

Patterns of spontaneous adverse event reporting following HPV vaccination in Korea and the United States



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Background & Objectives

Background The Human papilloma virus (HPV) vaccine, which was licensed to use in Korea since 2007, was recently included in Korean national immunization program (NIP) in June 2016. However, several studies related to HPV vaccines have raised safety issues such as syncope and dizziness^{1,2}.

Objectives To compare the adverse event following immunization (AEFI) reporting patterns of human papilloma virus (HPV) vaccines in Korea and the United States.

1) Bonaldo G, Vaccheri A, D'Annibali O, Motola D. Safety profile of human papilloma virus vaccines: an analysis of the US Vaccine Adverse Event Reporting System from 2007 to 2017. British Journal of Clinical Pharmacology. 2019;85(3):634-43.
 2) Mauro AB, Fernandes EG, Miyaji KT, Arantes BA, Valente MG, Sato HK, et al. Adverse events following Quadrivalent HPV vaccination reported in Sao Paulo State, Brazil, in the first three years after introducing the vaccine for routine immunization (March 2014 to December 2016). Rev Inst Med Trop Sao Paulo. 2019;61:e43-e.

Methods

- We analyzed Korea adverse event reporting system (KAERS) and vaccine adverse event reporting system (VAERS) database involving HPV vaccines between 2008 and 2017.
- The demographic characteristics of individual case safety reports (ICSRs) and proportion of serious AE reports were compared between KAERS and VAERS.
- Types of AEFIs were categorized into
 - Vaccine-related reaction
 - Immunization error-related reaction
 - Immunization anxiety-related reaction (defined as Preferred terms (PTs) related to *syncope* or *hyperventilation* (46 PTs & ITs in WHO-ART for KAERS, 21 PTs in MedDRA for VAERS)) according to the report of CIOMS/WHO WG on Vaccine Pharmacovigilance³.
- The number and seriousness of ICSR reports including *syncope* related terms (31 PTs & ITs in WHO-ART, 12 PTs in MedDRA) were compared in KAERS and VAERS.

3) Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Geneva: CIOMS,2012

Results

Table 1. Characteristics of HPV vaccine reports and all other vaccine reports reported to KAERS and VAERS from January 2008 to December 2017.

Year	KAERS		VAERS		p value
	HPV vaccines* N of ICSRs	%	HPV vaccines N of ICSRs	%	
Total	2,845	(100.0)	38,443	(100.0)	<0.0001
2008	32	(1.1)	6,062	(15.8)	
2009	56	(2.0)	3,261	(8.5)	
2010	116	(4.1)	2,770	(7.2)	
2011	202	(7.1)	2,363	(6.1)	
2012	126	(4.4)	2,513	(6.5)	
2013	1,062	(37.3)	3,401	(8.8)	
2014	639	(22.5)	3,766	(9.8)	
2015	127	(4.5)	4,779	(12.4)	
2016	159	(5.6)	5,660	(14.7)	
2017	326	(11.5)	3,868	(10.1)	
Sex					
					<0.0001
Male	33	(1.2)	5,782	(15.0)	
Female	2,689	(94.5)	23,290	(60.6)	
Unknown	123	(4.3)	9,371	(24.4)	
Age					
					<0.0001
<19 years	364	(12.8)	20,155	(52.4)	
≥19 years	1,285	(45.2)	6,172	(16.1)	
Unknown	1,196	(42.0)	12,116	(31.5)	
Seriousness					
					0.0921
SAE	200	(7.0)	2,397	(6.2)	
Non-SAE	2,645	(93.0)	36,046	(93.8)	

The number of ICSRs including HPV vaccines was **2,845** and **38,443** for KAERS and VAERS, respectively.

Reports for male were 1.2% and 15.0%, and reports for cases aged under 19 years were 13.0% and 52.5%, in KAERS and VAERS.

* If HPV vaccine and other vaccines were reported together in one report, it was classified as HPV vaccine-related report

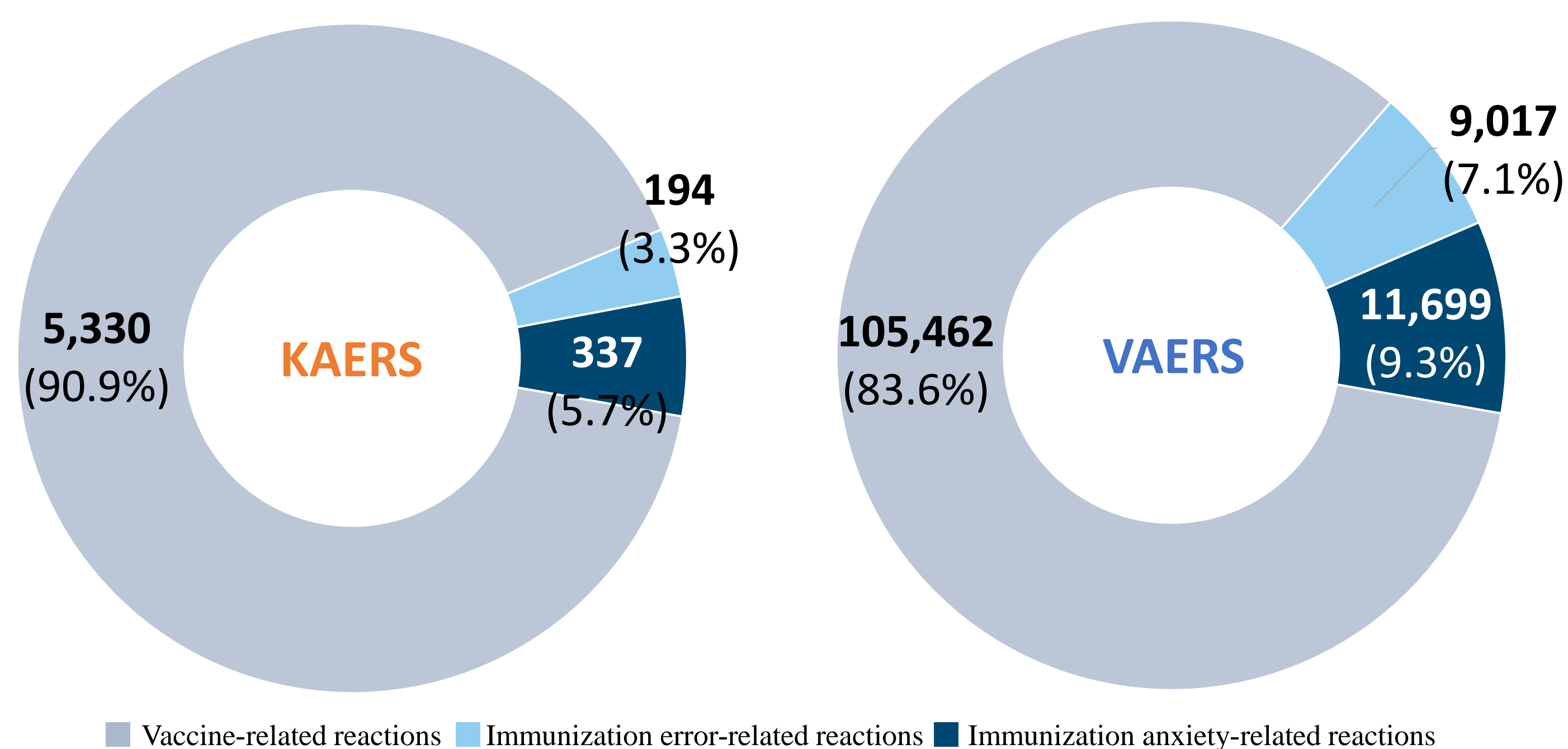


Figure 1. The number of HPV vaccine-AE pairs by types of AEFI

- Error-related and anxiety-related reactions were more reported in VAERS (7.1%, 9.3%) than in KAERS (3.3%, 5.7%) (both of p value<0.001)

Table 2. Top 20 Preferred Terms related to HPV vaccines in KAERS and VAERS

	KAERS (PTs in WHO-ART)	N (%)	VAERS (PTs in MedDRA)	N (%)
1	Injection site pain	1,200 (20.5)	No adverse event	10,067 (8.0)
2	Injection site reaction	248 (4.2)	Incorrect product storage	4,981 (3.9)
3	Fever	236 (4.0)	Dizziness	3,757 (3.0)
4	Dizziness	202 (3.4)	Syncope	3,685 (2.9)
5	Inappropriate schedule of drug administration	162 (2.8)	Headache	2,806 (2.2)
6	Myalgia	159 (2.7)	Inappropriate schedule of drug administration	2,663 (2.1)
7	Headache	146 (2.5)	Nausea	2,358 (1.9)
8	Urticaria	124 (2.1)	Pyrexia	1,810 (1.4)
9	Nausea	115 (2.0)	Loss of consciousness	1,705 (1.4)
10	Drug exposure in pregnancy	111 (1.9)	Injection site pain	1,675 (1.3)
11	Pharyngitis	107 (1.8)	Injection site erythema	1,558 (1.2)
12	Injection site pruritus	105 (1.8)	Fatigue	1,507 (1.2)
13	Vomiting	97 (1.7)	Vomiting	1,475 (1.2)
14	Injection site rash	91 (1.6)	Pain	1,453 (1.2)
15	Pruritus	89 (1.5)	Incorrect storage of drug	1,380 (1.1)
16	Pain	85 (1.5)	Pallor	1,361 (1.1)
17	Paraesthesia	83 (1.4)	Injection site swelling	1,355 (1.1)
18	Leg pain	83 (1.4)	Pain in extremity	1,328 (1.1)
19	Medication error	76 (1.3)	Urticaria	1,193 (0.9)
20	Syncope	74 (1.3)	Drug exposure during pregnancy	1,160 (0.9)

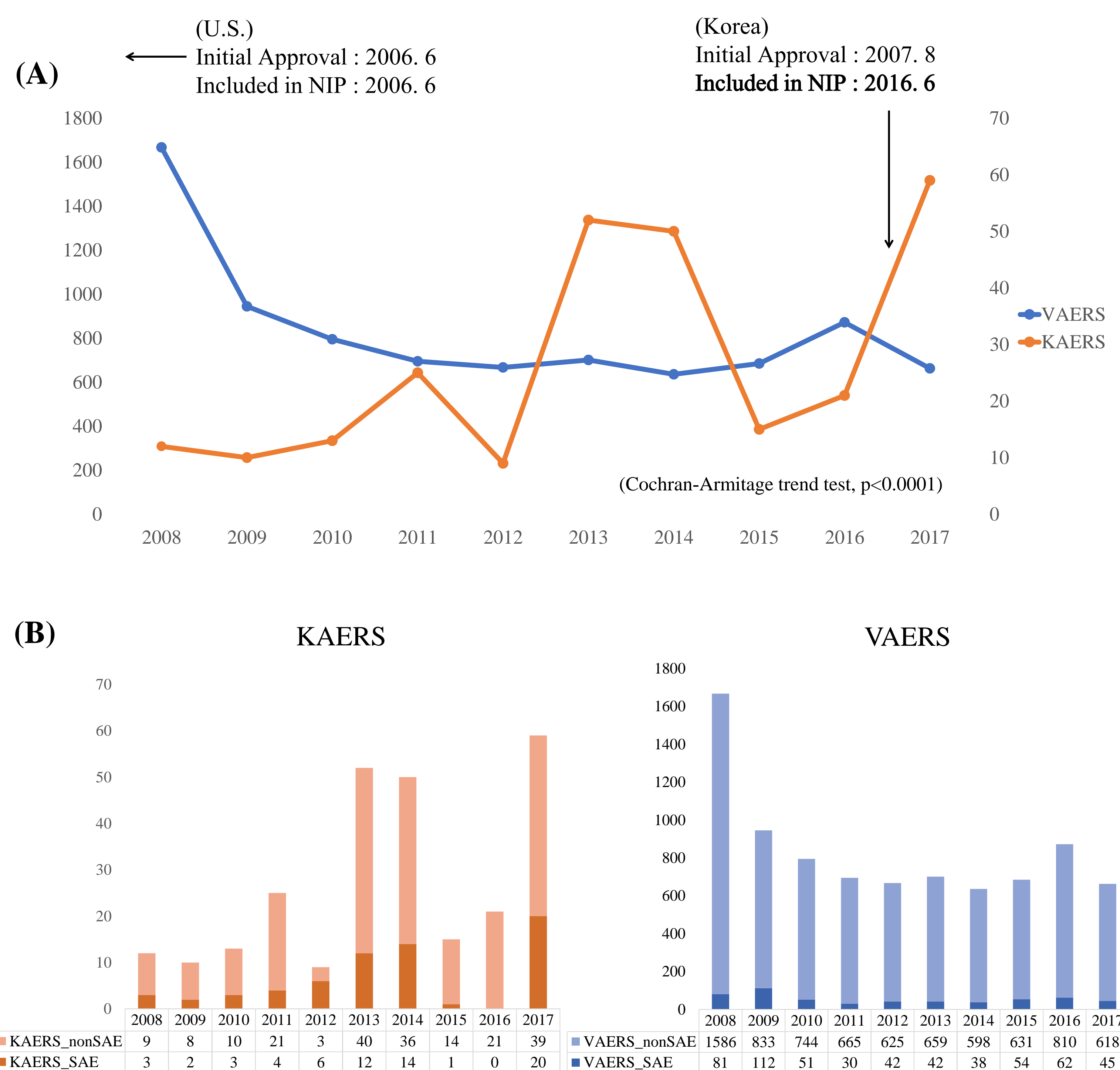


Figure 2. Trends in syncope-related reporting
 (A) The number of ICSRs containing syncope related terms by year
 (B) Trends in KAERS and VAERS by the seriousness of (A)

*NIP : National Immunization Program ; SAE : Serious Adverse Event

Conclusions

- Although the demographic characteristics of the KAERS and VAERS reports were somewhat different, frequently reported AEs were similar.
- However, immunization error-related and anxiety-related reactions were reported less in Korea (7.1% vs. 3.3%, 9.3% vs. 5.7%). Differences of AE terminology system and AEFI reporting system should be considered.
 - With the introduction of MedDRA in Korea, the terms of the two databases (KAERS and VAERS) will match and more accurate analysis would be possible.
- The HPV vaccines was introduced in 2016 as a Korean NIP, but this analysis only used ICSRs up to 2017. Therefore, further research is needed.

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