision-making (12).

Operational Workflow

The framework operationalizes risk identification for imported respiratory infectious diseases through four linked modules: risk signal collection, integration, assessment, and escalation (Figure 1). These modules successively transform heterogeneous information into actionable public health intelligence. Information from routine surveillance, event-based intelligence, and frontline observations is standardized into candidate risk signals, integrated across time, space, epidemiological characteristics, and information sources to identify risk signals, and assessed on signal characteristics, pathway position, and potential consequences; those meeting predefined evidence and priority criteria are escalated to warning signals supporting corresponding public health action.

Risk signal collection. The first module, risk signal collection, systematically identifies early information on imported infectious disease risks. The framework integrates three complementary sources: indicator-based surveillance, event-based surveillance, and frontline observations. Indicator-based surveillance provides structured epidemiological information on disease incidence, international mobility, border health screening, and laboratory testing. Event-based surveillance draws on epidemic intelligence platforms, official notifications, media reports, and reports of unusual health events. Frontline observations from border health officers, healthcare professionals, and public health practitioners provide contextual information that may be unavailable through routine surveillance. Information from these sources is then standardized and preliminarily classified into candidate risk signals for integration and assessment.

Risk signal integration. Risk signal integration combines heterogeneous observations to identify coherent patterns of emerging imported infectious disease risk. Three forms of consistency are evaluated: temporal (persistence or an increasing abnormality over time), spatial (geographic concentration across source

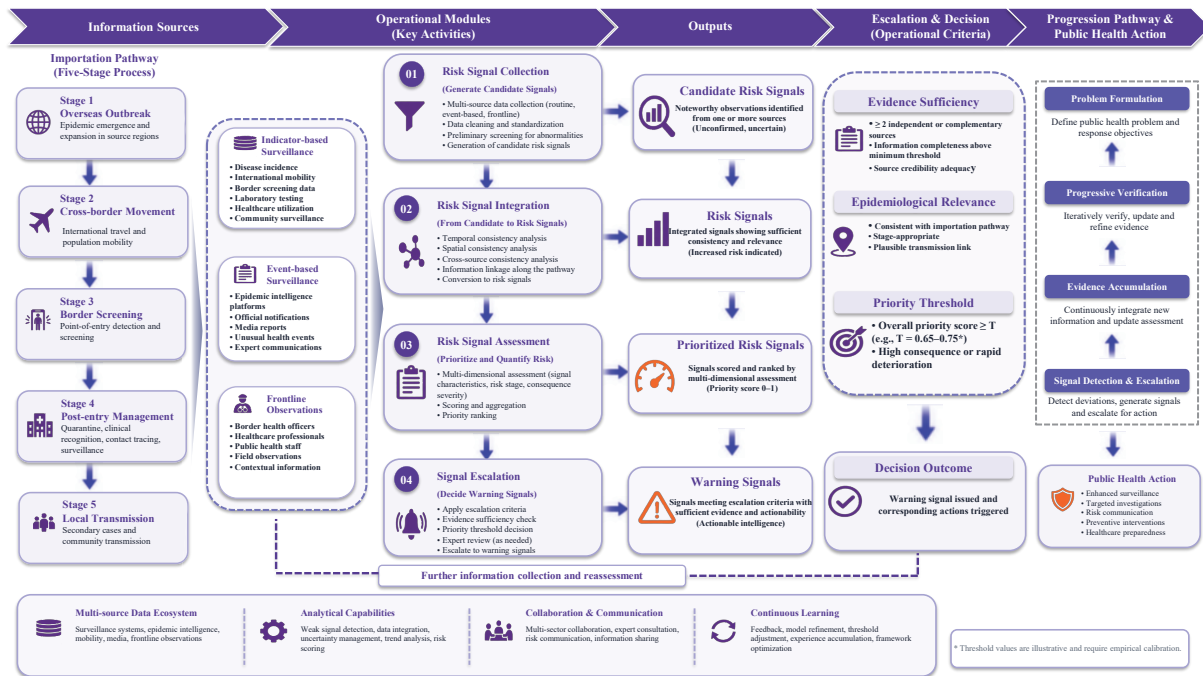


FIGURE 1. Workflow for imported infectious disease risk signal identification and assessment.

regions, travel routes, ports of entry, or destination areas), and cross-source (concordant findings across independent surveillance systems or information sources). Signals consistent across these dimensions are more likely to represent genuine epidemiological changes than isolated observations. Information is standardized, organized along the imported disease risk formation pathway, and linked across epidemiological contexts. Rather than simply aggregating data, integration establishes relationships among observations and evaluates whether their convergence provides sufficient evidence of a changing risk pattern. Candidate risk signals showing sufficient relevance and consistency are classified as risk signals, whereas isolated or weakly supported observations remain candidate risk signals and may be monitored as evidence accumulates.

Risk signal assessment and prioritization. Each integrated risk signal is assessed across three dimensions (Table 1):

Signal characteristics (S): strength, temporal persistence, spatial coherence, credibility, and uncertainty;

Epidemiological stage (T): source epidemic stage, importation stage, intervention position, and evidence of progression toward downstream transmission;

Consequence severity (C): potential importation scale, public health impact, and intervention feasibility.

Each component is standardized to 0–1, with higher

values indicating greater priority. Category-based, baseline-based, or percentile-based normalization may be used according to the indicator and context. Uncertainty and protective factors are reverse-coded where appropriate.

For each dimension, the component scores are averaged:

$$S = \frac{1}{n_S} \sum_{i=1}^{n_S} s_i, T = \frac{1}{n_T} \sum_{i=1}^{n_T} t_i, C = \frac{1}{n_C} \sum_{i=1}^{n_C} c_i \quad (1)$$

The overall priority score (P) is:

$$P = w_S S + w_T T + w_C C \quad (2)$$

For illustrative implementation, equal weights are assigned:

$$P = \frac{S + T + C}{3} \quad (3)$$

This formulation provides a transparent prioritization structure while allowing weights and normalization rules to be recalibrated for different pathogens, settings, and datasets.

Signal escalation and warning criteria. Assessment alone does not determine whether a signal should trigger public health action; the framework therefore applies an explicit escalation rule based on evidence sufficiency, epidemiological relevance, and priority level.

A risk signal is eligible for classification as a warning signal when it meets all of the following:

1) support from at least two independent or

TABLE 1. Operational assessment matrix for prioritizing imported respiratory infectious disease risk signals.

Dimension	Assessment component	Operationalization	Scoring
Signal characteristics (S)	Signal strength	Magnitude of anomaly, frequency, or spatial clustering relative to the expected baseline	0–1
	Temporal characteristics	Persistence, increasing trend, and rate of change	0–1
	Spatial characteristics	Geographic concentration or relevance to importation routes	0–1
	Credibility	Source authority and consistency across independent or complementary sources	0–1
	Uncertainty	Completeness and reliability of available information; higher uncertainty receives a lower score	0–1
Epidemiological stage (T)	Source epidemic stage	Stage and trajectory of epidemic activity in the source region	0–1
	Importation stage	Pre-entry, entry, or post-entry status	0–1
	Intervention position	Position within the prevention and control pathway and remaining intervention opportunities	0–1
	Stage transition	Evidence of progression toward downstream transmission	0–1
Consequence severity (C)	Potential importation scale	Expected scale of introduction or number of potentially exposed individuals	0–1
	Potential public health impact	Potential impact on population health, healthcare systems, and public health resources	0–1
	Intervention feasibility	Availability and feasibility of effective control measures; lower feasibility corresponds to greater consequence severity	0–1

Note: All components are standardized to 0–1. Protective factors and uncertainty are reverse-coded where necessary so that higher scores consistently indicate greater priority. For illustrative implementation, equal weights are assigned to the three dimensions.

complementary information sources;

2) temporal persistence, a meaningful increasing trend, or clear relevance to the human-mediated importation pathway; and

3) a priority score that reaches the predefined escalation threshold.

Escalation is initially defined as follows:

Warning Signal =

$$\begin{cases} 1, & N_{\text{sources}} \geq 2, E_{\text{temporal/pathway}} = 1, P \geq 0.75 \\ 0, & \text{otherwise} \end{cases} \quad (4)$$

The threshold of 0.75 is illustrative rather than a validated universal cutoff. In practice, the threshold and weights should be calibrated using historical events, expert elicitation, and prospective surveillance data. This rule operationally distinguishes risk signals, which identify potentially meaningful changes in imported disease risk, from warning signals, which have accumulated sufficient evidence and priority to support public health action.

Hierarchical Indicator System for Imported Respiratory Infectious Disease Risks

To operationalize the framework, we developed a hierarchical indicator system for imported respiratory infectious diseases comprising four domains (Figure 2):

(A) pathogen and disease characteristics, (B) overseas epidemic characteristics and export potential, (C) cross-border importation channels and exposure level, and (D) post-entry local transmission and dissemination risk. They capture pathogen hazards, overseas epidemic pressure and export potential, cross-border introduction and exposure, and post-entry transmission and response capacity. The domains include 18 second-level categories and operational indicators spanning epidemiological intelligence, international mobility, border surveillance, healthcare response, and community transmission. By organizing indicators around the evolution of imported disease risk rather than data sources or administrative sectors, the system provides a common structure for integrating heterogeneous information and identifying and assessing risk signals. Indicators can be adapted to the pathogen, epidemiological context, and surveillance objectives.

Mapping the indicator system to signal assessment.

The five-stage risk formation pathway describes where and how risk evolves, whereas the four indicator domains specify the observable information characterizing it; the two structures are therefore complementary rather than one-to-one. Indicators from each domain may inform one or more assessment dimensions, including signal characteristics (S),

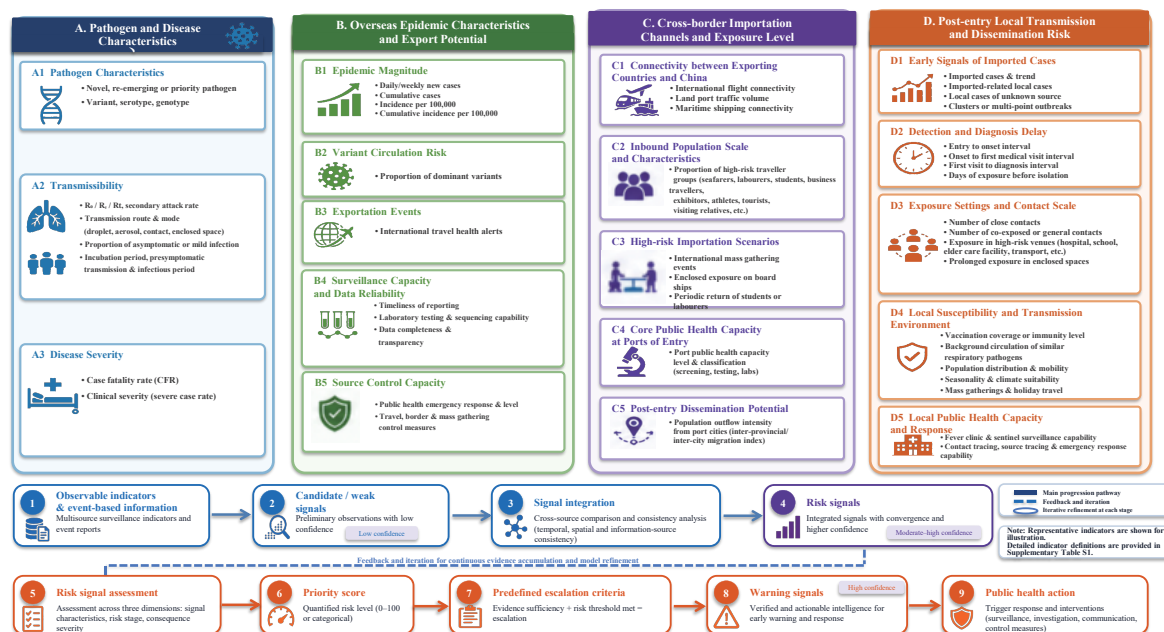


FIGURE 2. Application of the proposed framework: hierarchical indicator system for imported respiratory infectious disease risk identification.

epidemiological stage (T), and consequence severity (C), depending on the observation context (Supplementary Table S3, available at <https://weekly.chinacdc.cn/>). For example, epidemic magnitude may inform signal strength and source epidemic stage, whereas mobility, exposure, and diagnosis delay may inform importation risk, transmission progression, and potential consequences. Thus, indicators are not risk signals themselves; abnormal or convergent patterns identified from them constitute candidate risk signals, which are then integrated and assessed. This mapping links the indicator system to the S-T-C assessment matrix by specifying how observable evidence becomes structured signal assessment.

Illustrative Case Application

To illustrate the framework's practical application, we retrospectively reconstructed imported COVID-19 risk in Beijing using published epidemiological evidence from 2020–2021 (13). The case is illustrative and not a retrospective validation of predictive performance. Early in the epidemic, increasing overseas transmission and international travel generated importation pressure. Surveillance identified imported cases through entry screening, centralized isolation, and post-entry testing. Although most imported cases were detected within 14 days after entry, seven were detected later, including one asymptomatic case identified 32 days after entry and associated with 41

secondary cases. Delayed detection, repeated negative test results, and subsequent local transmission provided convergent evidence of residual post-entry risk, demonstrating the transition from isolated observations to an integrated risk signal. Within the framework, the signal would be assessed across S, T, and C and prioritized using $P=(S+T+C)/3$. When multisource evidence, temporal persistence or clear pathway relevance, and the predefined priority threshold are simultaneously met, the signal can be escalated to a warning signal supporting enhanced surveillance and targeted public health action. The workflow is summarized in Supplementary Table S4 (available at <https://weekly.chinacdc.cn/>).

Practical Considerations

The framework is intended as a conceptual and methodological guide, not a fixed operational protocol. Indicator selection, analytical methods, and assessment thresholds should be adapted to pathogen characteristics, surveillance capacity, and local context. Implementation requires multisource data sharing, standardized signal-management procedures, and interdisciplinary collaboration among surveillance agencies, border health authorities, healthcare institutions, and public health decision-makers. It complements, rather than replaces, existing indicator-based surveillance, providing an intelligence-driven approach for integrating heterogeneous information

and supporting earlier identification of imported infectious disease risks. Although this study applies the framework to imported respiratory infectious diseases, the same approach can be adapted to others by modifying pathogen-specific indicators and data sources. Future work should pursue quantitative implementation by integrating artificial intelligence, automated epidemic intelligence systems, and probabilistic risk assessment models to support real-time signal detection and adaptive early warning.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Conceptual components and operational roles in the imported respiratory infectious disease risk signal framework.

Component	Definition	Operational role in risk identification	Position in the signal identification process
Risk factors	Underlying epidemiological, pathogen-related, population, environmental, and health-system conditions that influence the likelihood or potential consequences of imported respiratory infectious diseases.	Define the underlying conditions that may drive or amplify importation risk.	Upstream drivers of risk
Surveillance indicators	Quantifiable variables routinely collected through surveillance systems that reflect changes in pathogen characteristics, overseas epidemic activity, cross-border exposure, and post-entry transmission conditions.	Provide measurable and continuously monitored evidence of changes in imported disease risk.	Observable information for signal generation
Event-based information	Unstructured or semi-structured information from official reports, media reports, expert communications, and other non-routine sources that may indicate emerging or rapidly evolving public health events.	Capture weak, unexpected, or rapidly evolving information that may not yet be reflected in routine surveillance indicators.	Complementary information for signal generation and verification
Candidate risk signals	Abnormal, changing, or otherwise notable observations identified from one or more surveillance indicators or event-based information sources that may indicate emerging imported disease risk.	Trigger further collection, cross-source comparison, and preliminary assessment.	Initial signal-detection stage
Risk signals	Candidate risk signals that show sufficient relevance, consistency, or convergence across time, space, epidemiological characteristics, and information sources to indicate a potentially increasing imported disease risk.	Identify risks that warrant enhanced surveillance, verification, or further risk assessment.	Integrated and assessable signal stage
Warning signals	Risk signals that meet predefined evidence and priority criteria and provide sufficient confidence and actionability for public health response or early intervention.	Trigger predefined public health actions, including enhanced surveillance, targeted investigation, risk communication, and intervention.	Decision and action stage

SUPPLEMENTARY TABLE S2. Information sources and risk factors across the imported respiratory infectious disease risk formation pathway.

Risk formation stage	Primary information sources	Observable information	Major risk drivers
Overseas outbreak	World Health Organization Disease Outbreak News, official surveillance reports, event-based surveillance, and media intelligence	Epidemic intensity, epidemic growth, geographic expansion, reported clusters, and pathogen characteristics	Pathogen characteristics, transmissibility, disease severity, and overseas epidemic intensity
Cross-border movement	Flight networks, passenger mobility data, and border traffic records	Travel volume, connectivity, travel patterns, traveler composition, and exposure opportunities	International mobility, travel volume, and exposure intensity
Border screening	Port surveillance, symptom screening, and laboratory testing	Screening findings, symptomatic cases, testing results, and detection failures	Screening sensitivity, diagnostic performance, and incubation period
Post-entry management	Healthcare facilities, quarantine systems, contact tracing, and community surveillance	Clinical presentations, delayed diagnosis, contact exposure, and quarantine outcomes	Clinical recognition, quarantine effectiveness, contact tracing, and surveillance responsiveness
Local transmission	Contact tracing, healthcare utilization, and community surveillance	Secondary cases, clusters, local transmission patterns, and healthcare demand	Population susceptibility, exposure intensity, intervention effectiveness, and healthcare response

SUPPLEMENTARY TABLE S3. Mapping of the hierarchical indicator domains to risk signal assessment dimensions.

Domain	Second-level category	Representative indicators	Signal characteristics	Epidemiological stage	Consequence severity
A	A1 Pathogen characteristics	Novel or re-emerging pathogen; variant or genotype	Signal relevance and credibility	Stage relevance	Potential impact
A	A2 Transmissibility	$R_o / R_e / R_i$; transmission mode; infectious period	Signal strength and temporal relevance	Stage transition	Transmission potential
A	A3 Disease severity	Case fatality rate; severe-case rate	Not applicable	Not applicable	Health impact
B	B1 Epidemic magnitude	New cases, incidence, and epidemic growth	Signal strength and temporal characteristics	Source epidemic stage	Potential importation scale
B	B2 Variant circulation	Dominant variant proportion	Signal strength and temporal characteristics	Source epidemic stage	Transmission and impact potential
B	B3 Exportation events	Travel health alerts	Credibility and spatial relevance	Pre-entry stage	Potential importation scale
B	B4 Surveillance and data reliability	Reporting timeliness, testing or sequencing capacity, and data completeness	Credibility and uncertainty	Not applicable	Not applicable
B	B5 Source control capacity	Emergency response and travel or border measures	Temporal characteristics	Source or pre-entry stage	Intervention feasibility
C	C1 Connectivity	Flight, land, and maritime connectivity	Spatial characteristics and signal strength	Cross-border movement	Importation scale
C	C2 Inbound population	High-risk traveler proportion	Signal strength	Cross-border movement	Importation scale
C	C3 High-risk scenarios	Mass gatherings and enclosed-space exposure	Signal strength and spatial characteristics	Cross-border movement	Exposure and consequence potential
C	C4 Point-of-entry capacity	Screening, testing, and laboratory capacity	Credibility and uncertainty	Border screening	Intervention feasibility
C	C5 Post-entry dissemination	Population outflow intensity	Spatial and temporal characteristics	Post-entry	Potential spread scale
D	D1 Early signals with imported cases	Imported cases, locally linked cases, and clusters	Signal strength; temporal and spatial characteristics	Post-entry or local transmission	Potential spread scale
D	D2 Detection or diagnosis delay	Entry-to-onset interval; onset-to-diagnosis interval	Temporal characteristics	Post-entry	Transmission opportunity
D	D3 Exposure/contact scale	Contacts, high-risk venues, and enclosed-space exposure	Signal strength and spatial characteristics	Post-entry or local transmission	Potential spread scale
D	D4 Local susceptibility and environment	Immunity, pathogen circulation, mobility, and seasonality	Temporal and spatial characteristics	Local transmission	Transmission potential
D	D5 Local response capacity	Sentinel surveillance, contact tracing, and emergency response	Credibility and uncertainty	Post-entry or local transmission	Intervention feasibility

SUPPLEMENTARY TABLE S4. Case walkthrough of risk signal collection, assessment, and warning escalation.

Stage	Observed information	Candidate or risk signal	Assessment	Potential action
Overseas outbreak	Increasing overseas COVID-19 activity	Elevated importation pressure	$S \uparrow, T \uparrow$	Enhanced epidemic intelligence
Cross-border movement	Imported cases among international travelers	Persistent introduction opportunity	$S \uparrow, C \uparrow$	Strengthen entry screening
Post-entry management	Delayed positivity after repeated negative tests	Residual post-entry risk	$S \uparrow, T \uparrow$	Extend testing and monitoring
Local transmission	Secondary cases associated with delayed detection	High-priority transmission signal	$S \uparrow, T \uparrow, C \uparrow$	Immediate investigation
Warning escalation	Multisource evidence, persistence, and high priority	Warning signal	$P \geq \text{threshold}^*$	Initiate public health response

Note: S, signal characteristics; T, epidemiological stage; C, consequence severity; P, priority score.

* Thresholds are illustrative and require further calibration.

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