Vital Surveillances

Post-Marketing Surveillance of Adverse Events Following Rotavirus Vaccination — China, 2013–2023

Yuan Li[1]; Keli Li[1,#]; Yan Li[1]; Chunxiang Fan[1]; Lina Zhang[1]; Minrui Ren[1]; Lei Cao[1]; Wenzhou Yu[1]; Zundong Yin[1]

ABSTRACT

Introduction: Two live attenuated rotavirus vaccines (RVs) were licensed in China. Passive surveillance for adverse events following immunization (AEFI) provides valuable evidence for potential safety signal detection of RV in China.

Methods: We obtained data on RV doses administered and RV AEFI reports from the Chinese National Immunization Information System (CNIIS) during January 2013 to December 2023. We conducted a descriptive analysis of RV AEFI characteristics and estimated incidences of RV AEFI.

Results: During the study period, 77.36 million doses of RV were administered, and 20,556 RV AEFI reports were made, yielding an overall incidence of 26.57 AEFI per 100,000 doses administered; incidences were 26.42 for RV1 and 26.85 for RV5. Among all RV AEFI, 20,334 (98.92%) were non-serious. Vaccine product-related reactions accounted for 95.68% of AEFI reports, including 18,192 (88.50%) common and 1,476 (7.18%) rare vaccine reactions. Among common vaccine reactions, case reports per 100,000 doses administered were 16.85 (13,031 reports) for fever, 5.84 (4,520 reports) for gastrointestinal disorders, and 1.28 (988 reports) for rash. Among rare vaccine reactions, case reports per 100,000 doses were 1.43 (1,104 reports) for allergic rash, 0.07 (56 reports) for thrombocytopenic purpura, 0.03 (26 reports) for febrile convulsion, and 0.01 (5 reports) for intussusception.

Conclusions: Most RV AEFIs were mild and non-serious, and the incidence of rare vaccine reactions was very low. RVs have reasonable safety surveillance profiles and AEFI evaluation should be continued.

Diarrheal disease is a significant cause of mortality and child death worldwide. Rotavirus infection represents the leading cause of severe diarrhea and dehydrating gastroenteritis in young children globally, particularly affecting children under 2 years of age in developing countries (*1*–*4*). Rotavirus vaccine (RV) effectively prevents rotavirus gastroenteritis and related hospitalizations in children (*5*–*6*). Since the first RV was withdrawn from markets in 1999 due to a strong, likely causal association with intussusception (*7*), the safety profile of RVs has received considerable attention worldwide.

As of 2023, two live attenuated RVs have been in use for several years in China: a monovalent RV (RV1, licensed in 2001) and a pentavalent reassortant RV (RV5, licensed in 2018). Both vaccines are non-program (family-pay) vaccines; RV1 is indicated for children 2 months to 3 years of age, while RV5 is indicated for infants 6–32 weeks of age.

Post-marketing surveillance and studies are essential for evaluating vaccine safety. China established a nationwide, online, passive surveillance system for adverse events following immunization (AEFI) — the Chinese National AEFI Information System (CNAEFIS) — which was integrated into the Chinese National Immunization Information System (CNIIS). To contribute to the evidence base on RV safety, we analyzed RV AEFI reports submitted to CNAEFIS from January 2013 to December 2023 and report our evaluation results.

METHODS

Our observational surveillance study utilized data from the CNIIS, which integrates both the AEFI surveillance database and the vaccination database for China. The CNAEFIS functions as a passive surveillance tool that collects spontaneous reports from all types of reporters. According to the national AEFI surveillance guidelines, AEFI reports are classified into five categories: vaccine product-related reactions, coincidental events, psychogenic reactions, program error-related reactions, and vaccine quality defect-related reactions. Vaccine product-related reactions

include common (usually minor) and rare (possibly serious) vaccine reactions. A serious AEFI is defined as one that is life-threatening and results in permanent or significant disability, causes impairment of organ function, or leads to death. In 2022, the revised national AEFI surveillance guidelines expanded this definition to include cases requiring inpatient hospitalization or prolongation of existing hospitalization. To enhance AEFI reporting quality, county surveillance staff review data reporting issues during routine work, and an annual revision and summary of the national AEFI data is conducted.

We extracted data on AEFI reports related to either RV1 or RV5 vaccine from CNIIS for the study period of January 1, 2013 to December 31, 2023. Microsoft Office Excel software (version 2016; Microsoft Corporation, Redmond, Washington, USA) and Python (version 3.12.1) were used for descriptive analysis of RV AEFIs. The AEFI reports per 100,000 doses administered was calculated by dividing the number of AEFI reports by the doses administered and multiplying by 100,000.

RESULTS

During the study period, 77.36 million doses of RV were administered, comprising 49.27 million RV1 doses and 28.09 million RV5 doses. A total of 20,556 AEFI reports for RV were documented; 63.31% were for RV1 and 36.69% for RV5. The overall incidence of RV AEFI was 26.57 per 100,000 doses administered, with similar rates for RV1 (26.42 per 100,000 doses) and RV5 (26.85 per 100,000 doses).

Among RV AEFI reports, 19,668 (95.68%) were classified as vaccine product-related reactions, representing 25.43 reports per 100,000 doses administered. And, 18,192 (88.50%) were common vaccine reactions, and 1,476 (7.18%) were rare vaccine reactions, corresponding to 23.52 and 1.91 reports per 100,000 doses, respectively. In addition, 868 (4.22%) were coincidental events and 6 (0.03%) were psychogenic reactions, with respective incidences of 1.12 and 0.01 reports per 100,000 doses. Serious AEFI reports totaled 222, accounting for 1.08% of all RV reports and representing 0.29 reports per 100,000 doses.

Table 1 shows characteristics of the RV AEFI reports. The majority (63.71%) of RV AEFI reports occurred in infants, with 55.04% in boys. The eastern region accounted for 53.58% of reports, and 31.72% occurred during the third quarter of the year. Most reports (68.14%) followed the first dose of RV, and 97.53% occurred within 3 days after vaccination, with 59.74% on the day of vaccination, 37.79% during days 1–3, 2.12% during days 4–14, and 0.35% more than 15 days after vaccination.

Table 2 shows RV AEFI incidence by vaccine type. There was an overall upward trend in RV AEFI incidence from 2016 to 2019, followed by a downward trend through 2021. The relative proportion of RV5 AEFI increased since 2019. Among all reports, 98.92% were non-serious AEFIs, with serious AEFIs accounting for only a small percentage during the study period. Non-serious AEFI reports per 100,000 doses reported for RV1 and RV5 were 26.22 and 26.39, respectively. Common and rare vaccine reactions were the most frequently reported categories, accounting for 88.50% and 7.18% of all AEFI reports, respectively. Similar AEFI incidences were in RV1 (26.42 per 100,000 doses) and RV5 (26.85 per 100,000 doses).

Table 3 presents the diagnoses and incidences of vaccine product-related reactions. Most vaccine product-related reactions were common vaccine reactions. The most commonly reported common vaccine reactions were fever, gastrointestinal disorders, and rash, with reported incidences of 16.85, 5.84, and 1.28 per 100,000 doses, respectively. Other reported common reactions included sleepiness and fussiness, with incidences of 0.34 and 0.28 per 100,000 doses. The most frequently reported rare vaccine reactions were allergic rash, thrombocytopenic purpura, and febrile convulsion, with incidences of 1.43, 0.07, and 0.03 per 100,000 doses. Other rare reactions were reported at even lower frequencies, including angioedema, Henoch-Schonlein purpura, anaphylactic shock, intussusception, and laryngeal edema, with incidences of 0.02, 0.01, 0.01, 0.01, and 0.001 per 100,000 doses, respectively.

DISCUSSION

Our study analyzed 20,556 AEFI reports after the administration of 77 million doses of RV during 2013–2023. The overall AEFI reported incidence was 27 per 100,000 doses administered, with similar incidences for both vaccine types: 26 per 100,000 for RV1 and 27 per 100,000 for RV5. During 2019–2023, when both vaccines were licensed and in use, AEFI incidences for RV1 and RV5 were nearly equivalent. The repoted incidence fluctuated throughout the study period, peaking in 2017–2019,

TABLE 1. Characteristics of AEFI reports for RVs, China, 2013–2023.

Characteristic	RV1		RV5		Total	
	Cases	Percentage (%)	Cases	Percentage (%)	Cases	Percentage (%)
Age (years)						
<1	5,582	42.89	7,515	99.66	13,097	63.71
1	4,776	36.70	–	–	4,776	23.23
2	2,134	16.40	–	–	2,134	10.38
3	494	3.80	–	–	494	2.40
Gender						
Male	7,156	54.98	4,157	55.13	11,313	55.04
Famale	5,859	45.02	3,384	44.87	9,243	44.96
Region*						
Eastern	6,851	52.64	4,162	55.19	11,013	53.58
Central	4,028	30.95	2,393	31.73	6,421	31.24
Western	2,136	16.41	986	13.08	3,122	15.19
Quarter						
1	2,087	16.04	1,436	19.04	3,523	17.14
2	4,091	31.43	2,152	28.54	6,243	30.37
3	4,350	33.42	2,170	28.78	6,520	31.72
4	2,487	19.11	1,783	23.64	4,270	20.77
Reaction interval time (days)†						
<1	7,964	61.19	4,317	57.25	12,281	59.74
1–3	4,820	37.03	2,947	39.08	7,767	37.79
4–14	201	1.54	235	3.12	436	2.12
≥15	30	0.23	42	0.56	72	0.35
Doses						
1	10,402	79.92	3,604	47.79	14,006	68.14
2	2,115	16.25	2,156	28.59	4,271	20.78
3	492	3.78	1,779	23.59	2,271	11.05
4	6	0.05	2	0.03	8	0.04
Total	13,015	100.00	7,541	100.00	20,556	100.00

Note: "–" means a several few reports cases were not included in the statistictables by age group due to contradictions between the vaccination age and the immunization schedule or incorrect information filled in.
Abbreviation: PLAD=provincial-level administrative division.
* The eastern region includes Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong and Hainan PLADs; the central region includes Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan PLADs; the western region includes Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Xizang, Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang PLADs, and Xinjiang Production and Construction Corps.
† Reaction interval time: Time between vaccination and onset of reaction.

possibly reflecting increased reporting sensitivity. Common and rare vaccine reactions constituted 89% and 7% of AEFI reports, respectively. The incidences of both common and rare reactions remained at low levels. Adverse events of special interest, such as intussusception and febrile convulsion, were extremely rare and showed no clustering by vaccine lot number. Based on these findings, both RVs demonstrate favorable safety profiles.

RV1 was licensed in China in 2001, while RV5 received licensure in 2018. Both vaccines are non-program (family-pay) vaccines, meaning they are voluntary and families must cover the cost of the vaccine and its administration. Since these vaccines are not included in the routine vaccination schedule, the timing of vaccination more closely follows the product package insert recommendations. RV1 is indicated for children 2 months to 3 years of age, while RV5 is

TABLE 2. AEFI reports and reports per 100,000 doses administered by vaccine, year, cause classification, and seriousness, China, 2013–2023.

Characteristic	RV1			RV5			Total		
	Cases	Percentage (%)	Reported incidence	Cases	Percentage (%)	Reported incidence	Cases	Percentage (%)	Reported incidence
Year									
2013	1,148	8.82	28.39	–	–	–	1,148	5.58	28.39
2014	1,129	8.67	24.02	–	–	–	1,129	5.49	24.02
2015	1,148	8.82	22.05	–	–	–	1,148	5.58	22.05
2016	838	6.44	20.73	–	–	–	838	4.08	20.73
2017	1,137	8.74	33.18	–	–	–	1,137	5.53	33.18
2018	1,655	12.72	34.60	7	0.09	–	1,662	8.09	34.74
2019	1,763	13.55	32.75	704	9.34	35.77	2,467	12.00	33.55
2020	1,490	11.45	26.31	1,190	15.78	26.10	2,680	13.04	26.22
2021	954	7.33	19.60	1,173	15.55	18.81	2,127	10.35	19.15
2022	796	6.12	20.12	1,547	20.51	20.89	2,343	11.40	20.62
2023	957	7.35	29.96	2,920	38.72	36.89	3,877	18.86	34.89
Classification by cause									
Common vaccine reaction	11,394	87.55	23.13	6,798	90.15	24.20	18,192	88.50	23.52
Rare vaccine reaction	1,029	7.91	2.09	447	5.93	1.59	1,476	7.18	1.91
Coincidental events	582	4.47	1.18	286	3.79	1.02	868	4.22	1.12
Psychogenic reactions	4	0.03	0.01	2	0.03	0.01	6	0.03	0.01
Others	6	0.05	0.01	8	0.11	0.03	14	0.07	0.02
Serious AEFI									
Yes	94	0.72	0.19	128	1.70	0.46	222	1.08	0.29
No	12,921	99.28	26.22	7,413	98.30	26.39	20,334	98.92	26.29
Total	13,015	100.00	26.42	7,541	100.00	26.85	20,556	100.00	26.57

Note: "–" means no related data.
Abbreviation: AEFI=adverse event following immunization; RV=rotavirus vaccine.

indicated for infants 6–32 weeks of age. We observed that very few reports documented administration outside the recommended age range specified in the pachage insert. This may remind that vaccination staff should careflly check the age of children before vaccination and vaccinate those who are in an appropriate age. The publicity effors are needed to enable parents to have a better understanding of the benefits of RV and take their children for vaccination at a right time.

The most frequently reported AEFIs were common vaccine reactions, primarily fever and gastrointestinal disorders. Although these reactions do not cause long-term or serious harm, high fever in infants can trigger febrile convulsions, which, while not damaging to the child, can be frightening for parents. As live attenuated oral vaccines, RVs may induce symptoms similar to natural infection, though considerably milder. Allergic rash was the most commonly reported rare vaccine reaction. Nearly all common and rare vaccine reactions occurred within 3 days after immunization, with the majority occurring on the day of vaccination, consistent with the pharmacological properties of the vaccines. Since serious allergic reactions typically manifest immediately, maintaining an observation period of half an hour after vaccination is crucial for promptly identifying and treating potential anaphylaxis in vaccinees.

The first RV licensed globally was withdrawn in 1999, one year after approval, due to a strong and likely causal association with intussusception. Consequently, RV safety has received worldwide attention. Our analysis revealed extremely low reported incidences of intussusception and other gastrointestinal disorders among rare vaccine reactions. Monovalent RVs used internationally, such as Rotarix, showed an increased potential risk of intussusception after vaccination in a post-marketing study in America (*8*),

TABLE 3. Vaccine product-related reactions reports per 100,000 doses administered of RVs, China, 2013–2023.

Diagnosis or symptom	RV1		RV5		Total	
	Cases	Reported incidence (%)	Cases	Reported incidence (%)	Cases	Reported incidence (%)
Common vaccine reaction	11,394	23.13	6,798	24.20	18,192	23.52
Fever (℃)	8,764	17.79	4,267	15.19	13,031	16.85
≥38.6	4,969	10.09	1,602	5.70	6,571	8.49
Gastrointestinal disorders	2,978	6.04	1,542	5.49	4,520	5.84
Rash	576	1.17	412	1.47	988	1.28
Sleepiness	123	0.25	139	0.49	262	0.34
Fussiness	96	0.19	123	0.44	219	0.28
Rare vaccine reaction	1,029	2.09	447	1.59	1,476	1.91
Allergic rash	817	1.66	287	1.02	1,104	1.43
Thrombocytopenic purpura	13	0.03	43	0.15	56	0.07
Febrile convulsion	24	0.05	2	0.01	26	0.03
Angioedema	11	0.02	2	0.01	13	0.02
Henoch-Schonlein purpura	1	0.002	8	0.03	9	0.01
Anaphylactic shock	3	0.01	3	0.01	6	0.01
Intussusception	4	0.01	1	0.004	5	0.01
Laryngeal edema	1	0.002	0	–	1	0.001
Others	155	0.31	101	0.36	256	0.33
Total	12,423	25.21	7,245	25.80	19,668	25.43

Note: "–" means no related data.
Abbreviation: AEFI=adverse event following immunization; RV=rotavirus vaccine.

but no increase was found in self-controlled-case-series studies in sub-Saharan Africa (*9*). RV5, in its randomized, double-blind, placebo-controlled, multicenter licensure study, demonstrated no risk of intussusception within 42 days of any dose (*10*); the same result was found in a retrospective birth cohort study in China (*11*). Other post-marketing studies in several countries, including Australia, New Zealand, and Canada, found no significant change in the overall incidence of intussusception during RV5 use, although some studies suggested intussusception was associated with RV5, especially following the first dose, despite the small risk and short time window (*12*–*15*). In 2013, the United States Food and Drug Administration approved the inclusion of new safety information on intussusception risk in the package insert and patient package insert of RV5. RVs apparently influence the gastrointestinal tract as described in their safety profiles, but the risk of increasing intussusception incidence is extremely low. The reported incidence of intussusception following RV immunization is significantly lower than that in general population. Whether RV administration could lead to earlier intussusception in predisposed children remains a topic for further research. Intussusception often occurs in children under 2 years old, with most cases being primary and secondary causes mostly related to infection, intestinal dysplasia, and other factors. Intussusception AEFI should be carefully investigated and classified.

Our study was subject to at least two limitations. First, data reported in CNIIS may be incomplete and contain inaccuracies, including incorrect determination of severity and causality classification. Second, passive reporting systems are prone to underreporting, resulting in underestimation of AEFI incidence. Generally, well-known AEFIs are recognized and reported more easily than unknown AEFIs, and expected minor AEFIs tend to be reported less frequently. Underreporting should be considered when interpreting results. Currently, no other sources provide such extensive AEFI data for vaccines in China. Despite these limitations, passive surveillance helps detect unusual or unexpected patterns of AEFI reporting.

In conclusion, the AEFIs reported for RV were mostly minor and transient, supporting a reasonable safety profile for these vaccines. Given that RVs play an important role in preventing rotavirus-associated severe diarrhea and mortality in children, especially those

younger than 5 years old, RV use should continue to be promoted. Parents should be informed of an observation period after vaccination.

Conflicts of interest: No conflicts of interest.

Acknowledgments: We thank the staff at the provincial, prefectural, and county CDCs, as well as all vaccination clinics involved in conducting the adverse event surveillance. We also thank Lance Rodewald, senior consultant at China CDC, for his insightful comments and recommendations on the manuscript.

Funding: Supported by grants from the Operation of the Public Health Emergency Response Mechanism in China CDC (102393220020010000017).

doi: 10.46234/ccdcw2025.093

[#] Corresponding author: Keli Li, Likl@chinacdc.cn.

[1] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases (NITFID), National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: March 25, 2025
Accepted: April 18, 2025
Issued: April 25, 2025

REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736 – 88. https://doi.org/10.1016/S0140-6736(18)32203-7.
2. Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine 2012;30(7):1244 – 54. https://doi.org/10.1016/j.vaccine.2011.12.092.
3. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet 2013;382(9888):209 – 22. https://doi.org/10.1016/s0140-6736(13)60844-2.
4. Wang LP, Zhou SX, Wang X, Lu QB, Shi LS, Ren X, et al. Etiological, epidemiological, and clinical features of acute diarrhea in China. Nat Commun 2021;12(1):2464. https://doi.org/10.1038/s41467-021-22551-z.
5. Troeger C, Khalil IA, Rao PC, Cao SJ, Blacker BF, Ahmed T, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA Pediatr 2018;172(10):958 – 65. https://doi.org/10.1001/jamapediatrics.2018.1960.
6. Aliabadi N, Antoni S, Mwenda JM, Weldegebriel G, Biey JNM, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008-16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health 2019;7(7):e893 – 903. https://doi.org/10.1016/s2214-109x(19)30207-4.
7. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344(8):564 – 72. https://doi.org/10.1056/nejm200102223440804.
8. Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, et al. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med 2014;370(6):513 – 9. https://doi.org/10.1056/nejmoa1311738.
9. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med 2018;378(16):1521 – 8. https://doi.org/10.1056/nejmoa1713909.
10. Keating GM. Rotavirus vaccine (RotaTeq). Paediatric drugs. 2006;8(3):197-202; discussion 3-4. https://doi.org/10.2165/00148581-200608030-00008.
11. Liu ZK, Li N, Liu GX, Xu L, Dong Y, Meng RG, et al. No increased risk of intussusception after pentavalent rotavirus vaccination in China: a retrospective birth cohort using electronic health records of Ningbo city. Emerg Microbes Infect 2023;12(2):2270062. http://dx.doi.org/10.1080/22221751.2023.2270062.
12. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 2011;29(16):3061 – 6. https://doi.org/10.1016/j.vaccine.2011.01.088.
13. McIlhone KA, Best EJ, Petousis-Harris H, Howe AS. Impact of rotavirus vaccine on paediatric rotavirus hospitalisation and intussusception in New Zealand: a retrospective cohort study. Vaccine 2020;38(7):1730 – 9. https://doi.org/10.1016/j.vaccine.2019.12.045.
14. Hawken S, Ducharme R, Rosella LC, Benchimol EI, Langley JM, Wilson K, et al. Assessing the risk of intussusception and rotavirus vaccine safety in Canada. Hum Vaccin Immunother 2017;13(3):703 – 10. https://doi.org/10.1080/21645515.2016.1240846.
15. Escolano S, Hill C, Tubert-Bitter P. Intussusception risk after RotaTeq vaccination: evaluation from worldwide spontaneous reporting data using a self-controlled case series approach. Vaccine 2015;33(8):1017 – 20. https://doi.org/10.1016/j.vaccine.2015.01.005.