Original Article
Yonsei Med J 2020 Mar;61(3):243-250
https://doi.org/10.3349/ymj.2020.61.3.243
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Signal Detection of Adverse Events Following Pneumococcal Vaccines from the Korea Adverse Event Reporting System Database, 2005–2016

Kwan Soo Kim[1], In-Sun Oh[2], Hyun Jeong Kim[2], Inmyung Song[3], Min Soo Park[1,4], and Ju-Young Shin[2]

[1]Department of Pharmaceutical Medicine and Regulatory Sciences, Yonsei University Graduate School, Seoul;
[2]School of Pharmacy, Sungkyunkwan University, Suwon;
[3]College of Nursing and Health, Kongju National University, Gongju;
[4]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea.

Purpose: We aimed to analyze the surveillance reports of adverse events (AEs) due to different types of pneumococcal vaccines, in addition to detecting and validating signals of pneumococcal vaccines by comparing AEs with labels.
Materials and Methods: We analyzed the percentages of AEs according to vaccine type [pneumococcal polysaccharide vaccines (PPSVs) and pneumococcal conjugate vaccines (PCVs)] in children and adults using data from the Korea Adverse Event Reporting System (KAERS) database from 2005 to 2016. A signal was defined as an AE that met all three indices of data mining: proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC). We validated the detected signals by calculating sensitivity, specificity, as well as positive and negative predictive values of the signals against label information.
Results: Of the 39933 AE reports on vaccination, 5718 (7.0%) were related to pneumococcal vaccine. The most frequent AE after vaccination with PPSV was fever (23.9%) in children and injection-site reaction in adults. The most frequent AE after vaccination with PCV in children was pharyngitis (26.2%). In total, 13 AEs met all three indices for signal detection. Among these, hypotension, apathy, sepsis, and increased serum glutamic oxaloacetic transaminase level were not listed on vaccine labels. In validation analysis, PRR and ROR performed slightly better than IC for adults who were vaccinated with PPSVs.
Conclusion: Overall, 13 new signals of PPSVs, including four signals not listed on the labels, were detected. Further research based on additional AE reports is required to confirm the validity of these signals for children.

Key Words: Signal detection, pneumococcal vaccines, data-mining, KAERS database

INTRODUCTION

Pneumonia was the fourth leading cause of mortality in South Korea in 2017, and *Streptococcus pneumonia* was the leading cause of bacterial pneumonia.[1,2] Despite the use of antibiotics and intensive care over the past 50 years, the case fatality rate of pneumococcal bacteremia has remained at 15–20% in children and young adults, and at 30–40% in the elderly.[3-5] Moreover, the rates of antimicrobial resistance in various pneumococci have been steadily increasing. Under these circumstances, vaccination has become the most cost-effective way to prevent pneumococcal infections.[6] The two main types of pneumococcal vaccines are 23-valent pneumococcal polysaccharide vaccines (PPSVs) and pneumococcal conjugate vaccines (PCVs), in which polysaccharides are conjugated to a protein.[7] The National Immunization Program (NIP) of South Korea introduced 23-valent PPSVs in 2013 for people aged 65 years and older,[8] and PCVs in 2014 for children under 5 years of age.[9] The expansion of NIP appears to have benefited both children

Received: September 3, 2019 **Revised:** January 8, 2020
Accepted: January 16, 2020
Co-corresponding authors: Min Soo Park, MD, PhD, Department of Pharmaceutical Medicine and Regulatory Sciences, Yonsei University Graduate School and Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2019-3351, Fax: 82-2-3461-9473, E-mail: minspark@yuhs.ac and
Ju-Young Shin, PhD, School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon 16419, Korea.
Tel: 82-31-290-7702, Fax: 82-31-292-8800, E-mail: shin.jy@skku.edu

•The authors have no potential conflicts of interest to disclose.

and adults in recent years; in 2017, more than 2 million doses of pneumococcal vaccines have been administered to both adults and children.[10]

Amidst the widespread use of pneumococcal vaccines, it would be interesting to analyze the difference in adverse events (AEs) between the two types of vaccines. While the most common adverse reactions after receiving PPSVs were local reactions, such as injection-site pain (soreness, tenderness) (60%), local swelling or induration (20.3%), headache (17.6%), local erythema (16.4%), asthenia and fatigue (13.2%), and myalgia (6.1%), less than 1% of the recipients developed fever or more severe local reactions.[11] In comparison, injection-site reactions (erythema) occurred in approximately 10% of PCV recipients, and there may have been an increase in milder injection-site reactions with subsequent doses in older age groups (12–15 months of age).[12] Overall, there was no difference between PCVs and PPSVs in terms of the incidence of serious adverse events (SAEs) reported within 1 month of an initial study dose. While these aforementioned studies evaluated the immunogenicity and safety of PPSVs and PCVs in adults who were older than 65 years, these studies were limited in that they were randomized clinical trials involving only 1000 older patients.[13,14] Therefore, the objective of this study is to analyze AEs after vaccination with different types of pneumococcal vaccines (PPSVs and PCVs) using a spontaneous AE reporting system, and to determine the signals of pneumococcal vaccines by comparing the identified signals with data on vaccine labels in South Korea.

MATERIALS AND METHODS

Data sources

The spontaneous AE reporting system was first introduced in South Korea in 1988 when the Ministry of Food and Drug Safety started collecting spontaneous AE reports. In 2012, the Korea Institute of Drug Safety and Risk Management (KIDS) developed the Korea Adverse Event Reporting System (KAERS) to facilitate computerized reporting and management of AE reports.

Data on the AEs of pneumococcal vaccines were taken from KAERS. The KAERS database contained a total of 39933 reports on AEs after vaccination with pneumococcal vaccines from January 2005 to December 2016. We classified all reported AEs into two subgroups: AEs after receiving PPSVs and those after receiving PCV. We then calculated the percentage of AEs according to vaccine type by dividing the number of AEs after receiving each vaccine type (i.e., PPSV and PCV) by the number of AEs after receiving all vaccines, and analyzed the temporal trends of AEs according to the year from 2005 and 2016. We excluded cases without basic patient data, such as age.

Definition of covariates

When comparing the AEs between PPSVs and PCVs, we included a number of covariates such as age, sex, type of reporter, SAE, and degree of causality. Age was divided into following groups: children aged 0 to 18 years and adults aged ≥19 years for PPSVs, and only children aged 0 to 18 years for PCVs. This was because there was only a single case of AE after receiving PCVs in an adult aged over 18 years in our data. As a result, we could not compare AEs in adults between PPSVs and PCVs. Reporters of AEs were categorized into four groups: physician, pharmacist, nurse, and consumer. SAEs were classified into death and non-fatal categories. The degree of causality was classified into seven terms: certain, probable, possible, unlikely, unclassified, unassessable, and not applicable. This categorization was based on the "World Health Organization-Uppsala Monitoring Centre System for standardized case causality assessment."[15]

Coding of AEs

All drug names in the database were coded using the Anatomical Therapeutic Chemical classification system, and AEs were coded using the World Health Organization Adverse Reaction Terminology (WHO-ART, ver. 092). The WHO-ART, developed to serve as a terminology for coding adverse reaction terms, covers most medical terms needed in AE reporting. Following a hierarchical structure, WHO-ART uses system-organ classes and preferred terms as the main and sub-categories, respectively. Symptoms that matched the same preferred terms were treated as the same event. Two or more preferred terms reported for one patient were counted as different vaccine AEs. According to the WHO criteria, SAEs were defined as one of three cases: fatal, causing hospitalization or persistent disability, and life-threatening.

Signal detection and validation

In pharmacovigilance analyses, data mining is a process of detecting signals to find statistical associations and patterns between drugs and AEs in a large database. Three indicators are used to detect signals from spontaneously reported data: proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC). PRR is the proportion of specific AEs for a particular vaccine divided by the proportion of specific AEs for other vaccines. ROR is calculated by dividing the odds of target AEs for patient exposure to a specific vaccine by those for exposure to other vaccines. For PRR and ROR, a signal is detected if PRR and ROR values are 2 or higher, χ^2 (chi-squared) values are 4 or higher, and the number of occurrences is 3 or greater. IC is a logarithmic metric of the value calculated by dividing the probability of target AEs associated with a target vaccine with the probability of all AEs associated with all vaccines in the database.[16] It is given by a Bayesian confidence propagation neural network. The IC criterion was set at the lower limit of 95% confidence interval greater than 0. A

https://doi.org/10.3349/ymj.2020.61.3.243

signal was defined as the AE that met all three indices of PRR, ROR, and IC.

The detected signals for each vaccine were compared with the information on vaccine labels in South Korea to determine whether the signal was listed on the vaccine label. Assuming the AE listed on the vaccine label is a true value, we examined how accurately the signal detected by data mining discriminated the known AE on the label. The detected signals were validated by calculating four indicators: sensitivity, specificity, positive predictive value, and negative predictive value.

Statistical analysis

We calculated the frequency and percentage (%) of all categorical variables. The Cochran-Mantel-Haenszel chi-squared test was used to compare the demographic characteristics. For testing the difference in proportions, we conducted the exact two-sided chi-squared test based on the test score.[17] All variables were considered statistically significant if the *p*-value was lower than 0.05. SAS (Windows version 9.30, SAS Institute Inc., Cary, NC, USA) and Excel 2013 (Microsoft Corp., Redmond, WA, USA) were used to create a dataset and perform all statistical procedures.

RESULTS

Among the patients vaccinated with PPSVs, females accounted for 62.3% (n=820) of the adult population and 44.9% (n=801) of the children population (Table 1). An equal number of male and female children was vaccinated with PCVs. Physicians reported 47.9% and 80.9% of AEs in adults and children vaccinated with PPSVs, respectively. Moreover, 0.5% (n=6) of adults and 0.9% of children (n=16) died after receiving PPSVs. Among the patients vaccinated with PPSVs, 2.9% and 16.2% of AEs were unlikely to be caused in adults and children, respectively; the causality of another 2.7% and 12.0% of AEs, respectively, was not assessable. Among the children vaccinated with PCVs, 2.4% of AEs were assessed to be possible to have been caused by the vaccines, and the causality of another 0.4% and 0.0% of AEs was assessed as probable and certain, respectively. Most (89.2%) of the adults who were vaccinated with PPSVs received only one pneumococcal vaccine, whereas 56.7% and 47.8% of the children who were vaccinated with PPSV and PCV, respectively, received another vaccine. The median interval between vaccination date and onset date of AEs was 7, 320, and 532.5 days for adults and children receiving PPSVs and children receiving PCV, respectively.

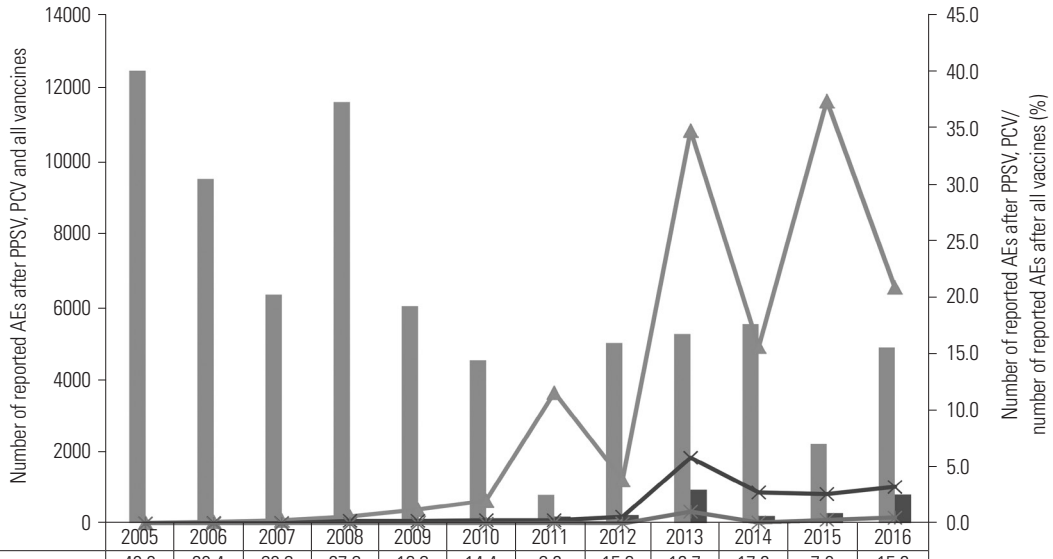
Of all the 39933 AE reports after pneumococcal vaccination, 5718 (14.3%) AEs were pneumococcal vaccine-related (Fig. 1). Injection-site reaction was the most common AE in adults vaccinated with PPSVs, accounting for 25.0% of all AEs. Respiratory system disorders, as a category, were the most frequent AEs in children vaccinated with PPSVs or PCVs (Table 2). Fever occurred frequently in both children and adults vaccinated with PPSVs, accounting for 23.9% and 18.4% of AEs, respectively. The most frequent AE occurring in children after receiving PCVs was pharyngitis (26.2%), followed by rhinitis (23.2%).

We summarized the AEs to compare the signals obtained through this study and labels in Tables 3, 4, and 5. In this study, signals were considered meaningful when all three criteria were significant. These signals were detected only in patients vaccinated with PPSVs. In the case of adults vaccinated with PPSVs, the most frequently reported AEs, such as injection-site reaction and fever, were labeled and represented as signals (Table 3). However, in the case of children vaccinated with PPSVs, the frequently reported respiratory system disorders, such as pharyngitis and rhinitis, were not mentioned on the labels and

Table 1. Demographic Characteristics of PPSV and PCV Recipients Whose Adverse Events Were Reported to the Korea Adverse Event Reporting System (KAERS), 2005–2016

	PPSV		PCV	
	Adults (n=1317)	Children (n=1784)	Children (n=500)	*p* value*
Age (yr)				<0.001
0–18	0 (0.0)	1784 (100.0)	500 (100.0)	
≥19	1317 (100.0)	0 (0.0)	0 (0.0)	
Sex				
Male	474 (36.0)	927 (52.0)	248 (49.6)	<0.001
Female	820 (62.3)	801 (44.9)	248 (49.6)	<0.001
Missing	23 (1.7)	56 (3.1)	4 (0.8)	0.002
Type of reporter				
Physician	631 (47.9)	1444 (80.9)	480 (96.0)	<0.001
Pharmacist	40 (3.0)	9 (0.5)	1 (0.2)	<0.001
Nurse	121 (9.2)	67 (3.8)	5 (1.0)	<0.001
Consumer	127 (9.6)	41 (2.3)	3 (0.6)	<0.001
Other	323 (24.5)	178 (10.0)	11 (2.2)	<0.001
Missing	75 (5.7)	45 (2.5)	0 (0.0)	<0.001
Serious adverse event				<0.001
Death	6 (0.5)	16 (0.9)	0 (0.0)	
Non-fatal	232 (17.6)	120 (6.7)	13 (2.6)	
Degree of causality				
Certain	91 (6.9)	71 (4.0)	0 (0.0)	<0.001
Probable	146 (11.1)	65 (3.6)	2 (0.4)	<0.001
Possible	316 (24.0)	105 (5.9)	12 (2.4)	<0.001
Unlikely	38 (2.9)	289 (16.2)	226 (45.2)	<0.001
Unclassified	93 (7.1)	96 (5.4)	27 (5.4)	0.125
Unassessable	36 (2.7)	214 (12.0)	52 (10.4)	<0.001
Missing	597 (45.3)	944 (52.9)	181 (36.2)	<0.001
Received one vaccine	1175 (89.2)	773 (43.3)	261 (52.2)	<0.001
Median interval (days)	7	320	532.5	

PPSV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine.
Data are presented as number (%).
*Compared by Cochran-Haenszel chi-squared test.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
% of PPSV	40.0	30.4	20.2	37.2	19.2	14.4	2.6	15.9	16.7	17.6	7.0	15.6
% of PCV	0.0	0.0	0.0	0.0	0.0	0.3	0.6	0.7	3.0	0.7	0.9	2.6
Number of reported AEs after all vaccines	20	46	89	196	385	631	3597	1204	10801	4861	11613	6490
Number of reported AEs after PPSV	8	14	18	73	74	91	92	192	1808	857	817	1011
Number of reported AEs after PCV	0	0	0	0	0	2	22	9	324	33	106	167

Fig. 1. Trends in reported AEs after vaccination with PPSV and PCV compared to reported AEs after vaccination with all vaccines from KIDS database in 2005–2016. AE, adverse event; PPSV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; KIDS, Korea Institute of Drug Safety and Risk Management.

Table 2. Comparison of Adverse Events Reported to KAERS after Receiving PPSV and PCV, 2005–2016

Adverse event	PPSV		PCV	*p* value*
	Adults (n=1317)	Children (n=1784)	Children (n=500)	
Body as a whole-general disorder				
Fever	328 (18.4)	426 (23.9)	60 (12.0)	<0.001
Crying abnormally	0 (0.0)	121 (6.8)	23 (4.6)	0.077
Respiratory system disorder				
Pneumonia	27 (1.5)	132 (7.4)	57 (11.4)	0.006
Pharyngitis	29 (1.6)	360 (20.2)	131 (26.2)	0.005
Upper respiratory tract infection	9 (0.5)	268 (15.0)	91 (18.2)	0.095
Rhinitis	9 (0.5)	263 (14.7)	116 (23.2)	<0.001
Coughing	21 (1.2)	164 (9.2)	63 (12.6)	0.028
Bronchitis	2 (0.1)	137 (7.7)	64 (12.8)	0.001
Psychiatric disorder				
Nervousness	0 (0.0)	223 (12.5)	60 (12.0)	0.818
Gastro-intestinal system disorder				
Vomiting	35 (2.0)	148 (8.3)	44 (8.8)	0.716
Diarrhea	30 (1.7)	120 (6.7)	49 (9.8)	0.026
Gastroenteritis	3 (0.2)	77 (4.3)	37 (7.4)	0.007
Skin and appendages disorder				
Rash	66 (3.7)	78 (4.4)	20 (4.0)	0.803
Dermatitis	1 (0.1)	51 (2.9)	18 (3.6)	0.378
Application site disorder				
Injection-site reaction	446 (25.0)	39 (2.2)	8 (1.6)	0.480
Resistance mechanism disorder				
Otitis media	0 (0.0)	74 (4.1)	34 (6.8)	0.017

KAERS, Korea Adverse Event Reporting System; PPSV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine.
*Compared by exact two-sided chi-squared test based on the test score.

not detected as signals (Table 4).

A total of 13 AEs after pneumococcal vaccination met the criteria of three data mining indices for signal detection. Twelve AEs reported for adults vaccinated with PPSVs satisfied all three indices for signal detection; three AEs (hypotension, sepsis, and apathy) were not listed on the vaccine label (Table 3). In the case of children vaccinated with PPSVs, only one AE [increased serum glutamic oxaloacetic transaminase (SGOT) level] satisfied all three indices, and it was not listed on the vaccine label (Table 4). No AE satisfied the criteria for signal detection in children vaccinated with PCVs (Table 5).

The results of validation analysis show that PRR and ROR had a sensitivity ranging from 0% to 40% and a specificity from 66.7% to 100% (Table 6). IC had a sensitivity ranging from 0% to 36% and a specificity from 0% to 100%. For adults vaccinated with PPSVs, PRR and ROR indices performed better than IC, albeit slightly. However, in comparing the signals for children, the results were not significant as there were cases of these indices having a value of 0.

DISCUSSION

This study represents a post-marketing safety review of pneumococcal vaccines based on AE reports in KAERS database between 2005 and 2016. The most common AE was pharyngitis in children vaccinated with PCVs and injection-site reaction in adults vaccinated with PPSVs. These results were consistent with the data on labels of PPSVs and PCVs.[18-21] Respiratory

https://doi.org/10.3349/ymj.2020.61.3.243

Table 3. Signals of Adverse Events Related to PPSVs in Adults Aged ≥19 Years Detected by Data Mining and the Presence of Information on Vaccine Label, 2005–2016

Adverse event	No. of reports	PRR	ROR	IC 95% LCI	Label*	Signal detection
Injection-site reaction	446	4.03	4.50	1.34	Y	Y
Fever	328	3.06	3.28	1.06	Y	Y
Injection-site pain	323	0.52	0.47	-1.02	Y	N
Myalgia	210	0.87	0.86	-0.38	Y	N
Injection-site rash	188	1.82	1.87	0.48	Y	N
Cellulitis	70	15.37	15.68	1.91	Y	Y
Rash	66	1.55	1.56	0.15	Y	N
Rigors	61	0.89	0.88	-0.52	Y	N
Rash erythematous	50	3.57	3.61	0.94	Y	Y
Dizziness	48	0.76	0.75	-0.76	Y	N
Headache	44	0.36	0.35	-1.74	Y	N
Pain	41	0.83	0.83	-0.68	Y	N
Nausea	38	0.64	0.63	-1.03	Y	N
Edema	37	2.23	2.24	0.43	Y	Y
Vomiting	35	0.95	0.95	-0.55	Y	N
Asthenia	31	0.89	0.89	-0.65	Y	N
Urticaria	30	0.85	0.85	-0.71	Y	N
Dyspnea	30	1.83	1.83	0.17	N	N
Injection-site mass	29	0.99	0.99	-0.53	Y	N
Pneumonia	27	9.76	9.84	1.46	Y	Y
Injection-site infection	24	7.38	7.42	1.27	Y	Y
Allergic reaction	22	3.07	3.09	0.60	Y	Y
Coughing	21	0.92	0.92	-0.70	N	N
Chest pain	20	1.86	1.87	0.08	N	N
Fatigue	11	0.09	0.08	-4.07	Y	N
Hypotension	10	2.28	2.28	0.06	N	Y
Sputum increased	7	2.15	2.15	-0.13	N	N
Apathy	6	4.61	4.62	0.42	N	Y
Vision abnormal	6	1.94	1.94	-0.29	N	N
Conjunctivitis	5	1.54	1.54	-0.59	N	N
Leukocytosis	5	7.68	7.68	0.61	Y	Y
Sepsis	5	6.15	6.16	0.50	N	Y
Angioedema	4	1.54	1.54	-0.67	Y	N
Hyperpyrexia	4	2.46	2.46	-0.24	Y	N
Neuritis	3	0.28	0.27	-2.80	N	N
Urine abnormal	1	3.07	3.07	-0.66	N	N
Breast pain	1	3.07	3.07	-0.66	N	N

PPSVs, pneumococcal polysaccharide vaccines; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval.
*Y: AE was listed on the vaccine label, N: AE was not listed on the vaccine label.

disorders, such as pharyngitis and rhinitis, in children receiving PCVs were mentioned on the vaccine labels in South Korea based on reassessment results. The result that injection-site reaction was the most frequent AE in adults after receiving PPSVs was consistent with the findings of previous studies.[22-24]

A controlled clinical trial involving adults reported that the degree of injection-site pain was higher for 23-valent PPSVs than for 13-valent PCVs, but there was no difference in the percentage of systemic AEs.[14] However, a safety profile comparison would yield different results according to research conditions and target patients. Our comparison of AE reports showed that the proportion of SAEs reported among children was similar for both PPSVs and PCVs. However, cases of death were only reported for PPSVs. In PPSV group, SAEs were reported for a greater proportion of adults than that of children (18.1% and 7.6%, respectively). Most adults (89.2%) received only one vaccine whereas 56.7% and 47.8% of the children vaccinated with PPSVs and PCVs, respectively, received other

Table 4. Signals of Adverse Events Related to PPSVs for Children Aged 0–18 Years Detected by Data Mining and the Presence of Information on Vaccine Label, 2005–2016

Adverse event	No. of reports	PRR	ROR	IC 95% LCI	Label*	Signal detection
Fever	426	1.32	1.36	0.17	Y	N
Diarrhea	120	1.20	1.21	-0.06	N	N
Rash	78	1.41	1.41	0.06	Y	N
Conjunctivitis	33	1.57	1.58	0.01	N	N
Injection-site infection	26	0.72	0.72	-0.95	Y	N
Urinary tract infection	25	1.23	1.23	-0.32	N	N
Injection-site pain	8	0.08	0.07	-4.31	Y	N
Infection viral	7	0.76	0.76	-1.26	N	N
Melaena	6	1.48	1.48	-0.58	N	N
Cellulitis	4	0.59	0.59	-1.75	Y	N
SGOT increased	3	16.28	16.29	0.43	N	Y
Hyperpyrexia	3	0.32	0.32	-2.59	Y	N
Intestinal obstruction	2	0.78	0.78	-1.63	N	N
Enterocolitis	2	2.71	2.71	-0.53	N	N
Bradycardia	1	2.71	2.71	-0.82	N	N
SGPT increased	1	5.43	5.43	-0.54	N	N
Apnea	1	1.81	1.81	-1.05	N	N
Respiratory insufficiency	1	5.43	5.43	-0.54	N	N

PPSVs, pneumococcal polysaccharide vaccines; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
*Y: AE was listed on the vaccine label, N: AE was not listed on vaccine label.

Table 5. Signals for Adverse Events of PCVs in Children Aged 0–18 Years Detected by Data Mining and the Presence of Information on Vaccine Label, 2005–2016

Adverse event	No. of reports	PRR	ROR	IC 95% LCI	Label*	Signal detection
Fever	60	0.57	0.55	-1.14	Y	N
Skin disorder	4	1.26	1.26	-0.72	Y	N
Rash erythematous	3	0.36	0.36	-2.49	Y	N
Sweet's syndrome	2	20.17	20.2	1.56	N	N

PCVs, pneumococcal conjugate vaccines; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval.
*Y: AE was listed on the vaccine label, N: AE was not listed on vaccine label.

Table 6. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for Each Index Following PPSV in Adults Aged ≥19 Years, and PPSV and PCV in Children aged 0–18 Years, 2005–2016.

Vaccine	Index	Known AEs			Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
			Yes	No				
PPSV in adults	PRR, ROR	Yes	10	4	40.0	66.7	71.4	34.8
		No	15	8				
	IC	Yes	9	5	36.0	58.3	64.3	30.4
		No	16	7				
PPSV in children	PRR, ROR	Yes	0	1	0.0	91.7	0.0	64.7
		No	6	11				
	IC	Yes	2	0	33.3	100.0	100.0	73.3
		No	4	11				
PCV in children	PRR, ROR	Yes	0	0	0.0	100.0	N/A	25.0
		No	3	1				
	IC	Yes	0	1	0.0	0.0	0.0	0.0
		No	3	0				

PPSV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; AE, adverse event; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval; N/A, not applicable.

https://doi.org/10.3349/ymj.2020.61.3.243

vaccines. Nonetheless, the percentage of AEs, for which the degree of causality was assessed to be more than possible, was higher for adults than for children. Our findings suggest that SAEs after pneumococcal vaccination are more frequent and probably more causal in adults than in children.

We identified 13 new signals for which all three of the data mining methods used (PRR, ROR, and IC) indicated significant results. Among these, four AEs (hypotension, apathy, sepsis, and increased SGOT level) after PPSV administration were not listed in the approved label. Hypotension and apathy after receiving PPSV have not been reported in South Korea or elsewhere, suggesting the need for further studies. Several cases of sepsis were reported after pneumococcal vaccination; however, they were presumed to have been caused not by the vaccination itself, but by the weakened immunity of the patients.[25] Our finding of increased SGOT level was consistent with the finding of a previous study, which showed that elevated C-reactive protein level after vaccination may cause an increase in the serum level of hepatic enzymes.[26] According to the results of our validation analysis, PRR and ROR were slightly better than IC for adults vaccinated with PPSVs. The same results could not be obtained for children due to the existence of 0 values for these indices in some cases. A future study with more cases is needed to determine which indicator is appropriate for signal detection in children.

In our data, pneumonia was reported in both adults and children who were vaccinated with pneumococcal vaccines. Although the labels of pneumococcal vaccines list pneumonia as one of the AEs, they only refer to pneumonia caused by serotypes that are not included in the vaccine. The actual case of compensation for the occurrence of pneumonia was rejected since the vaccine did not cause systemic infections.[27] Therefore, in order to establish the causality between pneumococcal vaccination and pneumonia, recipients experiencing pneumonia after vaccination should be followed up for serological studies.

To date, there has been no epidemiological study on AEs due to pneumococcal vaccinations in South Korea. To the best of our knowledge, this study is the first to detect signals of AEs after pneumococcal vaccinations by mining KAERS data. The KAERS database contains AE data and reassessment results collected from 27 local monitoring centers in South Korea. In order to increase the rigor of the current study, we used three different data mining methods to detect and validate signals after pneumococcal vaccinations. Due to these strengths, the findings of this study may be useful for analyzing post-marketing AEs of pneumococcal vaccines.

However, this study had a few limitations. The limitations with spontaneous reporting data used in this study include underreporting, inconsistent quality of reports (for example, reports may lack details and important information or contain errors), and the lack of non-vaccinated control groups.[28] Furthermore, the data we used did not provide information about other underlying diseases affecting patients or their recovery from SAEs. Therefore, additional studies, including literature reviews, randomized clinical trials, and cohort studies, are required to assess the causality. Moreover, KAERS data did not provide the specific brand names of the vaccines. As a result, AE data were analyzed based on vaccine type (PPSVs and PCVs) only. Finally, although PCVs are currently used for both adults and children, we could not compare the safety profiles of PCVs between adults and children, since only a single case of AE in an adult after receiving PCV was reported in 2016. Further research based on recent data is required to compare the AEs between children and adults after receiving PCVs. Even for children who received PCVs, no significant difference was observed between signal information obtained from our data and the approved label. Addressing the deficiencies highlighted in this study could lead to better management of AE cases in the future.

In conclusion, we identified 13 new signals of PPSVs for which all three data mining methods of PRR, ROR, and IC indicated significant results. Among these, four signals (i.e., hypotension, apathy, sepsis, and increased SGOT level) were not listed in the approved vaccine label. The results of our validation analysis showed that PRR and ROR were slightly better than IC for adults vaccinated with PPSVs, although the same results could not be obtained in children. A future study based on a larger number of AE reports is needed to confirm the validity of the detected signals for children receiving pneumococcal vaccination.

ACKNOWLEDGEMENTS

We would like to thank the staff of the Korea Institute of Drug Safety and Risk Management for providing access to the Korea Adverse Event Reporting System (KAERS) database.

This Study was supported by a Government-wide R&D Fund project for 212 infectious disease research (Grant no. HG18C 0068).

AUTHOR CONTRIBUTIONS

Conceptualization: Kwan Soo Kim, Min Soo Park, and Ju-Young Shin. Data curation: Kwan Soo Kim and In-Sun Oh. Formal analysis: In-Sun Oh. Supervision: Min Soo Park and Ju-Young Shin. Writing—original draft: Kwan Soo Kim. Writing—review & editing: Kwan Soo Kim, Hyun Jeong Kim, Inmyung Song, Min Soo Park, and Ju-Young Shin. Approval of final manuscript: all authors.

ORCID iDs

Kwan Soo Kim https://orcid.org/0000-0002-9412-4789
In-Sun Oh https://orcid.org/0000-0001-9878-4779
Hyun Jeong Kim https://orcid.org/0000-0003-3183-7199
Inmyung Song https://orcid.org/0000-0001-7772-6617
Min Soo Park https://orcid.org/0000-0002-4395-9938
Ju-Young Shin https://orcid.org/0000-0003-1010-7525

REFERENCES

1. Statistic Korea. Causes of death statistics in 2017 [accessed on 2019 September 19]. Available at: http://kostat.go.kr/portal/eng/pressReleases/8/10/index.board?bmode=read&bSeq=&aSeq=371140&pageNo=1&rowNum=10&navCount=10&currPg=&searchInfo=&sTarget=title&sTxt=.
2. File TM Jr. Streptococcus pneumoniae and community-acquired pneumonia: a cause for concern. Am J Med 2004;117 Suppl 3A:39S-50S.
3. Schrag SJ, Beall B, Dowell SF. Limiting the spread of resistant pneumococci: biological and epidemiologic evidence for the effectiveness of alternative interventions. Clin Microbiol Rev 2000;13:588-601.
4. Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med 2000;343:1917-24.
5. McCormick AW, Whitney CG, Farley MM, Lynfield R, Harrison LH, Bennett NM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nat Med 2003;9:424-30.
6. Kong Y, Zhang W, Jiang Z, Wang L, Li C, Li Y, et al. Immunogenicity and safety of a 23-valent pneumococcal polysaccharide vaccine in Chinese healthy population aged >2 years: a randomized, double-blinded, active control, phase III trial. Hum Vaccin Immunother 2015;11:2425-33.
7. Marra F, Vadlamudi NK. Efficacy and safety of the pneumococcal conjugate-13 valent vaccine in adults. Aging Dis 2019;10:404-18.
8. Kim ES, Shin JK, Oh HK. Elderly immunization program against invasive pneumococcal disease in Korea, 2013. Public Health Wkly Rep 2014;7:182-6.
9. Korea Centers for Disease Control and Prevention. Korea National Immunization Program, 2014 [accessed on 2019 September 19]. Available at: https://nip.cdc.go.kr/irgd/support.do?service=getNewsView&strNum=2&PROSEQNUM=305.
10. National Institute of Food and Drug Safety Evaluation. 2017 annual report of national lot release [accessed on 2019 September 19]. Available at: https://www.mfds.go.kr/brd/m_231/view.do?seq=32914.
11. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-9.
12. World Health Organization. Information sheet observed rate of vaccine reactions pneumococcal vaccine [accessed on 2019 September 19]. Available at: https://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/.
13. Jackson LA, Gurtman A, van Cleeff M, Jansen KU, Jayawardene D, Devlin C, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine 2013;31:3577-84.
14. Jackson LA, Gurtman A, Rice K, Pauksens K, Greenberg RN, Jones TR, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 2013;31:3585-93.
15. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia. Guideline for adverse drug events monitoring (pharmacovigilance). 3rd ed. Addis Ababa: Food, Medicine and Healthcare Administration and Control Authority of Ethiopia; 2014.
16. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998;54:315-21.
17. Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55:1202-9.
18. Merck Sharp and Dohme Corporation. PNEUMOVAX®23 (pneumococcal vaccine polyvalent) package insert [accessed on 2016 October 2]. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM257088.pdf.
19. Merck Sharp and Dohme Corporation. PRODIAX®23 (pneumococcal vaccine polyvalent) package insert [accessed on 2019 September 19]. Available at: https://www.msd-korea.com/assets/pdf/products/PRODIAX23.pdf.
20. Pfizer. Prevenar®13 (pneumococcal conjugate vaccine) package insert [accessed on 2019 September 19]. Available at: https://www.pfizer.co.kr/products/prevenar%C2%AE13-%ED%94%84%EB%A6%AC%EB%B2%A0%EB%82%98%C2%AE13%EC%A3%BC.
21. GlaxoSmithKline. Synflorix® (pneumococcal conjugate vaccine) package insert [accessed on 2019 September 19]. Available at: https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201002299.
22. Miller ER, Moro PL, Cano M, Lewis P, Bryant-Genevier M, Shimabukuro TT. Post-licensure safety surveillance of 23-valent pneumococcal polysaccharide vaccine in the Vaccine Adverse Event Reporting System (VAERS), 1990-2013. Vaccine 2016;34:2841-6.
23. Törling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine 2003;22:96-103.
24. Burwen DR, La Voie L, Braun MM, Houck P, Ball R. Evaluating adverse events after vaccination in the Medicare population. Pharmacoepidemiol Drug Saf 2007;16:753-61.
25. Brivet F, Herer B, Fremaux A, Dormont J, Tchernia G. Fatal post-splenectomy pneumococcal sepsis despite pneumococcal vac-cine and penicillin prophylaxis. Lancet 1984;2:356-7.
26. Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, et al. Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arterioscler Thromb Vasc Biol 2005;25:193-7.
27. Korea Centers for Disease Control and Prevention. Newsletter of National Immunization Program 2016 [accessed on 2019 September 19]. Available at: https://nip.cdc.go.kr/irgd/support.do?MnLv1=1.
28. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2015;33:4398-405.

https://doi.org/10.3349/ymj.2020.61.3.243