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RESEARCH ARTICLE

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A broad assessment of rotavirus vaccine safety in infants in Korea: Insights from a data-driven signal detection approach

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ABSTRACT

In light of the widespread use of rotavirus vaccines, there is a pressing need to perform thorough, large-scale surveillance to actively monitor safety. This study aimed to identify potential adverse events following rotavirus vaccination in infants. Using a nationwide linked database of the national immunization registry and health insurance claims data, we identified infants vaccinated with the first dose of rotavirus vaccine between January 2016 and October 2022. The self-controlled tree-temporal scan statistics method analyzed all incident diagnoses recorded within 56 days post-vaccination and evaluated all temporal risk windows. Among 1,720,778 rotavirus vaccine recipients 64,752 infants contributed to the analysis, yielding 72,970 incident diagnoses. Of these, 28 clusters were categorized as known adverse drug reactions (ADRs), including infection following immunization (Days 1–2, $p<.001$), viral infection (Days 1–5, $p<.001$), urticaria and erythema (Days 3–9, $p<.001$), acute upper respiratory infections (Days 28–42, $p<.001$), and pneumonia (Days 9–19 or 28–42, $p<.001$). Seventeen clusters were classified as ADR-related events, such as the ones clinically related to ADR or lower-level diagnostic codes of ADR. The remaining 26 clusters were classified as signals, including sepsis (Days 1–20, $p<.001$), meningitis (Days 1–23, $p<.001$), liver disease (Days 4–11, $p<.001$), and tubulo-interstitial nephritis (Days 11–38, $p<.001$). A cluster of intussusceptions was only found in monovalent vaccine-stratified analysis (Days 5–8, $p = 0.005$). This study confirmed known ADRs following rotavirus vaccination, while identifying potential safety signals requiring further investigation. These findings emphasize the importance of active vaccine surveillance and underscore the need for epidemiological studies with validated outcome definitions to confirm causal relationships between rotavirus vaccination and the detected outcomes.

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Introduction

Rotavirus is a leading cause of severe dehydrating gastroenteritis, characterized by diarrhea and vomiting, in infants and young children worldwide.[1] It commonly spreads through families, communities, hospitals, and daycare centers.[2] To prevent rotavirus gastroenteritis, the first rotavirus vaccine was licensed by the U.S. Food and Drug Administration in 1998.[3] The World Health Organization (WHO) recommends widespread rotavirus vaccination of infants, and as of August 2024, the vaccine has been introduced in 125 countries globally.[4] WHO has prequalified four oral, live attenuated rotavirus vaccines; Rotarix™, RotaTeq™, Rotavac™, and RotaSiil™.[5] In the Republic of Korea, two rotavirus vaccines are available; the pentavalent vaccine (RotaTeq™, Merck & Co., Inc, USA), first approved in June 2007, and the monovalent vaccine (Rotarix™, Glaxo Smith Kline Biologicals, Belgium), approved in March 2008.[6] As of March 2023, these vaccines have been included in Korea's National Immunization Program (NIP) and are provided free of charge to recommended recipients under the age of 8 months.

While infants are the primary recipients of the vaccine, this vulnerable group is often excluded or underrepresented in pre-approval clinical trials.[7] As a result, evidence of vaccine safety in infants and children, particularly for rare adverse events, typically derives from post-approval studies. Although the rotavirus vaccine has been in use for several decades and its safety profile is relatively well-established, most published studies focused on selected outcomes such as gastrointestinal disorders (e.g., intussusception) and systemic general symptoms (e.g., fever).[8–11] Given Korea's high rotavirus vaccination coverage representing over 88.0% in 2017,[12] finding an unvaccinated control group is especially challenging. Therefore, the use of longitudinal databases and effective signal detection methods is essential for identifying previously unknown potential safety signals within large populations, relying solely on data from vaccinated infants.

Tree-temporal scan statistics is a practical data mining method that evaluates a wide range of health outcomes to identify those that may be temporally associated with specific exposures.[13,14] This method can detect potential adverse events without prespecifying the specific outcomes or risk

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intervals of concern. Previous studies have shown its utility in detecting safety signals for vaccines such as human papillomavirus vaccine,[14,15] meningococcal conjugate vaccine,[16] live attenuated herpes zoster vaccine,[17] and COVID-19 vaccine.[18,19] Given that most rotavirus vaccines are administered to infants and young children, findings from studies applying this methodology provide valuable information that helps healthcare providers, including pediatricians, stay informed about potential risks they might not have otherwise anticipated. Although further rigorous epidemiological studies are required to confirm these signals, this approach can help identify previously unknown and unexpected safety issues.

In this study, we detected adverse events following rotavirus vaccination in infants using the tree-temporal scan statistics data mining method and identified potential safety signal that could be further investigated in targeted studies.

Materials and methods

Data sources and study population

The study population consisted of infants who received the first dose of rotavirus vaccine within 15 weeks of birth. To identify study population, we utilized a comprehensive database that combined the Korea Disease Control and Prevention Agency (KDCA)'s immunization registry and the National Health Insurance Service (NHIS) claims data.

Republic of Korea operates a national healthcare insurance program covering over 50 million residents. Health care providers provide medical services and claim medical fees to the Health Insurance Review and Assessment (HIRA) service, which reviews these claims and relays the findings to the NHIS.[20] Based on the records, the NHIS pays healthcare providers for medical services and maintains a comprehensive database including information about insurance eligibility, inpatient and outpatient medical services, prescription records, and medical institutions accumulated in the process.[21] Vaccines are not included in the NHIS database as they are not covered by the national health insurance. However, vaccines provided through the NIP are administered free of charge to eligible recipients by the KDCA. Since 2002, information on NIP vaccinations and recipients has been systematically managed and recorded in the KDCA's Immunization Registry Information System.[22]

This study utilized the database linking the KDCA vaccination registry data and the NHIS claims data from June 1, 2016, to December 31, 2022. Rotavirus vaccines administered between June 1, 2016, and October 31, 2022, were included. The two databases were linked using unique resident registration numbers, and researchers accessed the linked anonymized data within the NHIS analysis network.

Exposure and follow-up

An analysis was conducted on RotaTeq and Rotarix, the rotavirus vaccines introduced in the Republic of Korea. Rotarix (RV1), a monovalent vaccine, is recommended to be administered twice at 2 and 4 months of age, while RotaTeq (RV5), a pentavalent vaccine, is recommended to be administered three times at 2, 4, and 6 months of age. We considered the first dose of any type of rotavirus vaccine as the exposure. To avoid exposure misclassification or errors in vaccine administration records, we excluded infants who received rotavirus vaccination after 8 months of age, those with heterologous vaccinations, those with multiple vaccination records for the same dose, and those without rotavirus vaccination records within 15 weeks of birth.

The follow-up period was set from 1 to 56 days after the first dose of the rotavirus vaccine. This period was chosen based on studies of multi-dose vaccines[14,15] to minimize the possibility of time-varying confounding and to prevent overlap with the subsequent recommended dose, which occurs approximately 2 months later. This follow-up period has been validated in previous studies as an appropriate duration for detecting acute adverse events following vaccination, particularly when applying the tree-temporal scan statistic method.[16–18] The day of vaccination was excluded from the follow-up period to account for potential preexisting conditions that might have been diagnosed during the healthcare visit for vaccination.

Hierarchical diagnosis tree and incident outcomes

We identified outcomes using the Korean Standard Classification of Diseases, Seventh Revision (KCD-7) codes, which follow a hierarchical structure.[23] The KCD-7 codes are based on the International Classification of Diseases, Tenth Revision (ICD-10) codes. They have been refined to include subdivided categories for common and rare diseases in Korea, that are identifiable within the classification system.[24] The highest classification level (chapter) consists of 22 categories, with branches extending up to five levels of classification. To avoid detecting clusters that are too broad or too specific, we did not include clusters at level 1 (broadest) and level 5 (narrowest) (Supplementary Figure S1). For this study, we used a tree structure that excluded certain diagnostic codes deemed unrelated to vaccination or biologically implausible to occur within a few weeks post-vaccination (Supplementary Table S1). These excluded codes included those related to cancer, birth defects, external causes or factors of morbidity or health status, and conditions specific to pregnancy and the perinatal period.[15,18]

Only incident diagnoses that were recorded with the primary diagnosis code in an inpatient setting during the follow-up period were included in the analysis. Diagnoses were excluded if the patient had been diagnosed with a code sharing the same first three characters (i.e., the same third level of the tree) in any inpatient or outpatient setting from birth up to the first diagnosis date within the follow-up period. Each patient was allowed to contribute to multiple outcomes during the follow-up period, provided their diagnoses did not fall within the same three levels of the tree.

Risk and control window

The potential risk window for clustering was set to range from a minimum of 2 days to a maximum of 28 days. This window could start anywhere from 1 to 28 days following the first rotavirus vaccination and could end between 2 to 42 days post-

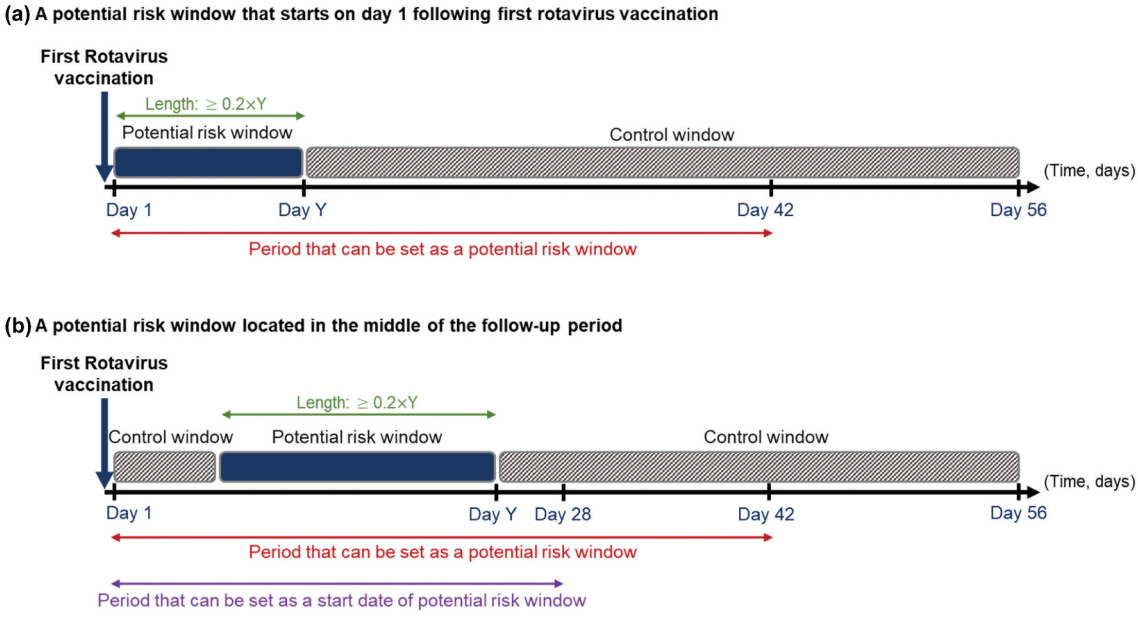


Figure 1. Illustration of risk and control windows for self-controlled tree-temporal tree-based scan statistics analysis.

vaccination. The control window was defined as the remaining period within the follow-up period, excluding each potential risk window. For example, if the risk window was set to days 1–5 following rotavirus vaccination, the control window would automatically be days 6–56 (Figure 1a). Similarly, if the risk window was days 6–30, the control window would be days 1–5 and 31–56 (Figure 1b). To exclude unreliable risk windows, such as short clusters starting long after vaccination, the length of the potential risk window was restricted to at least 20% of the interval between the vaccination date and the end of the risk window.

Statistical analysis

We applied the self-controlled tree-temporal scan statistics, which is based on tree-based scan statistics. This analysis method identifies a wide array of potential adverse events across diverse clinical outcomes and related outcome groups in any potential risk window.[14] This data mining method allows for the detection of potential adverse events with minimal prior assumptions, thereby eliminating the need to pre-specify safety outcome variables.[17] By employing a self-controlled design, the method compares the probability of outcome occurrence over time within individuals, thus controlling for time-invariant potential confounders such as gender, socioeconomic status, and individual chronic predispositions.[18] Under the null hypothesis, the probability of a specific adverse event occurring on any given day within the observation period is considered to be uniform across all time intervals and tree branches.[14] By adjusting for multiple comparisons across diverse conditions and time windows, the method compares the number of cases in the risk window with the number of cases expected by chance in the control window. This approach has been particularly useful in detecting safety signals for various medications, including vaccines.

The self-controlled tree-temporal scan statistics method, adjusted for nodes and time, was used to account for any purely temporal variation in the data that is common to the entire tree.[25] A log-likelihood ratio (LLR)-based test statistics was calculated for each potential adverse event and risk window. To obtain the empirical distribution of the test statistics under the null hypothesis, we generated random datasets[16] and selected the number of Monte-Carlo simulation as 9,999. The pre-specified p-value threshold for statistical significance to identify clusters was set at 0.01. If the test statistics from the real dataset ranked within the top 1% of all datasets, including the random datasets, the null hypothesis was rejected at the $\alpha = 0.01$ level. This conservative approach was employed to minimize false signals further, even though adjustments were already made for multiple comparisons across a large number of clusters. For detected clusters, the attributable risks per 100,000 vaccinees were calculated by dividing the excess number of cases by the total number of doses. The analysis was conducted for all subjects combined, as well as separately for groups divided by sex and type of rotavirus vaccine.

Classification of detected clusters

Statistically significant clusters identified as potential safety signals were categorized to determine whether they represented known or previously unknown adverse events. Each cluster was classified into one of the following categories; (1) Adverse drug reaction (ADR) – the condition is a known adverse event reported from domestic post-marketing surveillance and reexamination of drug labeling, or those listed in sections, such as 'Warnings and Precautions,' 'Adverse Reactions,' or 'Possible Side Effects' in the patient information of U.S. Food and Drug Administration website and package insert; (2) ADR-related event (ADR-r) – the condition is not explicitly noted in the known risk profile, but is clinically considered related to known ADRs; (3) Signal – the condition

is not specifically categorized as ADR or ADR-r. Broader disease categories encompassing the higher classification levels of ADR were classified as ADR-r. Three authors (NYJ, HC, and HK) independently classified statistically significant clusters, and any disagreements were resolved through discussion. In addition to the primary analysis focusing on the first dose, we performed a sensitivity analysis that included all doses up to the third, as long as they were not preceded by a prior dose within 56 days.

The study was approved by the Institutional Review Boards of Ewha Womans University (ewha -202,309-0010-01) and received a waiver of informed consent. All methods were carried out following the relevant guidelines and regulations. The analysis was implemented using SAS enterprise guide version 7.1 (SAS Inc., Cary, NC, USA) and TreeScan software version 2.1.[26]

Results

Characteristics of the study participants

From June 1, 2016, to October 31, 2022, a total of 1,720,778 infants who received the rotavirus vaccine met the eligibility criteria for the study. Among them 87,567 infants were hospitalized with diagnoses corresponding to the hierarchical tree structure during the 1–56 days follow-up period after the first rotavirus vaccination. After excluding those with a history of relevant conditions and those diagnosed with codes excluded from the tree structure 64,752 infants were included as subjects contributing to the incident outcomes of interest (Supplementary Figure 2). Table 1 shows the demographic and vaccination characteristics of the eligible rotavirus vaccine recipients and subjects included in primary analysis. Compared to all eligible subjects, the subjects for primary analysis with hospitalization records during the follow-up period had a higher proportion of males. The year of birth and the year of the first rotavirus vaccination were similarly distributed among the total vaccinated population, except for 2016 and 2022 which showed a dip due to data being limited to June through December and up to October, respectively. The number of vaccinated infants decreased slightly each year after 2017, with a notable drop in post vaccination hospitalizations after 2020, coinciding with the COVID-19 pandemic.

Tree-temporal scan statistical analysis

The tree-temporal scan statistical analysis identified 72,970 incident diagnoses during the follow-up period among the subjects included in the primary analysis, detecting 71 statistically significant clusters (Table 2). Of these, 28 clusters were classified as ADR, 17 as ADR-r, and 26 as Signal.

Clusters classified as ADR comprised unspecified adverse effects such as infection following immunization (KCD-7 code: T88.0, T88.1) occurring within Days 1–2 ($p < .001$) and unspecified viral infection (B34) within Days 1–5 ($p < .001$), and local or systemic adverse effects known to be associated with vaccines such as fever (R50) within Days 1–2 ($p < .001$) and

Table 1. Baseline characteristics of study participants.

Characteristics	Subjects Eligible for Study (N = 1,720,778)	Subjects Included in Primary Analysis (N = 67,772)
Sex, n (%)		
Male	882,168 (51.3)	40,857 (60.3)
Female	838,610 (48.7)	26,915 (39.7)
Year of birth, n (%)		
2016	191,921 (11.2)	8,852 (13.1)
2017	312,237 (18.1)	13,894 (20.5)
2018	291,355 (16.9)	13,556 (20.0)
2019	271,319 (15.8)	11,073 (16.3)
2020	254,341 (14.8)	6,291 (9.3)
2021	242,927 (14.1)	7,780 (11.5)
2022	156,678 (9.1)	6,326 (9.3)
Year of the first rotavirus vaccination, n (%)		
2016	135,171 (7.9)	6,733 (9.9)
2017	316,856 (18.4)	13,916 (20.5)
2018	296,082 (17.2)	13,951 (20.6)
2019	274,489 (16.0)	11,593 (17.1)
2020	258,470 (15.0)	6,504 (9.6)
2021	246,761 (14.3)	7,114 (10.5)
2022	192,949 (11.2)	7,961 (11.8)
Vaccine type (first dose), n (%)		
Rotarix (monovalent)	806,567 (46.9)	31,505 (46.5)
RotaTeq (pentavalent)	914,211 (53.1)	36,267 (53.5)
Vaccine type (second dose), n (%)		
Rotarix (monovalent)	798,544 (46.4)	30,867 (45.5)
RotaTeq (pentavalent)	908,170 (52.8)	35,744 (52.7)
Vaccine type (third dose), n (%)		
Rotarix (monovalent)	0 (0.0)	0 (0.0)
RotaTeq (pentavalent)	881,485 (51.2)	34,214 (50.5)
Fully vaccinated, n (%)		
Yes	1,679,733 (97.6)	65,072 (96.0)
No	41,045 (2.4)	2,700 (4.0)
Concomitant vaccination with other vaccines, n (%)		
Yes	1,617,085 (94.0)	63,592 (93.8)
No	103,693 (6.0)	4,180 (6.2)

Table 2. Clusters of adverse events detected after rotavirus vaccination using tree-temporal scan statistics (total).

KCD-7 code	Adverse Event	Total Number of Cases	Risk Window (Start Day–End Day)	Number of Cases in Risk Window	LLR Test statistics	Attributable Risk per 100,000 Doses	*P*-value	Category*
Certain infectious and parasitic diseases								
A00-A09	Intestinal infectious diseases	5,528	6–7	274	11.50	4.30	0.003	ADR-r
A08	Viral and other specified intestinal infections	2,024	6–7	128	16.15	3.30	<.001	ADR-r
A08.0	Rotaviral enteritis	397	2–7	118	32.51	4.50	<.001	ADR
A30-A49	Other bacterial diseases	7,887	1–20	4,660	255.37	140.00	<.001	Signal
A40	Streptococcal sepsis	40	9–15	24	18.64	1.30	<.001	Signal
A41	Other sepsis	7,019	1–20	4,250	264.30	130.00	<.001	Signal
A41.9	Sepsis, unspecified	3,329	1–20	2,031	129.38	64.00	<.001	Signal
A80-A89	Viral infections of the central nervous system	550	2–21	333	30.32	12.00	<.001	Signal
A87	Viral meningitis	544	2–21	332	31.21	12.00	<.001	Signal
A87.0	Enteroviral meningitis	201	2–21	123	11.67	4.30	0.003	Signal
B15-B19	Viral hepatitis	216	5–9	72	38.68	3.30	<.001	Signal
B17	Other acute viral hepatitis	186	5–9	62	33.30	2.80	<.001	Signal
B17.9	Acute viral hepatitis, unspecified	89	5–9	31	17.63	1.40	<.001	Signal
B19	Unspecified viral hepatitis	24	6–8	10	11.12	0.53	0.005	Signal
B25-B34	Other viral diseases	7,331	1–5	1,412	50.25	23.00	<.001	ADR-r
B25	Cytomegaloviral disease	124	2–7	42	14.85	1.70	<.001	Signal
B25.1	Cytomegaloviral hepatitis	29	2–8	18	12.02	0.93	0.002	Signal
B34	Viral infection of unspecified site	7,177	1–5	1,374	46.87	22.00	<.001	ADR
B34.9	Viral infection, unspecified	2,920	1–5	583	26.02	11.00	<.001	ADR
Diseases of the blood and blood-forming organs								
D65-D69	Coagulation defects, purpura and other hemorrhagic conditions	462	2–5	100	28.74	3.70	<.001	ADR-r
D69	Purpura and other hemorrhagic conditions	455	2–5	98	27.89	3.60	<.001	ADR
D69.3	Idiopathic thrombocytopenic purpura	182	2–6	45	11.90	1.60	0.002	ADR
Endocrine, nutritional and metabolic diseases								
E87	Other disorders of fluid, electrolyte and acid-base balance	34	4–6	12	10.97	0.61	0.006	ADR-r
Diseases of the nervous system								
G00-G09	Inflammatory diseases of the central nervous system	1,213	1–22	797	48.06	26.00	<.001	Signal
G03	Meningitis due to other and unspecified causes	1,062	2–22	654	53.21	22.00	<.001	Signal
G03.9	Meningitis, unspecified	506	2–23	327	27.24	26.00	<.001	Signal
Diseases or symptoms of the respiratory system								
J00-J06	Acute upper respiratory infections	6,180	28–42	1,757	21.73	20.00	<.001	ADR
J02	Acute pharyngitis	1,663	28–42	503	11.61	7.70	0.003	ADR
J09-J18	Influenza and pneumonia	18,827	28–42	5,277	55.90	55.00	<.001	ADR
J12	Viral pneumonia, NEC	3,732	9–19	918	21.44	13.00	<.001	ADR
J12.1	Respiratory syncytial virus pneumonia	1,335	9–19	345	11.78	6.00	0.003	ADR
J18	Pneumonia, organism unspecified	10,150	28–42	2,924	42.52	36.00	<.001	ADR
J18.9	Pneumonia, unspecified	3,857	28–42	1,113	16.28	14.00	<.001	ADR
J20-J22	Other acute lower respiratory infections	16,860	9–28	7,076	94.75	97.00	<.001	ADR-r
J20	Acute bronchitis	2,853	16–29	854	14.76	11.00	<.001	ADR
J21	Acute bronchiolitis	14,001	9–28	5,896	81.43	82.00	<.001	ADR
J21.0	Acute bronchiolitis due to respiratory syncytial virus	1,863	8–17	483	27.13	10.00	<.001	ADR
J21.9	Acute bronchiolitis, unspecified	4,611	9–28	1,882	16.87	22.00	<.001	ADR
J96	Respiratory failure, NEC	158	10–17	48	10.73	1.70	0.008	ADR-r
R06	Abnormalities of breathing	279	6–19	116	11.93	3.50	0.002	ADR
Diseases or symptoms of the digestive system								
K40-K46	Hernia	492	2–17	268	35.87	9.70	<.001	Signal
K40	Inguinal hernia	394	2–17	228	36.70	8.90	<.001	Signal
K55-K64	Other diseases of intestines	1,024	5–7	113	20.27	3.40	<.001	ADR-r
K56	Paralytic ileus and intestinal obstruction without hernia	609	5–6	62	22.90	2.40	<.001	ADR-r
K70-K77	Diseases of liver	314	5–10	140	87.86	6.80	<.001	Signal
K75	Other inflammatory liver diseases	288	4–11	154	81.81	7.50	<.001	Signal
K75.9	Inflammatory liver disease, unspecified	110	5–10	55	39.30	2.80	<.001	Signal
R10-R19	Symptoms and signs involving the digestive system and abdomen	1,322	5–29	729	14.04	14.00	<.001	ADR-r
R11	Nausea and vomiting	763	2–28	501	15.88	14.00	<.001	ADR
Diseases of the skin and subcutaneous tissue								
L50-L54	Urticaria and erythema	245	3–9	80	20.22	3.00	<.001	ADR
L51	Erythema multiforme	80	5–9	34	24.42	1.70	<.001	ADR
L51.9	Erythema multiforme, unspecified	37	5–9	16	11.71	0.80	0.003	ADR
Diseases of the musculoskeletal system and connective tissue								
M30-M36	Systemic connective tissue disorders	1,488	28–42	468	14.74	8.30	<.001	ADR-r
M30	Polyarteritis nodosa and related conditions	1,484	28–42	468	15.03	8.30	<.001	ADR-r
Diseases of the genitourinary system								
N10-N16	Renal tubulo-interstitial diseases	9,770	14–41	5,087	18.59	46.00	<.001	Signal
N10	Acute tubulo-interstitial nephritis	9,192	11–38	4,829	17.81	44.00	<.001	Signal

(*Continued*)

Table 2. (Continued).

KCD-7 code	Adverse Event	Total Number of Cases	Risk Window (Start Day–End Day)	Number of Cases in Risk Window	LLR Test statistics	Attributable Risk per 100,000 Doses	*P*-value	Category*
N30-N39	Other diseases of the urinary system	14,630	27–39	3,510	27.37	31.00	<.001	ADR-r
N39	Other disorders of urinary system	13,102	27–37	2,714	24.31	24.00	<.001	ADR-r
N39.0	Urinary tract infection, site not specified	6,549	27–37	1,357	12.09	12.00	0.002	ADR
Other Adverse Events								
R50-R69	General symptoms and signs	20,305	1–2	3,803	1,212.63	140.00	<.001	ADR-r
R50	Fever of other and unknown origin	18,507	1–2	3,686	1,314.53	140.00	<.001	ADR
R50.2	Drug-induced fever	119	1–2	87	119.76	4.90	<.001	ADR
R50.8	Other specified fever	295	1–2	66	28.10	2.80	<.001	ADR
R50.9	Fever, unspecified	8,840	1–2	1,690	554.71	64.00	<.001	ADR
R90-R94	Abnormal findings on diagnostic imaging and in function studies, without diagnosis	84	6–9	32	26.22	1.60	<.001	Signal
R94	Abnormal results of function studies	72	5–9	36	30.50	1.90	<.001	Signal
R94.5	Abnormal results of liver function studies	33	5–9	18	16.53	0.95	<.001	Signal
T80-T88	Complications of surgical and medical care, NEC	782	1–2	498	625.01	28.00	<.001	ADR-r
T88	Other complications of surgical and medical care, NEC	766	1–2	496	629.79	28.00	<.001	ADR-r
T88.0	Infection following immunization	107	1–2	63	74.65	3.50	<.001	ADR
T88.1	Other complications following immunization, NEC	257	1–2	178	236.48	10.00	<.001	ADR

Abbreviation: KCD-7, Korean standard classification of diseases seventh revision; LLR, log likelihood ratio; NEC, not elsewhere classified; ADR, adverse drug reaction; ADR-r, adverse drug reaction-related event.

*'ADR' refers to known adverse events reported from domestic post-marketing surveillance and reexamination of drug labeling, or those listed in the 'Warnings and Precautions,' 'Adverse Reactions,' or 'Possible Side Effects' sections of the U.S. Food and Drug Administration's patient information and package insert. 'ADR-r' denotes conditions that are not explicitly noted in the established risk profile but are clinically considered related to known ADRs. 'Signal' refers to conditions not specifically categorized as ADR or ADR-r.

urticaria and erythema (L50-L54) within Days 3–9 ($p < .001$). Another significant category of ADR encompassed acute upper respiratory infections (J00-J06) within Days 28–42 ($p < .001$), pneumonia (J09-J18) within Days 9–19 or 28–42 ($p < .001$), acute lower respiratory infections such as bronchiolitis (J21) within Days 8–28 ($p < .001$), intestinal infections or enteritis (A00-A09) within Days 2–7 ($p < .001$), purpura (D69) within Days 2–6 ($p < .001$), vomiting within Days 2–28 ($p < .001$), and urinary tract infection (N39.0) within Days 27–37 ($p = .002$).

The clusters of ADR-r consisted of fluid, electrolyte and acid-base balance disorders(E87) developed in Days 4–6 ($p = .006$), intestinal diseases including diarrhea (K55-K64) in Days 5–7 ($p < .001$), and polyarteritis nodosa and related conditions such as Kawasaki disease (M30) in Days 28–42 ($p < .001$).

Signal clusters included sepsis (A30-A49) within Days 1–20 ($p < .001$), viral meningitis (A87) and unspecified meningitis (G03) within Days 1–23 ($p < .001$), viral hepatitis (B15-B19), inflammatory liver disease (K75), and abnormal function results including liver (R94) within Days 4–11 ($p < .001$), hernia (K40-K46) within Days 2–17 ($p < .001$), and tubulointerstitial nephritis (N10) within Days 11–38 ($p < .001$). These clusters included conditions known to be potentially triggered by rotavirus infection or suggested to be associated with other vaccines. The cytomegaloviral disease (B25) cluster classified as signal was the only signal that was considered biologically implausible.

Stratified analysis by subgroup

Sex-stratified results revealed 51 statistically significant clusters in the 882,168 male rotavirus vaccine recipients and 42 clusters in the 838,610 female recipients (Supplementary Table S2 and S3). Vaccine-stratified results identified 43 statistically significant clusters in the analysis of 806,567 RV1 recipients and 54 clusters in the analysis of 914,211 RV5 recipients (Supplementary Table S4 and 5). Most diseases identified as statistically significant clusters in the analysis for combined subjects were similar to those detected in sex- and vaccine-stratified results. However, in sex-stratified results involving female recipients, clusters related to disorders of other endocrine glands (E20-E35) were detected within Days 17–20 ($p = .007$). These clusters included incident diagnoses of hypofunction and other disorders of the pituitary gland (E23) and other disorders of the adrenal gland (E27), classified as signal. In the vaccine-stratified results for RV1 recipients, an ADR-classified cluster of intussusception (K56.1) within Days 5–8 ($p = .005$) and a ADR-r-classified cluster of diseases of male genital organs (N40-N51) within Days 6–7 ($p < .001$), including penis disorders, were specifically detected. In the results for RV5 recipients, a cluster of burn and corrosion of the hip and lower limb (T24) was specifically detected as signal ($p = .004$) but was considered as biologically implausible.

Sensitivity analysis

In the sensitivity analysis, 4,036,193 doses administered to 1,720,778 rotavirus vaccinees were included. From this, a total of 147,621 incident diagnoses from 127,715 individuals were analyzed, and 70 statistically significant clusters were detected (Supplementary Table 6). Most of these clusters were aligned with the adverse events identified in the primary analysis. However, new clusters classified as ADR were detected, including viral infections characterized by skin (B00-B09) within Days 28–42 ($p = .003$), gastro-esophageal reflux disease (K21) within Days 2–18 ($p = .005$), and unspecified adverse effects of drug, including allergic reactions and

hypersensitivity (T88.7) within Days 1–2 ($p < .001$). Supplementary Table 7 summarizes the detected clusters and the sources that identify these clusters as potential adverse events.

Discussion

This study retrospectively analyzed longitudinal data using the self-controlled tree-temporal scan statistics method to confirm the safety profile of the rotavirus vaccine and to detect previously unknown potential adverse events. The analysis included over 1.7 million infants who received the rotavirus vaccine in South Korea. The primary analysis identified 71 statistically significant temporal clusters without prespecifying type of adverse events or time periods of concern. Of these, 28 clusters classified as ADR were indicated in drug labeling of Korea, U.S. patient information, or package inserts. Seventeen clusters classified as ADR-r were conditions clinically related to ADR based on previous knowledge or conditions classified as ADR in the lower-level diagnosis codes. The clusters identified as signal encompassed 26 clusters involving conditions suggestive of complications from rotavirus infection or immune responses.

The conditions classified as ADRs included disorders such as unspecified viral infections, local or systemic adverse events (e.g., fever), acute upper respiratory diseases (e.g., pharyngitis and pneumonia), and acute lower respiratory infections (e.g., bronchiolitis). These conditions were indicated in the drug labeling in Korea as adverse events reported from randomized clinical trials or domestic surveillance of drug use. Also, this was indicated in the sections, such as 'Adverse Reactions,' or 'Possible Side Effects' of the package insert or patient information in the U.S. FDA website. Notably, intussusception, detected as a cluster through the RV1-stratified analysis and classified as ADR, is known as one of the serious adverse events associated with the rotavirus vaccine. Both RV1 and RV5 are noted for adverse events related to intussusception, and epidemiological studies from various countries indicate an increased risk of intussusception following vaccination with both RV1 and RV5.[11,27] However, some studies suggest that the increased risk may be limited to RV1,[10,28,29] with no evidence supporting a similar risk for RV5.[30,31] This discrepancy suggests that the incidence of intussusception may vary by region and ethnicity, indicating potentially diverse results depending on the study population.

Disorders clinically associated with ADRs, such as electrolyte and fluid balance disorders, intestinal diseases and systemic connective tissue disorders were identified as ADR-r, as their lower-level diagnosis codes were classified as ADR, Disorders related to fluid, electrolyte and acid-base balance, such as hyponatremia, hyperkalemia, and acidosis, may occur in association with the ADRs, such as diarrhea and vomiting following rotavirus vaccination.[32,33] Kawasaki disease (KCD-7 M30.3), also known as mucocutaneous lymph node syndrome and classified under systemic connective tissue disorders, is explicitly mentioned in package inserts and patient information as an adverse event reported in clinical trials and post-marketing surveillance for both RV1 and RV5. Furthermore, concerning diseases of male genital organs identified as clusters in the RV1-stratified analysis, balanoposthitis (KCD-7 N48.1) were listed in the drug labeling in Korea as an unexpected adverse event. Although this is referenced in the RV5 labeling, it is not included in the RV1 documentation. It was classified as an ADR due to its potential association.

Although sepsis was categorized as a signal, rather than an ADR or ADR-r, they have been reported as a complication following rotavirus gastroenteritis[34–36] and they are considered suggestive conditions of rotavirus infection. The exact mechanism by which septicemia develops from rotavirus infection is not fully understood, but it is believed that damage to the intestinal epithelium by the rotavirus allows enteric bacteria to enter the bloodstream, increasing the risk of secondary septicemia.[35] While rotavirus infection most commonly causes gastroenteritis, it also affects other conditions, including central nervous system diseases, hepatobiliary diseases, and respiratory illnesses.[37] To date, no association has been established between rotavirus vaccination and liver diseases, including abnormal liver function, inflammatory liver diseases, or viral hepatitis, which were observed as clusters in this study. However, rotavirus itself can cause significant elevations in liver transaminases, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT),[38,39] and evidence suggests that it may lead to liver dysfunction, including hepatitis, elevated serum sodium, and increased liver transaminases.[40] Additionally, rotavirus has been detected in cerebrospinal fluid in cases of meningitis, indicating the potential for central nervous system complications associated with rotavirus infection.[41–43] Renal tubulo-interstitial diseases, including nephritis, were detected as statistically significant clusters but have not been associated with rotavirus vaccination to date. However, similar cases have been reported following vaccinations like the COVID-19 vaccine.[44,45] Acute interstitial nephritis is often drug-induced through a cell-mediated type Ⅳ hypersensitivity reaction. Some vaccines may trigger acute tubulo-interstitial nephritis by forming immunogenic haptens, which activate the immune response and lead to renal inflammation, as observed in cases of leukocytoclastic vasculitis and other immune cell infiltrations post-vaccination.[46] While no association between rotavirus vaccine and hernia has been established, conditions such as vomiting, which are considered ADRs of rotavirus vaccination, can increase abdominal pressure, potentially contributing to the development of hernia, including inguinal hernia.[47,48]

Cytomegaloviral disease, identified as a cluster in the analysis, is caused by cytomegalovirus and is biologically unrelated to the rotavirus vaccine. However, in cases where pregnant women are infected with cytomegalovirus, transmission to the child during pregnancy or birth is possible,[49] and latent cytomegalovirus infections may be reactivated by immune stimuli such as vaccinations. No direct association has been found between the rotavirus vaccine and burn injuries to the hip and lower limbs, which were identified as a cluster in the RV5-stratified analysis. The rarity of these cases, combined with the delayed diagnosis following vaccination, suggests that this cluster may represent false signals.

The strength of this study lies in its use of hospitalization data for all infants in Korea, making the findings highly

representative and enabling the detection of relatively rare adverse events. Additionally, this study evaluated diverse combinations of vaccine-adverse events without pre-specifying the risk period. However, there are several limitations. First, the outcomes of interest were defined solely by diagnostic codes from claims data, without validation. This may have led to the inclusion of individuals who did not actually experience the disease or the exclusion of those who did, introducing potential misclassification bias and affecting internal validity. To draw causal inferences, it is crucial to evaluate the validity of the operational definitions and apply robust epidemiological study designs. Furthermore, as this study focused on the entire infant population in Korea, caution should be exercised when generalizing the findings to other countries or populations. Second, those with an increased risk of long-term adverse events or with a constant risk throughout the follow-up period may not have been detected. Considering the significant differences in health conditions among children of varying age, a relatively short follow-up period of 56 days was set to minimize time-varying confounding. Consequently, long-term adverse events may not have been identified as statistically significant clusters in this study. Third, the study only included data from hospitalized patients, which could have led to the exclusion of less severe adverse events. As of 2021, the annual average number of outpatient care consultations per capita in Korea was 15.7, the highest among the OECD nations, whose average was 5.9.[50] To prevent excessive detection of false signals and focus on identifying more severe adverse events, only inpatient data were included in the analysis. Fourth, the impact of other concomitant vaccines recommended for the study population at the same age was not considered. Given the large numbers and varieties of NIP vaccines co-administered with rotavirus vaccines (e.g., diphtheria, tetanus toxoids, and acellular pertussis [DTaP] vaccine, pneumococcal conjugate vaccine, and polio vaccine), further research is needed to assess their impact on safety. Fifth, while the administrative data used in this study provide vaccination and diagnostic records, potential errors in exposure and outcome information cannot be completely excluded. Additionally, the cases included in the analysis were not limited to those with confirmed causal relationships with vaccination. This means that some cases occurring close in time to vaccination may have been coincidental, potentially leading to an overestimation of event incidence. Consequently, this study is limited to identifying signals of increased occurrences following rotavirus vaccination. Further studies specifically designed to evaluate causality are needed to thoroughly investigate these findings and draw definitive conclusions. Lastly, this study applied a hypothesis-generating method based on the self-controlled tree-temporal scan statistics. Therefore, causal conclusions cannot be drawn without a rigorous evaluation of the specific hypothesis that the exposure is associated with an increased risk of the outcome identified as signal.

In conclusion, this study used the tree-temporal scan statistics method to detect safety signals, including a number of well-known adverse events, which show consistency with the previously known risk profiles. We also identified unknown but biologically plausible events associated with immune response or complications following the rotavirus vaccination. The conditions detected as statistically significant signals may be considered as priority outcomes for evaluating potential associations with the rotavirus vaccine. Among over 1.7 million infants who received the rotavirus vaccine, only 87,567 were hospitalized during the follow-up period, regardless of whether the hospitalization was vaccine-related or incidental. This finding underscores the rarity of severe adverse events associated with rotavirus vaccination, further supporting the vaccine's robust safety profile.

Implementation of this screening approach for safety signal detection can provide timely access to the best available evidence on the safety of medications, especially for vaccines targeting broad population. This approach offers comprehensive information on potential safety concerns, particularly for healthcare providers and caregivers who administer vaccines to children to be informed about issues that may require special caution. However, the tree-temporal scan statistics serves only as the first step in vaccine active surveillance to detect potential adverse events among the thousands of potential events and risk windows. Therefore, safety signals detected from the analysis need further investigation through epidemiological studies and validated operational outcome definitions to confirm causal relationship between rotavirus vaccination and the events.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the Korea Disease Control and Prevention Agency (KDCA) and the National Health Insurance Service (NHIS). However, access can be limited, since these data are not publicly available. Data can be obtained from the authors upon reasonable request and with permission of the KDCA and NHIS.

Code availability

All code used in this study are available from the corresponding author on reasonable request.

Author contributions statement

N.Y.J. and N.K.C. contributed to the conception and design of the study. N.Y.J. conducted statistical analysis and drafted the original manuscript writing. H.C. and H.J.K. contributed to interpreting the results and editing the manuscript. N.Y.J. and H.C. accessed and verified the data. N.K.C. reviewed the manuscript and obtained the funding. All authors read and approved the final manuscript.

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