Vital Surveillances

Post-Marketing Surveillance Data of Adverse Events Following Immunization with Human Rabies Vaccine — China, 2021–2024

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Summary

What is already known about this topic?

Human rabies vaccine has been in use for many years and has played a vital role in rabies prevention and control in China.

What is added by this report?

From 2021 to 2024, the overall reported rate of adverse events following immunization (AEFI) with human rabies vaccine was 18.57 per 100,000 doses, of which 96.29% were common vaccine reactions. Rare vaccine reactions occurred at a rate of 0.49 per 100,000 doses; allergic rash was the most frequently reported rare reaction and usually was non-serious. The rate of rare and serious vaccine reactions was 0.07 per 100,000 doses.

What are the implications for public health practice?

Human rabies vaccine, one of the most commonly used non-program vaccines in China, its AEFI rate fell within an acceptable range. Continued AEFI surveillance is essential for evaluating the post-marketing immnization safety of this vaccine.

ABSTRACT

Introduction: Human rabies vaccine has been widely used as a non-program vaccine in China for many years. This study analyzed adverse events following immunization (AEFI) with human rabies vaccine from 2021 to 2024.

Methods: AEFI case reports and administered dose counts for human rabies vaccine during 2021–2024 were obtained from the Chinese National Immunization Information System of the China Information System for Disease Prevention and Control. AEFI characteristics and incidence rates were analyzed using descriptive epidemiological methods.

Results: During 2021–2024, a total of 34,684 AEFI cases were reported, yielding an overall incidence rate of 18.57 per 100,000 doses. Common vaccine reactions accounted for 96.29% of cases (17.88 per 100,000 doses), and rare vaccine reactions accounted for 2.62% (0.49 per 100,000 doses). Allergic rash was the most frequently reported rare vaccine reaction, with an incidence rate of 0.32 per 100,000 doses, followed by angioedema, Henoch-Schönlein purpura, anaphylactic shock, and febrile convulsion/convulsion, with incidence rates of 0.04, 0.02, 0.01, and 0.01 per 100,000 doses, respectively.

Conclusions: Most AEFI cases with human rabies vaccine were common vaccine reactions. Allergic reactions, particularly allergic rash, constituted the predominant rare vaccine reactions. Although several cases of anaphylactic shock were reported, the incidence was extremely low. Timely identification and immediate management of post-vaccination serious allergic reactions are important measures for ensuring the immunization safety of human rabies vaccine.

Rabies is an acute neurological infectious disease caused by lyssaviruses that is almost invariably fatal once clinical signs appear. According to the World Health Organization (WHO), rabies caused approximately 59,000 human deaths annually, which was reported in over 150 countries, and 95% of cases occurred in Asia and Africa (*1*). Human rabies vaccine has been used to prevent rabies and avert rabies-related deaths in China since the 1920s (*2*). The National Regulation for the Rabies Exposure Prophylaxis (2023 edition), issued by the National Disease Control and Prevention Administration and the National Health Commission (*3*), stipulated that a full-course rabies vaccination series should be completed on schedule. Standardized, full-course vaccination stimulates protective immunity against rabies virus. Currently, all authorized human rabies vaccines in mainland China are non-program vaccines (voluntary and self-paid). Several types are in use: hamster kidney cell rabies vaccine (HKCV), Vero cell rabies vaccine (VCV) in freeze-dried or liquid formulations, and human diploid

cell rabies vaccine (HDCV). HKCV and VCV were approved in 2005, and HDCV was approved in 2014. We analyzed adverse events following immunization (AEFI) surveillance data from 2021 to 2024 to evaluate the post-marketing immunization safety of human rabies vaccines used in China.

METHODS

Immunization Procedure

Post-exposure prophylaxis (PEP) for rabies follows either a five-dose Essen regimen, with intramuscular injections on days 0, 3, 7, 14, and 28, or a four-dose Zagreb regimen, with two doses on day 0 and single doses on days 7 and 21. If re-exposure occurs during the PEP series, remaining doses should continue to be administered on schedule. No booster dose is needed if vaccination was completed within the preceding 3 months. If re-exposure occurs more than 3 months after series completion, booster doses should be administered on days 0 and 3 relative to the re-exposure date. Pre-exposure prophylaxis (PrEP) consists of a three-dose series administered on days 0, 7, and 21 or 28. A booster dose is recommended one year after PrEP if no animal bite has occurred, followed by additional boosters every 3 to 5 years for individuals with ongoing rabies exposure risk.

Data Sources

AEFI case reports and administered dose data for all authorized human rabies vaccines during 2021–2024 were obtained from the Chinese National Immunization Information System of the China Information System for Disease Prevention and Control.

Case Classification

In accordance with applicable laws, regulations, and guidelines, AEFI cases are preliminarily classified as common vaccine reactions or undetermined classification by responsible reporters, including staff at vaccination clinics, medical institutions, and local Centers for Disease Control and Prevention (CDCs). For cases requiring causality assessment by an expert group, the responsible CDCs or medical associations organize specialists in different fields such as epidemiology and clinical medicine to conduct evaluations based on individual medical records and relevant information. By cause, cases are classified as common vaccine reactions, rare vaccine reactions (including cases not ruled out), anxiety-related events, coincidental events, suspected immunization error-related events, and vaccine quality-related events. By severity, cases are classified as serious or non-serious AEFI.

Statistical Analysis

Descriptive epidemiological methods were used to characterize reported AEFI and calculate incidence rates. Incidence rate was computed by dividing the number of reported AEFI cases by the number of administered doses and multiplying by 100,000. Analysis was performed using the Statistical Analysis System (SAS, version 9.4, SAS Institute Inc., Cary, NC, USA) and Microsoft Excel (version 2016, Microsoft Corporation, Redmond, WA, USA).

RESULTS

General Characteristics

During 2021–2024, a total of 34,684 AEFI reports were received for human rabies vaccine. Of these, 46.33% involved males and 53.67% involved females; 16.65% occurred among children younger than 3 years, 42.84% among those aged 3–17 years, 32.42% among those aged 18–59 years, and 8.09% among individuals aged 60 years or older. By region, 32.96% were from eastern China, 54.26% were from central China and 12.78% were from western China. By quarter, 17.74%, 28.59%, 29.33% and 24.34% occurred in the first through fourth quarters, respectively. By dose number, 66.34% followed the first dose, 12.68% followed the second dose, 10.51% followed the third dose and <11% followed more than three doses (Table 1).

Reporting Rate and Classification

The reported AEFI incidence rate for human rabies vaccine during 2021–2024 was 18.57 per 100,000 doses, based on over 186.78 million administered doses. Both the number of AEFI cases and incidence rates increased year by year, peaking in 2024 (Table 2).

By cause, there were 33,393 common vaccine reactions (17.88 per 100,000 doses) and 910 rare vaccine reactions (0.49 per 100,000 doses), accounting for 96.29% and 2.62% of cases, respectively. An additional 292 cases were classified as coincidental events (0.84%, 0.16 per 100,000 doses), 78 as anxiety-related events (0.22%, 0.04 per 100,000 doses), and 11 remained pending classification (0.03%, 0.01 per

TABLE 1. General Characteristics of Rabies Vaccine AEFI Reports, 2021–2024.

Characteristics	Serious		Non-serious		Total	
	N	Proportion (%)	*N*	Proportion (%)	*N*	Proportion (%)
Sex						
Male	92	43.60	15,978	46.35	16,070	46.33
Female	119	56.40	18,495	53.65	18,614	53.67
Age (years)						
<3	31	14.69	5,748	16.67	5,779	16.65
3–17	70	33.18	14,787	42.89	14,857	42.84
18–59	72	34.12	11,171	32.41	11,243	32.42
≥60	38	18.01	2,767	8.03	2,805	8.09
Region						
Eastern	78	36.97	11,357	32.95	11,435	32.96
Central	77	36.49	18,741	54.36	18,818	54.26
Western	56	26.54	4,375	12.69	4,431	12.78
Quarter of year						
1st	46	21.80	6,105	17.71	6,151	17.74
2nd	68	32.23	9,848	28.57	9,916	28.59
3rd	63	29.86	10,111	29.33	10,174	29.33
4th	34	16.11	8,409	24.39	8,443	24.34
Dose number						
1st	94	44.55	22,914	66.47	23,008	66.34
2nd	20	9.48	4,377	12.70	4,397	12.68
3rd	41	19.43	3,606	10.46	3,647	10.51
4th	36	17.06	2,401	6.96	2,437	7.03
5th	19	9.00	1,072	3.11	1,091	3.15
≥6th	1	0.48	103	0.30	104	0.29
Total	211	100.00	34,473	100.00	34,684	100.00

Abbreviation: AEFI=adverse events following immunization.

100,000 doses). No suspected immunization error-related or vaccine quality-related events were reported. By severity, 211 cases were serious (0.11 per 100,000 doses) and 34,473 were non-serious (18.46 per 100,000 doses). Among these, 131 were classified as rare and serious vaccine reactions (0.07 per 100,000 doses).

Vaccine Reaction Diagnoses

During the study period, among common vaccine reactions, 12,034 cases involved fever (axillary temperature ≥38.6 ℃), 5,505 involved injection site redness and swelling (diameter >2.5 cm) and 2,791 involved injection site induration (diameter >2.5 cm), representing 36.04%, 16.49%, and 8.36% of common reactions, with incidence rates of 6.44, 2.95 and 1.49 per 100,000 doses, respectively.

The most frequently diagnosed rare vaccine reaction was allergic rash, with 597 cases and an incidence rate of 0.32 per 100,000 doses. Angioedema, Henoch-Schönlein purpura (HSP), anaphylactic shock, and febrile convulsion/convulsion followed, with 75, 34, 24 and 16 cases and incidence rates of 0.04, 0.02, 0.01 and 0.01 per 100,000 doses, respectively. No vaccine lots were clustered associated with anaphylactic shock or laryngeal edema. The rates of thrombocytopenic purpura (TP) and other neurological diseases were no more than 0.01 per 100,000 doses (Table 3).

DISCUSSION

Advances in production technology — including strain selection, cell substrate development, and improved concentration and purification processes —

TABLE 2. Number of AEFI cases and incidence per 100,000 doses of human rabies vaccine by cause, severity, and year, 2021–2024.

Variables	*N*	Proportion (%)	Incidence
Cause			
Common vaccine reactions	33,393	96.29	17.88
Rare vaccine reactions	910	2.62	0.49
Coincidental events	292	0.84	0.16
Anxiety-related events	78	0.22	0.04
Pending determination	11	0.03	0.01
Severity			
Serious	211	0.61	0.11
Non-serious	34,473	99.39	18.46
Year			
2021	3,871	11.16	11.12
2022	6,256	18.04	14.28
2023	10,541	30.39	20.30
2024	14,016	40.41	24.93
Total	34,684	100.00	18.57

Note: Incidence was calculated by dividing the number of reported AEFI cases by the number of administered human rabies vaccine doses, then multiplying by 100,000.
Abbreviation: AEFI=adverse events following immunization.

have yielded mature, stable manufacturing of human rabies vaccines with reduced adverse effects (*2*). The 2018 WHO position paper on rabies vaccines noted that minor, transient injection site reactions such as erythema, pain, and swelling may occur in 35%–45% of vaccinees, while mild systemic adverse events such as fever, headache, dizziness, and gastrointestinal symptoms may occur in 5%–15% (*4*). Two meta-analyses reported AEFI rates for human rabies vaccine in China of 9.82% (*5*) and 5.6% (*6*), covering the periods 2006–2016 and 2012–2016, respectively. In contrast, our study found that the AEFI incidence rate during 2021–2024 was 18.57 per 100,000 doses (0.019%). Most cases occurred among children and adolescents, followed the first dose, and were reported during the second and third quarters. Both AEFI case counts and incidence rates increased annually, consistent with national AEFI trends in China (*7*–*8*). The proportion of AEFI reported among adults was higher than the national average for all vaccines, likely reflecting greater exposure opportunities for adults through pet contacts, outdoor activities, and occupational risks, as well as the broad age coverage of this vaccine. The higher rabies disease burden in central China may also have contributed to the higher proportion of AEFI reported from this region (*9*).

The majority of AEFI were common vaccine reactions, including fever and injection site redness and swelling, consistent with findings from studies in the United States (*10*) and India (*11*). These transient symptoms generally require no treatment. Rare vaccine reactions accounted for 2.62% of AEFI (0.49 per 100,000 doses), with the most common diagnoses being allergy-related conditions such as allergic rash and angioedema. The rates of allergic rash and angioedema were 0.32 and 0.04 per 100,000 doses, respectively — lower than or comparable to the national rates for all vaccines in China (*7*–*8*). These allergic reactions typically resolve within a few days without treatment, or more rapidly with appropriate therapy. The rates of anaphylactic shock and laryngeal edema, both life-threatening allergic reactions, were comparable to the national average reporting rates for all vaccines and fell below the WHO threshold for very rare events (*12*), as well as below the rate of anaphylaxis (1.31 per million doses) reported in the United States (*13*). Because rabies vaccine has no contraindications for post-exposure administration, an increased risk of allergic reactions cannot be excluded. Although extremely rare, anaphylactic shock and laryngeal edema can develop rapidly and require immediate treatment.

HSP, also known as immunoglobulin A vasculitis, is a condition predominantly affecting children with a complex and multifactorial etiology. HSP is generally self-limited. A systematic review covering 1994–2014 found no causal association between vaccination and

TABLE 3. Symptoms and diagnoses of adverse reactions for human rabies vaccine, 2021–2024.

Symptom or diagnosis	*N*	Proportion (%)	Incidence
Common vaccine reactions	33,393	100.00	17.88
Fever	22,754	68.14	12.18
37.1–37.5 ℃	2,554	7.65	1.37
37.6–38.5 ℃	8,166	24.45	4.37
≥38.6 ℃	12,034	36.04	6.44
Injection site redness/swelling	9,208	27.57	4.93
Diameter≤2.5 cm	3,703	11.09	1.98
Diameter>2.5 cm	5,505	16.49	2.95
Injection site induration	5,358	16.05	2.87
Diameter≤2.5 cm	2,567	7.69	1.37
Diameter>2.5 cm	2,791	8.36	1.49
Rare vaccine reactions	910	100.00	0.49
Allergic rash	597	65.60	0.32
Angioedema	75	8.24	0.04
HSP	34	3.74	0.02
Anaphylactic shock	24	2.64	0.01
Febrile convulsion/ convulsion	16	1.76	0.01
Laryngeal edema	11	1.21	0.01
TP	7	0.77	0.004
Arthus reactions	4	0.44	0.002
Lymphangitis/lymphadenitis	2	0.22	0.001
Sterile abscess	1	0.11	0.001
Other allergic reactions	88	9.67	0.05
Other neurological diseases	16	1.76	0.009
Other diagnosis	35	3.84	0.02
Total	34,303	100.00	18.37

Note: Incidence was calculated by dividing the number of reported AEFI cases by the number of administered human rabies vaccine doses, then multiplying by 100,000.
Abbreviation: HSP=Henoch-Schönlein purpura; TP=thrombocytopenic purpura/thrombocytopenia.

vasculitis, including HSP (*14*). Febrile convulsions can be triggered by fever, a common post-vaccination symptom; although alarming to parents, they are benign (*15*). Monitoring body temperature and providing antipyretic treatment can be beneficial. Certain neurological diseases were previously linked to older formulations of human rabies vaccines cultured in mammalian brain tissues; however, studies have found no association between neurological conditions such as acute disseminated encephalomyelitis and Guillain-Barré syndrome and newer vaccine formulations (*16*–*18*). The WHO position paper further stated that serious adverse events rarely occur with human rabies vaccine and that no causal relationship has been established between the vaccine and neurological symptoms (*4*). In our study, a few isolated cases of neurological symptoms were classified as rare vaccine reactions by local causality assessment expert panels based on individual clinical circumstances; however, these cases were insufficient to establish a definitive association between the vaccines and these conditions.

This study has several limitations. The AEFI data were derived from a passive surveillance system, which tends to underestimate the reporting rates. Additionally, variations in reporting sensitivity, investigation quality, and diagnostic accuracy across jurisdictions may have affected the results.

In conclusion, post-marketing AEFI surveillance in China demonstrated that the AEFI rates with human rabies vaccine were very low and within an acceptable range. The most common reactions were fever and

injection site reactions. Allergic rash was the most frequently reported rare vaccine reaction, while anaphylactic shock and laryngeal edema were extremely rare. These findings provide continued reassurance regarding the immunization safety of human rabies vaccine.

Conflicts of interest: No conflicts of interest.

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Ethical Statement: The AEFI surveillance and disposal of individual cases is a requirement of the existing law, regulation and guideline. This study is a retrospective analysis with surveillance data, and there is no need for ethical review.

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