International Journal of Clinical Pharmacy (2019) 41:1365–1372
https://doi.org/10.1007/s11096-019-00881-9

RESEARCH ARTICLE

Signal detection of human papillomavirus vaccines using the Korea Adverse Events Reporting System database, between 2005 and 2016

Jung Ran[1] · Ji-Young Yang[1] · Ji-Ho Lee[1] · Hye-Jun Kim[1] · Jun-Yeong Choi[1] · Ju-Young Shin[1]

Received: 13 October 2018 / Accepted: 8 July 2019 / Published online: 16 July 2019

Abstract

Background Adverse events (AEs) not listed on drug labels have recently been reported in young girls vaccinated against HPV, but signal detection related to the human papillomavirus (HPV) vaccine has never been conducted in South Korea using the Korea Adverse Event Reporting System database of Korea Institute of Drug Safety & Risk Management at Ministry of Food and Drug Safety. *Objective* To analyze signals associated with HPV vaccines using the Korean spontaneous AEs reporting system and data-mining methods and compare the results to current vaccine label information in South Korea and the United States of America, United Kingdom, European Union, and Japan to detect signals not currently listed on the labels. *Setting* We evaluated the Korea Institute of Drug Safety & Risk Management database from January 2005 to December 2016. After pre-screening the data, the adjusted total numbers of HPV-related AE reports and AEs were 2566 and 4748 and those of all other vaccine-related AE reports and AEs were 21,878 and 120,688, respectively. *Methods* Three data mining algorithms (proportional reporting ratio, reporting odds ratio and information component) were used to assess AEs. A signal was defined when the criteria for all three indicators were satisfied. The detected signals were compared to the label information of HPV vaccines from South Korea, the United States of America, United Kingdom, European Union, and Japan. *Main outcome measure* Signals of AE after HPV vaccination, which met all three data mining indices. *Results* In this study, we found a total 97 signals of AE after HPV vaccination. Of these, 78 AEs were already present on the HPV vaccine labels of South Korea and the following 19 AEs were not listed: neuralgia, tremor, neuritis, depersonalization, axillary pain, personality disorder, increased salivation, peptic ulcer, circulatory failure, hypotension, peripheral ischemia, cerebral hemorrhage, micturition disorder, facial edema, ovarian cyst, weight increase, pain anxiety, oral edema, and back pain. Moreover, AE information on the current HPV vaccine labels of South Korea, the United States of America, United Kingdom, European Union, and Japan was inconsistent. When comparing the 19 AE signals that were not listed on the drug label in South Korea with the labels from the other countries, neuritis, axillary pain, cerebral hemorrhage, facial edema, pain anxiety, and back pain appeared on the U.S. Food and Drug Administration HPV vaccine labels but not on the United Kingdom labels, and hypotension was listed only on labels in the European Union and Japan. *Conclusions* South Korea should develop a system for proactively updating HPV labels. These results also suggest potential research directions such as vaccination label expansion, pharmacovigilance studies, and identification of causality in AEs associated with HPV vaccination.

Keywords Data mining · Human papillomavirus vaccine · KAERS database · Korea Adverse Events Reporting System database · Signal detection · South Korea

Impacts on practice

- In South Korea, there were no adverse event signals regarding neurological disorder or stroke for HPV vaccines, but signals for hypertension and cerebral hemorrhage were identified.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11096-019-00881-9) contains supplementary material, which is available to authorized users.

Jung Ran and Ji-Young Yang have contributed equally.

✉ Ju-Young Shin
shin.jy@skku.edu

[1] School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon, Gyeonggi-do 16419, Republic of Korea

- Signals detected through the Korea Adverse Event Reporting System can be considered for inclusion on the drug labels.

Introduction

Cervical cancer is the fourth most common cancer among women worldwide, causing approximately 266,000 deaths each year [1]. Since the introduction of the first human papillomavirus (HPV) vaccine, cervical cancer has become one of the few cancers that can be prevented. More than 200 million doses of HPV vaccines have been administered to women [2], and HPV vaccines are included in the immunization programs of 71 countries [3]. Many HPV vaccine safety studies have reported no safety concerns and a favorable risk-benefits profile of HPV vaccines [3–12]. However, numerous countries have received reports alleging the association of HPV vaccination with a variety of adverse events (AEs); recently, the media reported a case of hypokinesia (abnormally decreased motion), serious neurological deficits (paraparesis and paraplegia), brain disease, and death in young women administered the HPV vaccine [2, 13–15].

Most of AE listed on HPV vaccine labels were observed in clinical trials and post-marketing surveillance studies; however, additional AEs may occur in the 'real-world'. In fact, AEs recently reported by the media in young girls who have been vaccinated for HPV are new and not listed on the current HPV vaccine label in South Korea. A signal in pharmacovigilance is a hypothesis regarding the risk of medicine use, with supporting data and arguments. The World Health Organization Uppsala Monitoring Center (WHO-UMC) defined a signal as "Reported information on a possible causal relationship between an AE and a drug; the relationship being unknown or incompletely documented previously [16]." The evidence for a signal is not conclusive, but the signal detection process may reveal previously unrecognized or incompletely documented suspected adverse drug reactions (ADRs) [17]. However, signal detection related to HPV vaccine has never been conducted in South Korea using the Korean spontaneous AE reporting system database. Therefore, we analyzed signals associated with HPV vaccines by using the Korean spontaneous AEs reporting system and data-mining methods and compared the results with current vaccine label information in South Korea and the USA, UK, EU, and Japan to detect signals not currently listed on the labels. These results provide the latest safety information on HPV vaccines in South Korea and further research directions for unlabeled signal information.

Aim of the study

The purpose of this study was to detect signals of AEs after HPV vaccination using the Korea Adverse Events Reporting System (KAERS) database.

Methods

Database and study drug

The KAERS system was developed by Korea Institute of Drug Safety & Risk Management (KIDS) to facilitate the reporting and management of AE reports in South Korea. All spontaneous AE reports have been added to the KAERS since 1988. We therefore used data for spontaneous AEs reports related to HPV vaccines and all other vaccines listed in the KAERS database. The data were collected from January 2005 to December 2016 and were pre-screened for missing medication information, missing Anatomical Therapeutic Chemical (ATC) codes, and initially unreported cases by drug and AE information before performing statistical analysis. The provided KAERS database included general information, suspected drug information, adverse drug reaction codes, serious adverse drug reaction cases, reporter information, and causality assessment information. The drugs were coded according to the ATC classification system, which is managed by the World Health Organization Collaborating Center for Drug Statistics Methodology. We also coded suspected AEs according to the System Organ Class and Preferred Terms, which are two out of four classified levels of the WHO Adverse Reactions Terminology 092 (WHO-ART 092). The WHO-ART was developed and maintained by the WHO-UMC for approximately 30 years for coding adverse reaction terms, including most medical terms required to report AEs [18].

Definition of AE reports and AEs

In general, more than one AE can be listed in each AE report. For example, after vaccine administration, patient 'A' can report multiple symptoms at once, such as dizziness, headache, and injection site pruritus. In this case, the number of AE reports is one, but several AEs are listed on each AE report. In this study, we investigated the frequency of AEs associated with HPV vaccines and all other vaccines (all other vaccines include adolescent vaccines and infant vaccines) using Preferred Term codes.

Data mining indices

Data mining is a technique used to detect signals in large databases, which includes the proportional reporting ratio (PRR), reporting odds ratio (ROR), and information

component (IC) of the Bayesian Confidence Propagation Neural Network. The PRR is the ratio of the proportion of a specific AE divided by all AEs observed for the drug of interest to the proportion of this AE divided by all AEs observed for all other drugs in the database. The ROR is the odds of a specific AE occurring in a patient exposed to a drug of interest divided by the odds of occurrence of an AE specific to another drug. The IC is a logarithmic metric of the value which is calculated by dividing the probability of drug use and a specific AE by the product of the probability of drug use and probability of a specific AE occurring when drug use and specific AE occurring are independent. The criteria for signal detection were a PRR or ROR ≥ 2, χ^2 values (Chi square value) ≥ 4, and number of AEs ≥ 3. The IC value was set as the 95% confidence interval, and the lower limit was greater than 0 [19–22]. PRR, ROR, and IC were calculated using 2×2 contingency tables for drug-event counts; that is, HPV vaccines and all other vaccines were placed on the rows and specific AEs and all other AEs were categorized in columns. In this study, we used three data mining algorithms (PRR, ROR, and IC) to assess AEs, and a signal was defined when it satisfied the criteria for all three indicators (PRR, ROR, and IC).

HPV vaccine label information in South Korea, the USA, UK, EU, and Japan

Label information for HPV vaccines was confirmed using the website of the Korea Ministry of Food and Drug Safety (MFDS), U.S. Food and Drug Administration, Medicines and Healthcare products Regulatory Agency in the UK, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency in Japan [23–34].

Statistical analysis

We analyzed the number of AE reports and AEs following administration of the HPV vaccine and all other vaccines. The demographic characteristics of gender, age, and reporter among the basic reports' information were analyzed. In South Korea, the ages at which men and women were administered the HPV vaccine were 9–26 years, but the inoculated available age was up to 54 years old; therefore, subjects were divided into 5 sub-groups based on age: under 9, 9–27, 28–45, and over 46 years and unknown (Table 1).

Signals satisfying the criteria for all three indicators (PRR, ROR, and IC) were selected and compared to the label information of the HPV vaccine from South Korea, the USA, UK, EU, and Japan. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and Excel 2010 (Microsoft Corp., Redmond, WA, USA).

Table 1 Demographic characteristic for adverse events after administration of HPV vaccine or all other vaccines from January 2005 to December 2016

Category	Subcategory	HPV vaccines No. of AE	All other vaccines No. of AE
Gender	Male	44	56,224
	Female	4540	62,665
	Unknown	164	1799
Age	Under 9 years	2	23,470
	9–27 years	1713	9583
	28–45 years	737	13,331
	Over 45 years	115	24,302
	Unknown	2181	50,002
Reporter	Physicians	2435	96,915
	Pharmacists	50	3331
	Nurses	601	2369
	Consumers	966	3124
	Other	400	5969
	Unknown	0	42
	Missing	296	8938
	Total	4748	120,688

AE adverse event, *HPV* human papillomavirus

Results

The total numbers of AE reports and AEs for all vaccines accumulated in the KEARS between January 2005 and December 2016 were 25,010 and 131,113, respectively. After pre-screening of the data (excluding data with missing ATC/AEs codes and only the initially reported case), the adjusted total numbers of AE reports and AEs for all vaccines were 24,104 and 125,436, respectively. During the same period, the numbers of HPV-related AE reports were 2566 and AEs were 4748, while those of all other vaccine-related AE reports and AEs were 21,878 and 120,688, respectively (Fig. 1).

The characteristics of AEs for HPV vaccines are presented in Table 1. All characteristics differed between HPV vaccines and all other vaccines. In terms of gender, the proportion of women was higher than that of men: 4540 (95.6%) subjects were female and 44 (0.9%) were male. In subgroup analysis by age, HPV-related AEs were reported as follows: 2 reports in subjects under 9 years (0.0%), 1713 reports in subjects 9–27 years (36.1%), 737 reports in subjects 28–45 years (15.5%), 115 reports in subjects over 46 years (2.4%), and 2181 reports in subjects of unknown age (45.9%). A large proportion of AEs was generated by health professionals [physicians in 2435 cases (51.3%), pharmacists in 50 cases (1.1%), and nurses in 601 cases (12.7%)] (Table 1).

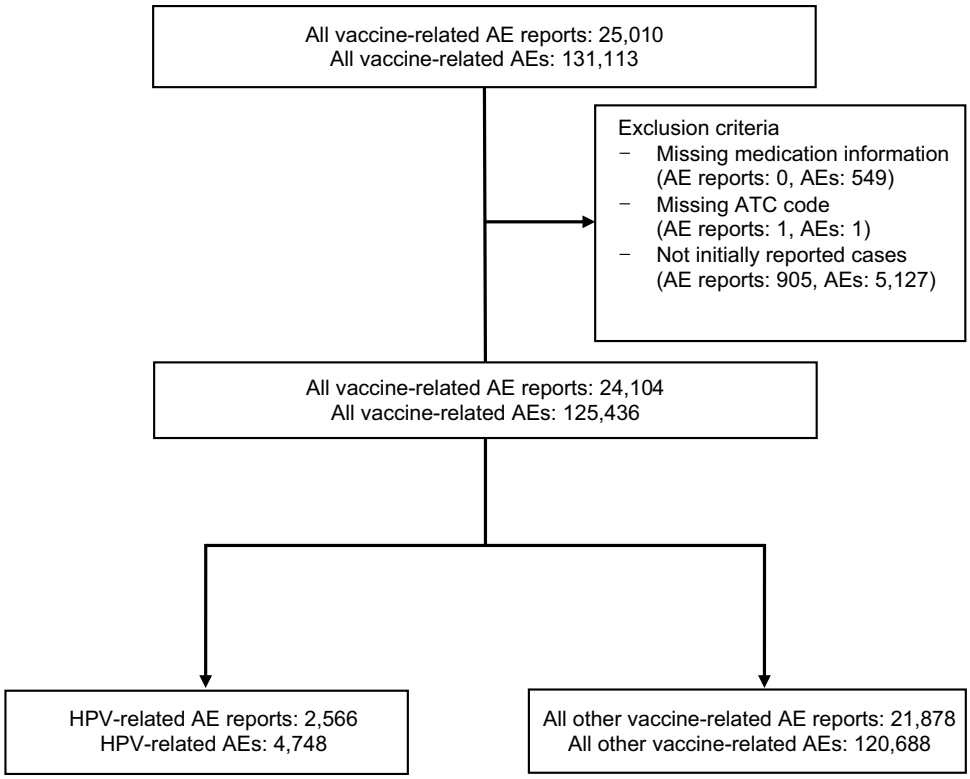

Fig. 1 Flow diagram of case inclusion in this study

The frequency of AEs associated with HPV vaccines and all other vaccines with respect to the WHO-ART System Organ Class are presented in Supplementary Table 1. Among the 4748 AEs, the most common events associated with HPV vaccines were 1278 cases (28%) of application site disorders, followed by 564 cases (13%) of body as a whole/general disorders, 439 cases (9%) of central and peripheral nervous system disorder, 277 cases (7%) of gastrointestinal system disorders, and 262 cases (6%) of skin and appendage disorders. Among the 120,688 cases of AEs reported for all other vaccines, the most common were application site disorders (19,468 cases, 17%), followed by 19,248 cases (16%) of body as a whole/general disorders, 4688 cases (4%) of reproductive disorder, 3642 cases (3%) of resistance mechanism disorders, 3000 cases (2%) of gastrointestinal system disorders, 2210 cases (2%) of central and peripheral nervous system disorders, and 2196 cases (2%) of fetal disorders.

In data-mining analysis, the number of signals detected by the PRR and ROR method was 97 individually and 220 by the IC method. Finally, 97 signals satisfied the criteria of all three data mining indices. Among them, 78 AEs are already presented on the HPV vaccine labels of South Korea and 19 AEs were not listed: tremor (49 cases), back pain (15 cases), neuritis (12 cases), hypotension (12 cases), circulatory failure (11 cases), pain axillary (11 cases), neuralgia (9 cases), facial edema (7 cases), ovarian cyst (6 cases), micturition disorder (6 cases), cerebral hemorrhage (5 cases), increased salivation (4 cases), personality disorder (4 cases), axillary pain (4 cases), oral edema (4 cases), depersonalization (3 cases), peptic ulcer (3 cases), peripheral ischemia (3 cases), and weight increase (3 cases), (Table 2). Additionally, 19 signals not listed on the current labels in South Korea were compared to the labels from 4 other countries (the USA, UK, EU, and Japan). Six of the above 19 signals (neuritis, axillary pain, cerebral hemorrhage, facial edema, pain anxiety, and back pain) were listed on the U.S. Food and Drug Administration HPV vaccine labels and none were listed on the labels in the UK and 1 signal (hypotension) was listed on the labels in the EU and Japan (Table 2 and Supplementary Table 2).

Discussion

This study describes signal detection after HPV vaccination based on KEARS data between January 2005 and December 2016. In this study, approximately 51.6% of AEs were reported in the 9–27 years-olds group. Such result appears to be associated with the HPV vaccine campaign targeting women between the ages of 9 and 27 years who have had no sexual experiences. In addition, consumer AE reporting for all other vaccine groups is approximately 2.6%, while that for HPV vaccine group is approximately 20%. High percentage of consumer spontaneous reporting is correlated with the type of medical institutions where vaccination takes place.

Table 2 AEs not listed on the drug labels of South Korea, the USA, the UK, EU, and Japan

System-organ classes	Adverse event (AE)	No. of reports	PRR	ROR	χ^2	IC 95%	Drug label-Korea	Drug label-USA	Drug label-UK	Drug label-EU	Drug label-Japan
Central and peripheral nervous system disorder	Neuralgia	9	9.2	9.2	44.4	1.7	N	N	N	N	N
	Tremor	49	4	4	90.9	1.4	N	N	N	N	N
	Neuritis	12	2.4	2.4	9.1	0.4	N	Y	N	N	N
Psychiatric disorders	Depersonalization	3	58	58	42	2.1	N	N	N	N	N
	Axillary pain	4	12.9	12.9	26.3	1.7	N	Y	N	N	N
	Personality disorder	4	11	11	23.2	1.5	N	N	N	N	N
Gastro-intestinal system disorders	Increased salivation	4	77.3	77.3	60.2	2.3	N	N	N	N	N
	Peptic ulcer	3	9.7	9.7	15.5	1.3	N	N	N	N	N
Cardiovascular disorders	Circulatory failure	11	10.6	10.6	61.9	2	N	N	N	N	N
	Hypotension	12	4.5	4.6	26.9	1.2	N	N	N	Y	Y
Vascular disorders	Peripheral ischemia	3	19.3	19.3	26.1	1.7	N	N	N	N	N
	Cerebral hemorrhage	5	12.1	12.1	31.3	1.7	N	Y	N	N	N
Urinary system disorders	Micturition disorder	6	10.5	10.6	33.5	1.7	N	N	N	N	N
	Facial edema	7	3.1	3.1	8.8	0.6	N	Y	N	N	N
Neoplasms	Ovarian cyst	6	58	58	84	2.5	N	N	N	N	N
Body as a whole/general disorders	Weight increase	3	19.3	19.3	26.1	1.7	N	N	N	N	N
	Pain, anxiety	11	11.8	11.8	67.6	2	N	Y	N	N	N
	Oral edema	4	4.5	4.5	9	0.8	N	N	N	N	N
	Back pain	15	3.2	3.2	19.3	0.8	N	Y	N	N	N

PRR proportional reporting ratio, *ROR* reporting odds ratio, *IC* information component, χ^2 Chi square, *Y* Yes, *N* No

As vaccines are usually administered at primary and secondary hospitals and clinics rather than tertiary hospitals, it is assumed that spontaneous AE reports have been more frequently made by consumers.

The major finding of this study was the detection of 13 signals that are not listed on the drug label in South Korea, the USA, UK, EU, and Japan, such as neuralgia, tremor, depersonalization, personality disorder, increased salivation, peptic ulcer, circulatory failure, peripheral ischemia, micturition disorder, ovarian cyst, weight increase, and oral edema. Our study also showed that the AE information presented on the current HPV vaccine labels in South Korea, the USA, UK, EU, and Japan was inconsistent. AE information is initially reported during clinical trials and is updated by pharmacovigilance studies and real-world data; therefore, the information on the drug label may vary between countries and over time [35]. In this regard, numerous studies have been conducted to compare safety information from different countries. Shimazawa and Ikeda [36] conducted a cross-sectional study using 189 new molecular materials approved in the USA, UK, and Japan and found inconsistencies in the safety information in drug labeling across countries. Lee and Shin [37] compared label information for 50 cardiovascular drugs in 4 countries, including South Korea, the USA, UK, and Japan, and found that label information in pregnancy varies greatly. Jeong et al. [35] also showed that the label information regarding drug interactions in drug labels was inconsistent for 38 drugs in the USA, UK, China, Japan and South Korea. Different regulations and guidance regarding drug labeling in various countries explain some of this inconsistent information. In South Korea, safety information is reported to KEARS, but labeling updates are not required by law, and thus the latest safety communications and warnings may not be included on the product label [35].

Neuritis is listed on the USA label, but not on the labels in South Korea, the UK, EU, and Japan. Sridhar et al. reported that patients with a history of autoimmune disease have a higher incidence of optic neuritis, and Chang et al. estimated that the association between the production of neuromyelitis optica antibody and HPV vaccination was related to recurrent optic neuritis [38, 39]. In cardiovascular groups, 11 cases of circulatory failure and 12 cases of hypotension were reported. A MedAlerts search of the US vaccine adverse event reporting system databased in March 2018 revealed 74 cases of orthostatic hypotension and 391 cases of low blood pressure incidents in patients administered the HPV vaccine [40]. In this study, 23 cases of cardiovascular disorder including hypotension and circulatory failure were also reported. However, circulatory failure is not listed on the label of all studied countries and hypotension is on the label of only the EU and Japan. The exact mechanism of circulatory failure and hypotension caused by the HPV vaccine are unclear, and the causal relationship of these AEs and HPV vaccination has not been determined, but a variety of studies are underway to determine the common items and mechanisms of each AE. Furthermore, cerebral hemorrhage is an AE that has recently become a social issue along with "paraplegia and death cases" [41–43] and negatively impacts the vaccination rate. However, this AE is also not listed on the labels from all studied countries except for the USA.

The current major controversies regarding HPV vaccine safety involve autoimmune diseases [44]. A large cohort study of more than 2 million young girls in France revealed an increased risk of Guillain–Barre syndrome (GBS) following HPV 2 and 4 vaccination (adjusted hazard ratio: 3.78 [1.79–7.98]) and no increase in the risk of several autoimmune disease other than GBS [45]. In contrast, several other studies reported no increased risk of GBS following HPV vaccination. Grimaldi-Bensouda et al. [46] conducted a large case control study to assess the risk of autoimmune disorders following HPV 4 vaccination of young French female subjects and found no increased risk of all autoimmune diseases (idiopathic thrombocytopenic purpura, central demyelination, connective tissue disorders, GBS, type 1 diabetes mellitus, and autoimmune thyroiditis). Andrews et al. [47] conduced a self-controlled case-series study of females in England administered the HPV 2 and 4 vaccines. In 101 cases, the relative incidence (RI) of GBS at 3, 6, and 12 months were 1.04 [0.47–2.28], 0.83 [0.41–1.69], and 1.10 [0.57–2.14], respectively, indicating that HPV vaccination did not increase the risk of GBS [47]. Geier et al. [48] also conducted a case–control study to assess the risk correlation between HPV 4 vaccines and serious autoimmune adverse events and found that the risk of GBS was not high compared to in the control group (odds ratio 0.839 [0.601–1.145]).

This study has a few strengths. First, we used a large spontaneous AE reporting database, which contains the data of nearly 1.2 million patients which has been collected for over 10 years. Second, by comparing current drug labels between South Korea and the USA, UK, EU, and Japan, we identified signals not listed on the labels of all studied countries and observed some differences between them.

This study also had some limitations. First, the KAERS database is a passive spontaneous adverse event reporting system. The frequency and impact of a given ADR is underestimated in this system, and thus the sensitivity for detecting ADRs may be decreased by underreporting [49, 50]. Second, because of the characteristics of spontaneous reporting, this study may provide limited information or partial information on the cases. This may have influenced our analysis. Additionally, some patient information, drug information, and AEs, among other factors, were missing, making it difficult to confirm the causality of AEs with HPV vaccination. Third, the signal results of data-mining (PRR, ROR, IC) do not support that HPV vaccine causes an

increased risk of AEs or new safety concerns, and thus this study is insufficient to confirm whether the detected signal is causally related to HPV vaccination. Therefore, further studies should be conducted to assess the causal relationship between HPV vaccine and signals.

Although we did not conduct causality assessment, early detection of signals is meaningful for securing public health and providing up-to-date information on drug safety.

Conclusion

In this study signals were identified that had not been previously reported in South Korea, but some of these signals (e.g., neuritis, hypotension, circulatory failure, and cerebral hemorrhage) are already listed on the drug labels in other countries. South Korea should have a system that can update the label more proactively, and global harmonization of label information is needed for healthcare professions and consumers. The current study suggests further research directions such as expanding vaccination labels, greater pharmacovigilance, and identifying the causality of AEs associated with HPV vaccination. Additionally, this information may help health professionals provide better care to patients based on the scientific data.

Acknowledgements We sincerely thank the Korea Institute of Drug Safety and Risk Management for their cooperation in providing access to the Korea Adverse Event Reporting System Database. We also thank Editage for their assistance with English language editing and Junyeong Choi of the School of Pharmacy, SungKyunKwan University for his important contributions.

Funding This study was supported by a Government-wide R&D Fund project for 212 infectious disease research (Grant no. HG18C0068).

Conflicts of interest Author Jung Ran, Author Ji-Young Yang, Author Ji-Ho Lee, Author Hye-Jun Kim, and Author Ju-Young Shin declare that they have no conflict of interest.

Ethics approval Sungkyunkwan University Institutional Review Board approval was granted on April 12, 2017 (IRB File Number: 2017-12-001).

References

1. WHO website. Human papillomavirus (HPV), 2018. http://www.who.int/immunization/diseases/hpv/en/. Accessed 17 Mar 2018.
2. WHO website. Building the case and capacities for successful HPV vaccine introduction, 2016. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/news/news/2016/03/building-the-case-and-capacities-for-successful-hpv-vaccine-introduction. Accessed 17 Mar 2018.
3. Stillo M, Carrillo Santisteve P, Lopalco PL. Safety of human papillomavirus vaccines: a review. Expert Opin Drug Saf. 2015;14(5):697–712.
4. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)–United States, 1991–2001. MMWR Surveill Summ. 2003;52(1):1–24.
5. CDC website. Frequently asked questions about HPV vaccine safety. https://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html. Accessed 17 Mar 2018.
6. Monika B. HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS. European Medicines Agency. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/11/WC500196762.pdf. Accessed 17 Mar 2018.
7. Cameron RL, Ahmed S, Pollock KG. Adverse event monitoring of the human papillomavirus vaccines in Scotland. Intern Med J. 2016;46(4):452–7.
8. Harris T, Williams DM, Fediurek J, Scott T, Deeks SL. Adverse events following immunization in Ontario's female school-based HPV program. Vaccine. 2014;32(9):1061–6.
9. Stokley S, Jeyarajah J, Yankey D, Cano M, Gee J, Roark J, et al. Human papillomavirus vaccination coverage among adolescents, 2007–2013, and postlicensure vaccine safety monitoring, 2006–2014–United States. MMWR Morb Mortal Wkly Rep. 2014;63(29):620–4.
10. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer. 2008;113(10 Suppl):3036–46.
11. Chatterjee A. The next generation of HPV vaccines: nonavalent vaccine V503 on the horizon. Expert Rev Vaccines. 2014;13(11):1279–90.
12. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–301.
13. Ozawa K, Hineno A, Kinoshita T, Ishihara S, Ikeda SI. Suspected adverse effects after human papillomavirus vaccination: a temporal relationship between vaccine administration and the appearance of symptoms in Japan. Drug Saf. 2017;40(12):1219–29.
14. Nicol AF, Andrade CV, Russomano FB, Rodrigues LL, Oliveira NS, Provance DW Jr. HPV vaccines: a controversial issue? Braz J Med Biol Res. 2016;49(5):e5060.
15. Weinbaum CM, Cano M. HPV vaccination and complex regional pain syndrome: lack of evidence. EBioMedicine. 2015;2(9):1014–5.
16. World Health Organization-Uppsala Mornitoring Centre. What is a signal? http://www.who-umc.org/research-scientific-development/signal-detection/what-is-a-signal/. Accessed 10 Feb 2019.
17. World Health Organizaion-Uppsala Mornitoring Centre. Signal Detection at UMC. https://www.who-umc.org/research-scientific-development/signal-detection/signal-detection-at-umc/. Accessed 10 Feb 2019.
18. World Health Organizaion-Uppsala Monitoring Centre. What is WHO-ART? http://www.who-umc.org/vigibase/services/learn-more-about-who-art/. Accessed 10 Feb 2019.
19. Ye X, Fu Z, Wang H, Du W, Wang R, Sun Y, et al. A computerized system for signal detection in spontaneous reporting system of Shanghai China. Pharmacoepidemiol Drug Saf. 2009;18(2):154–8.
20. Yi H, Lee JH, Shin JY. Signal detection for cardiovascular adverse events of DPP-4 inhibitors using the Korea Adverse Event Reporting System Database, 2008–2016. Yonsei Med J. 2019;60(2):200–7.
21. Kim S, Park K, Kim MS, Yang BR, Choi HJ, Park BJ. Data-mining for detecting signals of adverse drug reactions of fluoxetine using the Korea Adverse Event Reporting System (KAERS) database. Psychiatry Res. 2017;256:237–42.

22. Park K, Soukavong M, Kim J, Kwon KE, Jin XM, Lee J, et al. Signal detection of imipenem compared to other drugs from Korea Adverse Event Reporting System database. Yonsei Med J. 2017;58(3):564–9.
23. Food and Drug Administration. Approved products. Human papillomavirus vaccine. https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm172678.htm. Accessed 2 Feb 2019.
24. Korean MFDS—Gardasil label information. https://nedrug.mfds.go.kr/bbs/63/136. Accessed 30 Jan 2019.
25. Korean MFDS—Gardasil 9 label information. https://nedrug.mfds.go.kr/bbs/63/390. Accessed 30 Jan 2019.
26. Korean MFDS—Cervarix label information. https://nedrug.mfds.go.kr/bbs/63/162. Accessed 30 Jan 2019.
27. England EMC—Cervarix label information. https://medicines.org.uk/emc/product/1177. Accessed 30 Jan 2019.
28. England EMC—Gardasil label information. https://medicines.org.uk/emc/product/261/smpc. Accessed 30 Jan 2019.
29. England EMC—Gardasil 9 label information. https://medicines.org.uk/emc/product/7330/smpc. Accessed 30 Jan 2019.
30. EMA—Gardasil label information. https://www.ema.europa.eu/documents/product-information/gardasil-epar-product-information_en.pdf. Accessed 30 Jan 2019.
31. EMA—Gardasil 9 label information. https://www.ema.europa.eu/documents/product-information/gardasil-9-epar-product-information_en.pdf. Accessed 30 Jan 2019.
32. EMA—Cervarix label information. https://www.ema.europa.eu/documents/product-information/cervarix-epar-product-information_en.pdf. Accessed 30 Jan 2019.
33. Japan PMDA—Gardasil label information. http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/170050_631340TG1020_1_05. Accessed 30 Jan 2019.
34. Japan PMDA—Cervarix label information. http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/340278_631340QG1022_1_13. Accessed 30 Jan 2019.
35. Jeong S, Kam G, Li J, Lee S, Lee H, Noh Y, et al. Assessment of consistency of drug interaction information in drug labels among the United States, the United Kingdom, China, Japan, and Korea. Clin Pharmacol Ther. 2019;105(2):505–14.
36. Shimazawa R, Ikeda M. Safety information in drug labeling: a comparison of the USA, the UK, and Japan. Pharmacoepidemiol Drug Saf. 2013;22(3):306–18.
37. Lee SH, Shin JY, Park MJ, Park BJ. Agreement of label information of cardiovascular drugs in pregnancy among Korea, the USA, the UK, and Japan. Regul Toxicol Pharmacol. 2014;68(3):363–9.
38. Sridhar G, Tian F, Forshee R, Kulldorff M, Selvam N, Sutherland A, et al. Evaluation of optic neuritis following human papillomavirus vaccination. Hum Vaccin Immunother. 2017;13(7):1705–13.
39. Chang H, Lee HL, Yeo M, Kim JS, Shin DI, Lee SS, et al. Recurrent optic neuritis and neuromyelitis optica-IgG following first and second human papillomavirus vaccinations. Clin Neurol Neurosurg. 2016;144:126–8.
40. MedAlerts Home. Case details: found 74 cases where vaccine is HPV or HPV2 or HPV4 and Symptom is Orthostatic hypotension. National Vaccine Information Center. https://medalerts.org/. Accessed 17 Mar 2018.
41. Is HPV vaccine to blame for a teen's paralysis? https://health.usnews.com/health-news/blogs/on-women/2008/07/02/is-hpv-vaccine-to-blame-for-a-teens-paralysis. Accessed 30 Jan 2019.
42. Death by Gardasil? Not so fast there… https://sciencebasedmedicine.org/death-gardasil-not-so-fast/. Accessed 30 Jan 2019.
43. Can HPV Vaccine Cause Injury and Death? https://www.nvic.org/vaccines-and-diseases/hpv/vaccine-injury.aspx. Accessed 30 Jan 2019.
44. DeStefano F, Bodenstab HM, Offit PA. Principal controversies in vaccine safety in the United States. *Clin Infect Dis* 2019. https://doi.org/10.1093/cid/ciz135.
45. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: a large cohort study of over 2 million young girls in France. Vaccine. 2017;35(36):4761–8.
46. Grimaldi-Bensouda L, Guillemot D, Godeau B, Benichou J, Lebrun-Frenay C, Papeix C, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med. 2014;275(4):398–408.
47. Andrews N, Stowe J, Miller E. No increased risk of Guillain–Barré syndrome after human papilloma virus vaccine: a self-controlled case-series study in England. Vaccine. 2017;35(13):1729–32.
48. Geier DA, Geier MR. Quadrivalent human papillomavirus vaccine and autoimmune adverse events: a case–control assessment of the vaccine adverse event reporting system (VAERS) database. Immunol Res. 2017;65(1):46–54.
49. de Villiers EM. Cross-roads in the classification of papillomaviruses. Virology. 2013;445(1–2):2–10.
50. Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJ, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet. 2005;366(9490):991–8.