

Safety analysis of pneumococcal vaccine in Korea using the KAERS database from 2005 to 2017

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Background & Objectives

Background

The pneumococcal vaccine, which was recently included in the Korean national immunization program (NIP) in 2013 and 2014, has two types: pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV). PPSV targets high-risk populations, and PCV targets infants, children and adolescents.

Objectives

- To describe the characteristics of Individual Case Safety Reports (ICSRs) including pneumococcal vaccines and all other vaccines.
- To detect safety signals related to pneumococcal vaccines using Korea Adverse Event Reporting System (KAERS) database.

Materials and Methods

Data source

ICSRs containing vaccines reported to KAERS between 2005 and 2017

Study drug

Pneumococcal vaccines (PPSV (WHO-ATC, J07AL01), PCV (WHO-ATC, J07AL02))

Analysis

1. Characteristics of ICSRs

- Demographic & report characteristics of ICSRs on Pneumococcal vaccine were compared with ICSRs on other vaccines.
- Time to recognize serious adverse events (SAEs) of Pneumococcal vaccine
 - From ‘occurrence to AE’ to ‘recognition of AE’: compared according to report characteristics including 1) type of report, 2) reporter, 3) original reporter

2. Safety signals related to pneumococcal vaccines

- Disproportionality analysis⁽¹⁾
 - For all reported preferred terms (PT)
 - Calculated proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC), and chi-square
- Tree-based scan statistic (TBSS)⁽²⁾
 - Calculated the log-likelihood ratio (LLR) and validated by Monte Carlo simulation
 - The tree included system organ class (SOC) and high-level term (HLT) level as well as PT level

Examined whether the detected signals were reflected in the drug label.

ref1. Van Puijenbroek, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions, 2002
 ref2. Olivia Mahaux, et al. Tree-based scan statistic - Application in manufacturing-related safety signal detection, 2019

Results

Table 1. Characteristics of ICSRs, Pneumococcal Vaccine and Other Vaccine

	Total N = 29,270 N(%)	Pneumococcal Vaccine N = 5,738 N(%)	Other Vaccine N = 23,532 N(%)	p-value
Age				<.0001
< 18 years old	8,605(29.4)	1,674(29.2)	6,931(29.4)	
19 - 64 years old	9,942(34)	915(15.9)	9,027(38.4)	
> 64 years old	1,738(5.9)	516(9)	1,222(5.2)	
Unknown	8,985(30.7)	2,633(45.9)	6,352(27)	
Sex				<.0001
Male	10,152(34.7)	2,537(44.2)	7,615(32.4)	
Female	17,890(61.1)	2,923(50.9)	14,967(63.6)	
Unknown	1,228(4.2)	278(4.9)	950(4)	
Year report was received				<.0001
2005 ~ 2008	276(0.9)	89(1.6)	187(0.8)	
2009 ~ 2012	3,437(11.7)	475(8.3)	2,962(12.6)	
2013 ~ 2014	10,791(36.9)	3,456(60.2)	7,335(31.2)	
2015 ~ 2017	14,766(50.5)	1,718(29.9)	13,048(55.4)	
Original reporter				<.0001
Healthcare professionals	18,969(64.8)	4,472(77.9)	14,497(61.6)	
Consumers	2,127(7.3)	326(5.7)	1,801(7.6)	
Others (including KCDC)	4,339(14.8)	795(13.9)	3,544(15.1)	
Unknown	3,835(13.1)	145(2.5)	3,690(15.7)	
Serious adverse event				0.3335
Yes	2,197(7.5)	448(7.8)	1,749(7.4)	
No	27,073(92.5)	5,290(92.2)	21,783(92.6)	

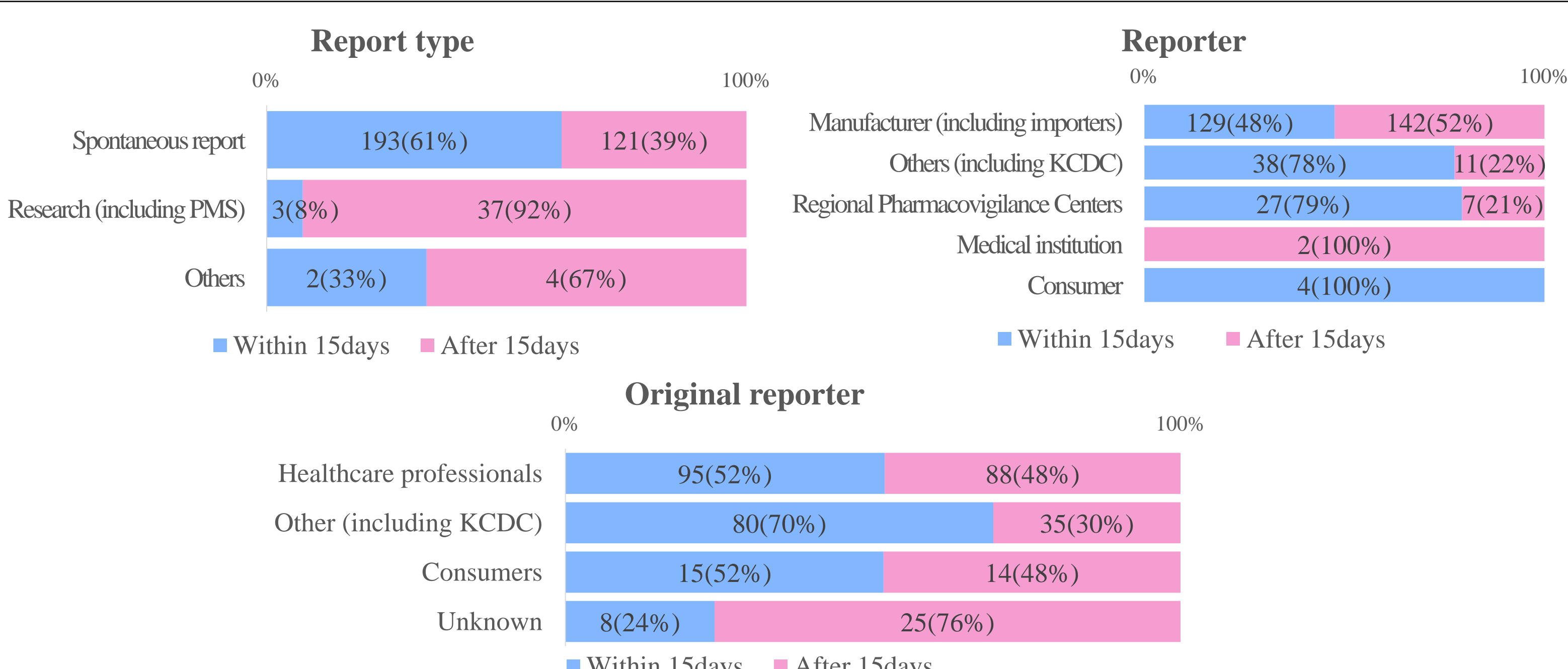


Fig 1. Time to recognize SAEs within 15 days : according to report characteristics

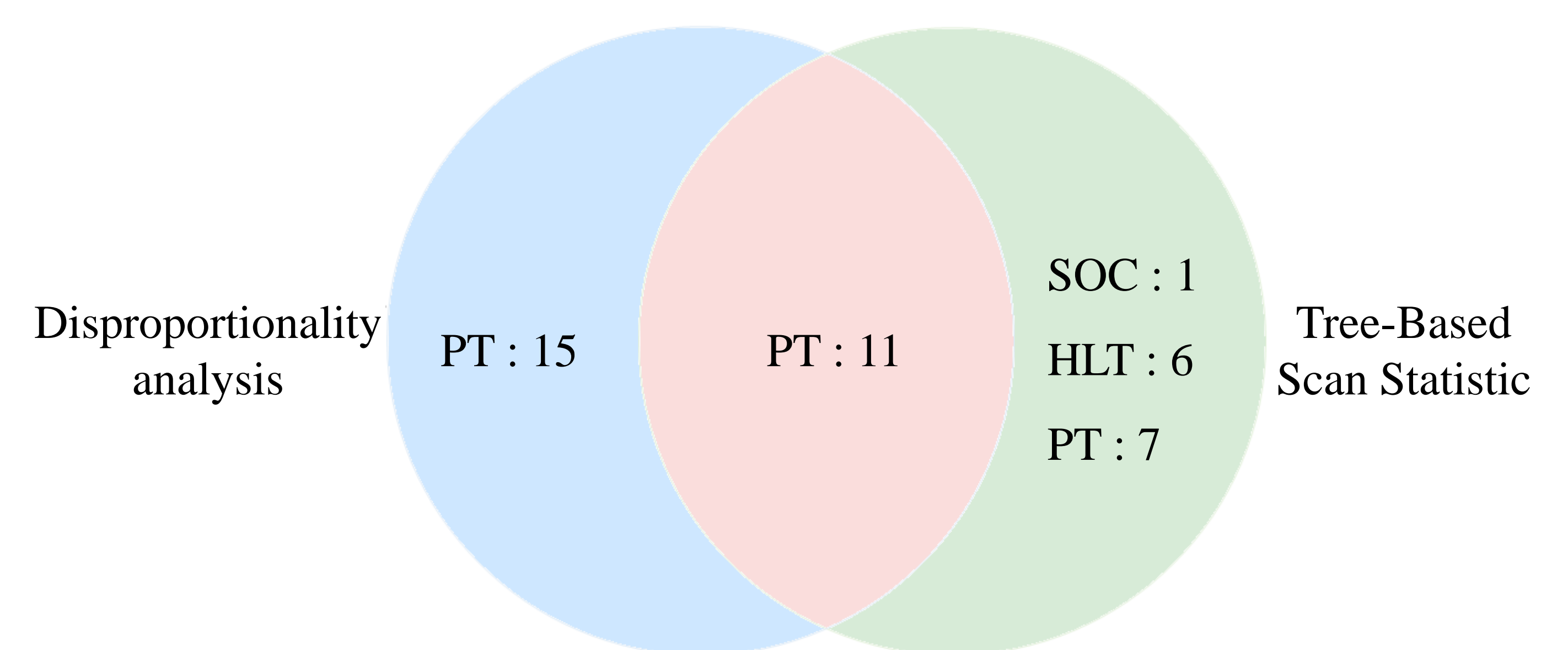


Fig 2. Ben-diagram of signals detected in disproportionality analysis and TBSS

Table 2. Detected signals of pneumococcal vaccine fulfilling the criteria for disproportionality analysis and TBSS

Adverse event	Pneumococcal / Other Vaccine	Disproportionality Analysis				Tree-Based Scan Statistic				Drug label (Korea)
		PRR	ROR	IC025	χ^2	Expected	Relative Risk	LLR	P-value	
#Skin and appendages disorders										
†Skin reaction localized	12/17	3.88	3.88	1.49	15.02					Labeled
†Livedo reticularis	8/13	3.38	3.38	1.41	8.30					Labeled
†Angioedema	16/37	2.37	2.38	1.03	8.89					Labeled
†Rash	257/1,007					200.12	1.28	8.96	0.007	Labeled
*Rash	352/1,423					281.02	1.25	10.00	0.002	Labeled
#Collagen disorders										
†LE syndrome	9/15	3.29	3.30	1.38	8.99					Labeled
#Central&peripheral nervous system disorders										
†Dyskinesia	32/39	4.51	4.51	1.57	47.98	11.24	2.85	16.83	0.001	Labeled
†Dyskinesia	64/90					24.38	2.62	28.93	0.001	Labeled
†Hypokinesia	32/51	3.45	3.45	1.35	34.16	13.14	2.44	12.43	0.001	Labeled
#Gastro-intestinal system disorders										
†Mouth dry	5/8	3.43	3.43	1.48	5.30					Unlabeled
#Liver and biliary system disorders										
†SGOT increased	8/18	2.44	2.44	1.11	4.71					Unlabeled
#Myo-, endo-, pericardial & valve disorders										
†Heart valve disorders	5/8	3.43	3.43	1.48	5.30					Unlabeled
#Heart rate and rhythm disorders										
†Cardiac arrest	4/5	4.39	4.39	1.70	5.82					Unlabeled
#Respiratory system disorders										
†Haemoptysis	4/1	21.96	21.97	2.44	16.01	3297.07	1.09	16.25	0.001	Labeled
†Respiratory disorder	45/89	2.78	2.78	1.14	34.02	21.22	2.12	12.76	0.001	Labeled
†Pulmonary disorders	4/0					0.63	6.32	7.37	0.041	Unlabeled
#White cell and RES* disorders										
†Leukocytosis	11/9	6.71	6.72	1.89	24.06	3.17	3.47	8.06	0.014	Labeled
#Urinary system disorders										
†Micturition frequency	3/1	16.47	16.48	2.38	10.90					Labeled
†Oliguria	4/2	10.98	10.98	2.21	12.10					Labeled
†Face oedema	14/38	2.02	2.02	0.88	5.30					Labeled
#Foetal disorders										
†Naevus	3/2	8.24	8.24	2.11	7.63					Labeled
#Body as a whole - general disorders										
†C-reactive protein increased	6/1	32.94	32.96	2.51	26.55	1.11	5.41	8.36	0.012	Labeled
†Medicine ineffective	26/29	4.92	4.93	1.65	42.88	8.71	2.99	14.88	0.001	Unlabeled
*Medicine ineffective	26/29					8.71	2.99	14.88	0.001	Unlabeled
†Temperature changed sensation	26/45	3.17	3.18	1.28	24.53	11.24	2.31	9.04	0.007	Labeled
†Oedema peripheral	40/94	2.34	2.34	0.98	21.48	21.22	1.89	8.24	0.013	Labeled
†Crying abnormal	96/228	2.31	2.32	0.95	50.48	51.3	1.87	19.34	0.001	Labeled
†Fever	1,183/4,551					907.82	1.3	46.03	0.001	Labeled
†Oedema	68/196					41.8	1.63	8.50	0.009	Labeled
*Oedema	118/351					74.25	1.59	13.43	0.001	Labeled
#Application site disorders										
†Cellulitis	108/105	5.65	5.69	1.72	204.13	33.72	3.2	69.54	0.001	Labeled
†Injection site reaction	962/1,848	2.86	3.00	1.15	790.28	444.89	2.16	285.95	0.001	Labeled
†Injection site urticaria	15/41	2.01	2.01	0.87	5.57					Labeled
†Injection site rash	398/1,414					286.88	1.39	23.33	0.001	Labeled
†Pneumonia	450/1,649					332.32	1.35	22.75	0.001	Unlabeled
*Pneumonia	452/1,662					334.69	1.35	22.46	0.001	Unlabeled
#Resistance mechanism disorders										
†Sepsis	12/28	2.35	2.35	1.04	6.54					Labeled
†Upper respiratory tract infection	810/3,229					639.47	1.27	25.30	0.001	Labeled
*Upper respiratory tract infection	2,273/11,058					2110.6	1.08	7.27	0.042	Labeled

*: System Organ Class; †: High Level Term; ‡: Preferred Term; IC025, lower limit of 95% of confidence interval for information component

Conclusions

- The number of AE reporting on pneumococcal vaccines increased following introduction to the Korean NIP in 2013 and 2014.
- Among SAE reports, others (including KCDC), health care professionals, and consumers tend to recognize within 15 days from occurrence of the AEs.
- Along with disproportionality analysis, TBSS could be used as a supplementary tool for signal detection with analyzing all-level hierarchical structural term AEs.
- The safety signals of ‘medicine ineffective’ or ‘pneumonia’ may be due to comorbid conditions of vaccine recipients’ high-risk of infection, which warrants further study.

Acknowledgement

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