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Signals and trends of Guillain–Barré syndrome after the introduction of live-attenuated vaccines for influenza in the US and South Korean adverse event reporting systems

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ABSTRACT

Background: With the advent of live-attenuated, quadrivalent, and cell-cultured vaccines for influenza, there have been discussions on the safety of these vaccines compared to conventional vaccines (such as inactivated, trivalent, and egg-cultured vaccines) because of the development of neurological adverse events (AEs). This study aimed to compare the trends and safety signals in the AE reporting systems of the US and South Korea and, more particularly, to evaluate the association between influenza vaccination and Guillain–Barré syndrome (GBS).

Methods: In total, 400,535 AE reports from the US Vaccine Adverse Event Reporting System (VAERS) and 28,766 AE reports from the Korea Adverse Event Reporting System (KAERS) between 2005 and 2017 were assessed. Disproportionality analysis was performed to detect the safety signals and examine the potential risk of GBS with influenza vaccination using the case/non-case approach.

Results: In both databases, GBS was the most frequently reported AE following influenza immunization. Using the case/non-case approach, the adjusted reporting odds ratio (ROR) of GBS was 3.57 (95% confidence interval [CI], 3.16–4.03) and 3.09 (95% CI, 0.83–11.45) in the VAERS and KAERS data, respectively. People vaccinated with live-attenuated vaccines reported 2.30 times (95% CI, 1.74–3.05) more cases of GBS than those vaccinated with other types of vaccines.

Conclusions: Our analysis of the VAERS and KAERS reports for AEs following immunization (AEFI) for influenza shows the need for cautious monitoring regarding the development of GBS after influenza vaccination, particularly, after live-attenuated vaccination. However, owing to potential reporting bias caused by limited AEFI reports after the introduction of new types of influenza vaccines, further prospective safety studies are needed.

1. Introduction

In the US, Guillain–Barré syndrome (GBS) is the most frequently reported serious adverse event following immunization (AEFI) for influenza [1]. GBS is a paralytic disorder of the peripheral nervous system [2]. Owing to an unexplained increase in the risk of GBS occurrence after influenza vaccination during the 1976–77 A/New Jersey season, GBS has attracted special attention as an AEFI for influenza [3]. In particular, as influenza itself is a major cause of GBS [4], it is assumed that, theoretically, live-attenuated vaccines will have a relatively higher risk of causing GBS.

Vaccination is the cornerstone of the efforts to prevent influenza and its efficacy, which ranges 59% to 83% [5]. The World Health Organization (WHO) annually announces the subtypes of influenza virus that are predicted to prevail each year, which, in turn, helps the production of effective vaccines against these viruses [6]. Many countries administer influenza vaccination in accordance with the WHO guidelines, which recommend influenza

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AEFI, adverse events following immunization; CIOMS, Council for International Organizations of Medical Sciences; GBS, Guillain–Barré syndrome; IC, information component; ICH, International Conference on Harmonisation; KAERS, Korea Adverse Event Reporting System; LAIV, Live attenuated influenza vaccine; PTs, preferred terms; PRR, proportional reporting ratio; ROR, reporting odds ratio; SAE, Serious adverse events; VAERS, Vaccine Adverse Event Reporting System.

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vaccination for high-risk groups, such as the elderly and children [7,8]. Owing to the increase in the coverage rate for influenza vaccination and an increase in the number of subjects needing vaccination [9,10], the need for the management of AEFIs is further magnified. Most AEFIs usually include mild symptoms, such as swelling and pain at the injection site; however, rarely occurring serious AEFIs, such as GBS, can threaten an individual's health and economic status [11].

To collect spontaneous reports regarding AEFI and manage vaccine safety, the US and South Korean governments have established monitoring systems, namely, the Vaccine Adverse Event Reporting System (VAERS) and the Korea Adverse Event Reporting System (KAERS), respectively [12–14]. Although studies using spontaneous AEFI reports have found that GBS was the most common influenza vaccination-related serious adverse event (AE) [1,15] and results from a recent *meta*-analysis have shown that the relative risk of GBS after influenza vaccination was slightly higher [16] than no vaccination, the biological mechanism and plausibility of these results remain controversial [17,18]. Additionally, with the advent of new types of influenza vaccines (i.e., live-attenuated, quadrivalent, or cell-based vaccines) [19,20], the need to examine the recent trends in AEFI is increasing. To alleviate the recipients' fear of AEFI, especially GBS, and implement a vaccine policy based on safety, we need to continuously monitor and investigate the incidence of GBS after influenza vaccination and evaluate its association with the vaccine.

Considering the knowledge gaps explained earlier, this study was designed with the following objectives using a case/non-case approach: 1) to explore the trends of the major AEFI for influenza according to the types of influenza vaccines, 2) to capture the characteristics of serious neurological AE reports, including GBS, 3) to detect the safety signals by comparing two spontaneous AE reporting databases, and 4) to generate a valid signal of the association between influenza vaccination and the incidence of GBS. With the South Korean government's ongoing expansion of the target groups for influenza vaccination, this study examines trends and signals by comparing well-established AE reporting systems, i.e., VAERS and KAERS. The results of this study may contribute to the evidence-based implementation of an influenza vaccine policy based on safety.

2. Materials and methods

2.1. Data sources

AE data from January 2005 to December 2017 were obtained from VAERS. This system was established in the US in 1990 by the Centers for Disease Control and Prevention (CDC) considering the National Childhood Vaccine Injury Act of 1986. According to this system, anyone can report an AE, including healthcare professionals, vaccine manufacturers, patients, parents, and others. VAERS does not discern the clinical causality and approves all reports [13]. The CDC makes VAERS data readily available to the public as an online downloadable dataset consisting of three comma-separated value files and medical covariates [21]. As the VAERS data covers only vaccination-related AE reports, we were able to use this data in its original format without any extraction. AE symptoms in VAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system, which differs from the WHO Adverse Reaction Terminology (WHO-ART) system used in the KAERS database. The MedDRA system is based on terminology belonging to the UK Medicines and Health products Regulatory Agency and was created by the International Conference on Harmonisation (ICH) partners, including the WHO, using the ICH process [22].

We also obtained vaccine AE data from January 2005 to December 2017 from the KAERS. The KAERS was developed in 2012 by the Korean Institute of Drug Safety & Risk Management (KIDS) to facilitate the computerized reporting and management of AE reports [14]. The KAERS database comprises general information, suspected drug information, adverse drug reaction (ADR) codes, serious ADR cases, reporter information, and causality assessment information. As the KAERS data covers all drug-related AE reports and vaccines, we extracted only the AE reports related to vaccination (J07 of the WHO-Anatomical Therapeutic Chemical classification system in drug code) [23]. The AEs registered in the KAERS database were based on the WHO-ART (ver. 092), which uses a hierarchical structure [24]. The subcategory consisted of the respective WHO-ART system's preferred terms (PTs). More than two recorded PTs were counted as distinct accounts of vaccine-related AEs in one patient. According to the WHO criteria, serious AE (SAE) reports were defined as cases that were related to fatal, life-threatening, caused hospitalization or persistent disability, or medically miscellaneous reasons [25].

2.2. Selection of AE reports and AE pairs

We extracted AE reports from the VAERS and KAERS databases and then divided them into two groups—influenza-related AE reports and all other vaccines-related AE reports. In the VAERS data, we defined influenza-related AE reports as those that were filed with text that included the word "FLU" in the vaccine code (**Supplementary** Table 1). In the KAERS data, if the WHO-ATC code of the influenza vaccine in the variable was called "drug chem" (J07BB, J07BB01, J07BB02, and J07BB03), we categorized it as an influenza-related AE report. As the VAERS data included only the initial reports of the patients [26], we excluded the follow-up reports from the KAERS data before comparing the two databases.

A single AE report may have more than two AEs. We divided a single AE report as a separated case by the number of AEs. And then, we made combinations with a vaccine and a related AE in the AE reports called as vaccine-AE pairs. Based on this, 130,753 influenza-related AE pairs (105,216 AE reports) and 24,693 influenza-related AE pairs (12,815 AE reports) were included from the VAERS and KAERS databases, respectively (Fig. 1).

2.3. Selection of neurological adverse events

As described earlier, the VAERS and KAERS use different coding systems for AEs. We defined neurological AEs based on the VAERS method, which has a more advanced distinction of AE terminologies. We then matched these with the KAERS data. In the VAERS data, AEs were coded as a MedDRA term under a variable "symptom," and no code number was provided. In the KAERS system, however, AEs were coded as the PT code of the WHO-ART coding system.

We first defined neurological AEs based on a literature review and expert opinion using the following symptom variable terms, as described in the VAERS database: "dysesthesia," "encephalitis," "encephalopathy," "facial paralysis," "Guillain-Barré syndrome (GBS)," "nerve injury," "nerve palsy," "neuritis," "neuropathy," "meningism," "meningitis," "myelitis," "paresthesia," "seizure," "narcolepsy," and "Miller Fisher syndrome." We converted the MedDRA terms to the WHO-ART terms used in the KAERS database. A detailed algorithm to convert neurological AE reports from VAERS to KAERS data has been provided in **Supplementary** Table 2.

2.4. Descriptive analysis and signal detection

The following demographic characteristics of AE pairs were compared between the two databases: sex, age group, year of

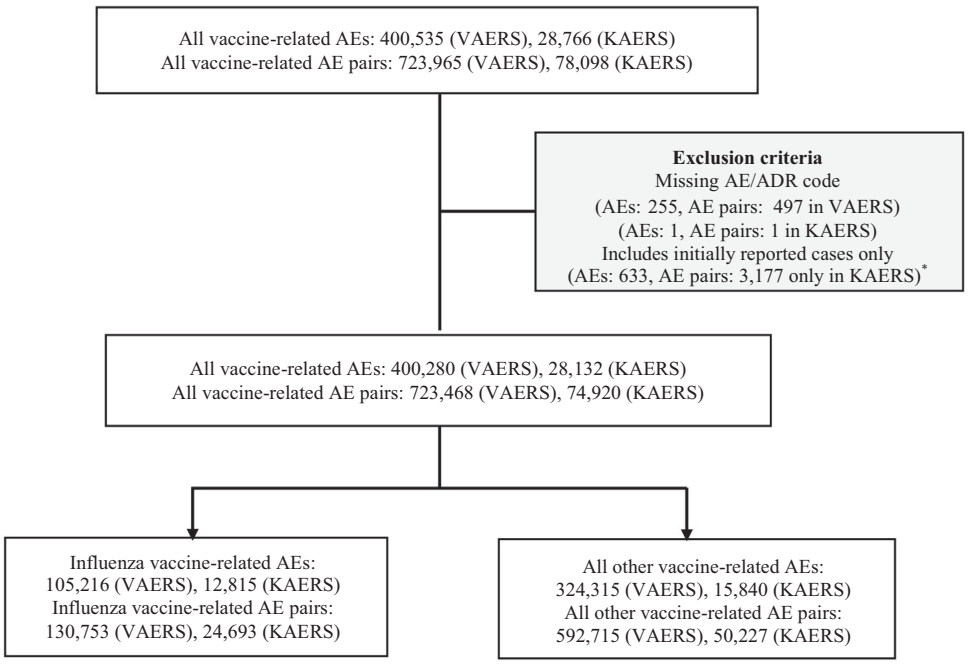

Fig. 1. Flow diagram of influenza vaccine-related AEs from the VAERS and KAERS databases between 2005 and 2017. AE, adverse event; ATC, anatomical therapeutic chemical classification system; ADR, adverse drug reaction; VAERS, Vaccine Adverse Event Reporting System; KAERS, Korea Adverse Event Reporting System. *AEs in the VAERS were always initially reported cases.

reporting, serious reporting, and type of influenza vaccine. A SAE was defined, according to the United State-Food and Drug Administration (US-FDA) and ICH definition, as any AE that was life-threatening; resulted in death, hospitalization, or prolongation of hospitalization; or caused persistent or significant disability and other medically serious results. Influenza vaccines were classified based on the following criteria: 1) the number of influenza viruses included: trivalent or quadrivalent, 2) the type of influenza virus: live-attenuated or inactivated, and 3) the type of culture: egg based or non-egg based (cell-cultured).

To detect safety signals, we applied disproportionality analysis [27] to compare the proportion of AE pairs (a specific AE and an influenza vaccine) with the proportion of reports involving the same AE and other vaccines. In the disproportionality analysis, four indicators were used to detect signals in spontaneously reported data—the proportional reporting ratio (PRR), the reporting odds ratio (ROR), the information component (IC), and chi-square (χ^2) values. These four indicators have been used by the KIDS, which is the Korean Regulatory Safety body [14]. A signal was detected when the PRR and ROR values were two or more, the χ^2 value was four or more, and the number of occurrences was three or more. If the IC criterion was set with the lower limit of the 95% confidence interval greater than zero, a signal was found [28].

2.5. The case/non-case approach

The case/non-case approach measures the disproportionality of a combination of a vaccine and a particular AE in a pharmacovigilance database. This approach was similar to the one used in a case-control study that assessed the association between the exposure of interest and the outcome, with the results being reported as ROR [29,30]. After excluding AE reports without information on sex and age, we defined cases as AE reports of GBS and others as non-cases in the KAERS and VAERS. Then, we included only cases developed within 45 days of vaccination. We selected sex, age group, and the onset season as matching variables and used the exact matching technique (**Supplementary** Table 5) with a case: non-case ratio of 1:10 to decrease confounders (Fig. 2). Additionally, the impact of live-attenuated vaccines on GBS reporting was analyzed and compared to that of inactivated vaccines in the VAERS database. In the KAERS database, there were no GBS cases after live-attenuated influenza vaccination.

Subgroup analysis was performed to decrease any bias due to differences in pharmacovigilance reporting and improve the detection of statistical signals in the VAERS database owing to paucity of cases after classification in the KAERS database. The ROR values of AE reports detected in each subgroup were separated according to sex, age group, and onset season. Subgroup analysis also showed clear advantages over crude analyses with regard to sensitivity and precision.

3. Results

3.1. Comparison of AEFI in the VAERS and KAERS databases

About two-thirds of AE pairs were reported in females in both the databases. The age groups with the maximum number of patients in the VAERS and KAERS databases were 45–64 and 19–44 years, respectively. The proportion of serious reporting in the VAERS (38.9%) was higher than that observed in the KAERS (6.9%). Hospitalization or prolongation of hospitalization was the most commonly reported SAE in both the databases (VAERS: 23.2% and KAERS: 76.9%) except for miscellaneous cases. The most common type of vaccine in both the databases were trivalent, inactivated, or egg-based influenza vaccines (Table 1).

Table 2 shows that GBS was the most frequently reported neurological AE after influenza immunization in both the databases (VAERS: 56.6%, 1,042 cases and KAERS: 29.9%, 79 cases), regardless of the type of influenza vaccines. In the VAERS database, of all reported neurological AEs, GBS was more commonly reported after inoculating trivalent influenza vaccines (61.4%, 916 cases) than after inoculating quadrivalent influenza vaccines (36.0%, 126 cases). Differences in the frequency of GBS reporting by type of vaccines were also observed; however, the gap was not huge.

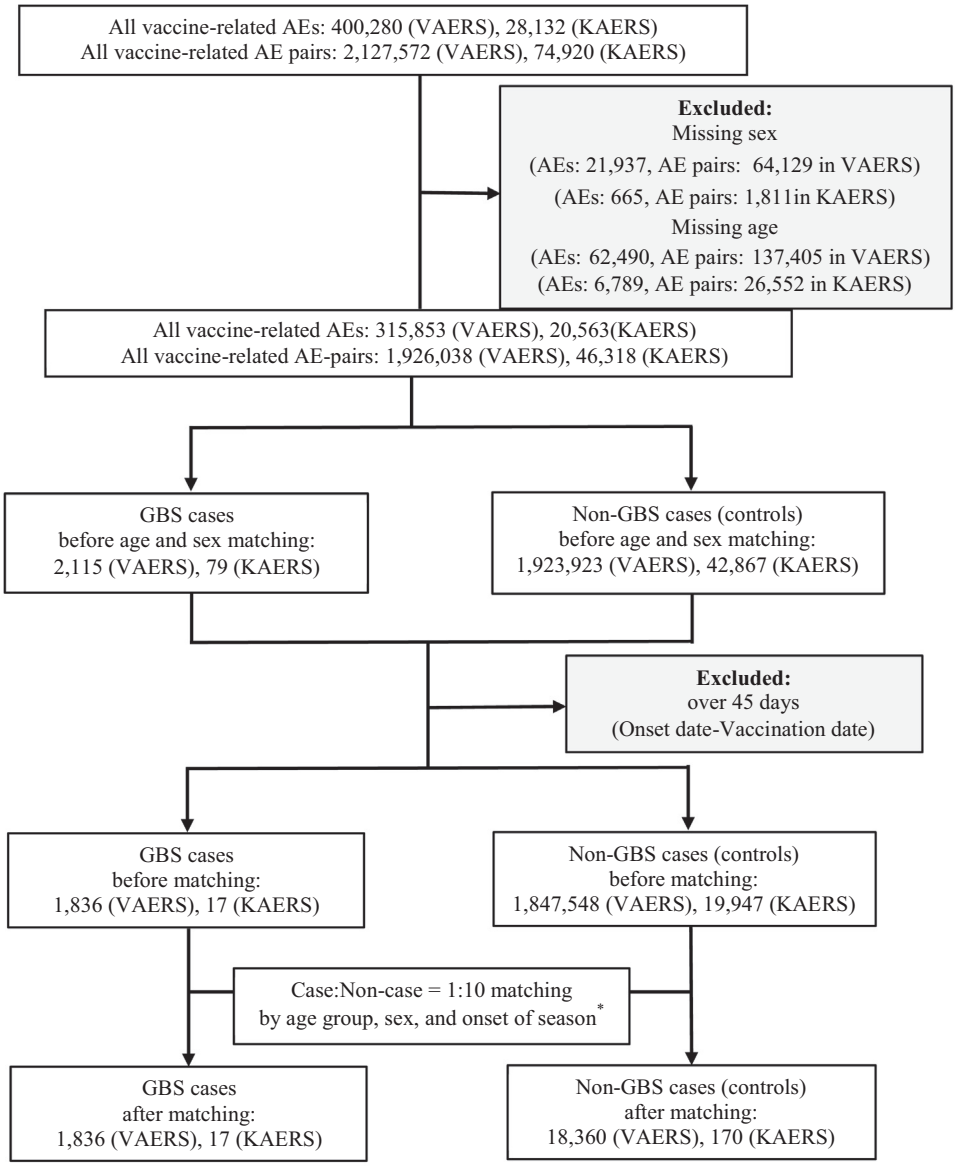

Fig. 2. Selection of Guillain–Barré syndrome for the case/non-case approach from the VAERS and KAERS databases between 2005 and 2017. AE, adverse event; GBS, Guillain–Barré syndrome; VAERS, Vaccine Adverse Event Reporting System; KAERS, Korea Adverse Event Reporting System. *Age was classified into seven groups—0–3, 4–6, 7–12, 13–18, 19–44, 45–64, and > 65 (unit: years).

Although GBS accounted for an overwhelming proportion of the reported neurological AEs, especially in the VAERS, other neurological AEs were relatively higher in the KAERS. In the KAERS database, seizure/convulsion (19.2%, 49 cases) was the second most frequent AE, followed by dysesthesia/paresthesia (15.7%, 40 cases).

As shown in **Supplementary** Table 3, mild AE reports, such as injection site pain and inflammation, were detected largely because of signal detection by the disproportionality analysis of the VAERS and KAERS data. The most frequently detected neurological symptom after influenza vaccination in both the VAERS and KAERS was paresthesia (VAERS: 4,918 cases and KAERS: 177 cases). Of the total cases of neurological AEs in the VAERS, GBS was reported in 1,867 cases, which was a meaningful signal in our study.

3.2. Differences in GBS reporting by sex

Table 3 shows that GBS was statistically more significantly reported among males than among females (VAERS: 53.3% ($p < 0.01$) vs. 46.7% and KAERS: 64.7% vs. 35.3% ($p < 0.01$)) before matching and after all kinds of immunizations. **Supplementary** Table 4 demonstrates the impact of sex in GBS reporting following all kinds of immunizations. However, after adjusting for age group, type of vaccination, and onset season, matching results showed no significant difference in GBS reporting by sex (ROR: 1.00, 95% confidence interval [CI]: 0.91–1.11 in the VAERS and ROR: 0.78, 95% CI: 0.20–3.08 in the KAERS).

The result of the subgroup analysis (Table 5), which focused on the association between influenza immunization and GBS reporting by sex, demonstrates that males who got the influenza immunization were 3.35 times (95% CI: 2.85–3.94) more likely to report GBS than those who got other vaccines. In females, the ROR against GBS reporting was 3.86 (95% CI: 3.23–4.62).

3.3. Assessment of the relationship between GBS and influenza vaccine using the case/non-case approach

For all vaccine-related AEs, the total number of AE pairs, obtained from the VAERS and KAERS databases, were 723,468

Table 1
Demographic characteristics of the reports of adverse events following influenza immunization from VAERS and KAERS between 2005 and 2017.

Characteristics	AE pairs		*p*-value
	VAERS n (%)	KAERS n (%)	
Total	130,753 (100.0)	24,693 (100.0)	
Sex			<0.01
Male	40,540 (31.0)	8,861 (31.6)	
Female	85,522 (65.4)	15,517 (67.2)	
Unknown	4,691 (3.6)	315 (1.2)	
Age group (years)			<0.01
0–3	10,564 (8.1)	1630 (6.6)	
4–6	5,387 (4.1)	727 (2.9)	
7–12	7,000 (5.4)	1,311 (5.3)	
13– 18	5,301 (4.1)	2,107 (8.5)	
19– 44	31,137 (23.8)	6,337 (25.7)	
45–64	35,183 (26.9)	3,477 (14.1)	
>65	29,289 (22.4)	1,804 (7.3)	
Unknown	6,892 (5.3)	7,300 (29.6)	
Year of reporting			<0.01
2005	4,082 (3.1)	7 (0.0)	
2006	3,674 (2.8)	8 (0.0)	
2007	5,012 (3.8)	28 (0.1)	
2008	6,829 (5.2)	16 (0.1)	
2009	9,859 (7.5)	90 (0.4)	
2010	12,250 (9.4)	132 (0.5)	
2011	11,204 (8.6)	1,128 (4.6)	
2012	10,932 (8.4)	864 (3.5)	
2013	12,135 (9.3)	5,838 (23.6)	
2014	13,249 (10.1)	1,331 (5.4)	
2015	14,588 (11.2)	8,083 (32.7)	
2016	13,688 (10.5)	2,756 (11.2)	
2017	13,251 (10.1)	4,412 (17.9)	
Serious reporting			
Yes (any kind)	50,828 (38.9)	1,702 (6.9)	<0.01
Death	851 (0.7)	60 (0.2)	<0.01
Life-threatening events	3,750 (2.9)	39 (0.2)	<0.01
Hospitalization or prolongation of hospitalization	11,800 (9.0)	1,309 (5.3)	<0.01
Persistent or significant disabilities	3,223 (2.5)	5 (0.0)	<0.01
Miscellaneous	45,463 (34.8)	476 (1.9)	<0.01
Type of influenza vaccine			
Number of strains included			<0.01
Trivalent	110,711 (84.7)	20,537 (83.2)	
Quadrivalent	20,042 (15.3)	4,156 (16.8)	
Type of strains			<0.01
Inactivated	120,811 (92.4)	22,183 (89.8)	
Live-attunated	9,942 (7.6)	2,510 (10.2)	
Type of culture method			<0.01
Egg-based	128,509 (98.3)	22,767 (92.2)	
Non-egg-based (cell-cultured)	2,244 (1.7)	1,926 (7.8)	

AE, adverse event; VAERS, Vaccine Adverse Events Reporting System; KAERS, Korean Adverse Events Reporting System.

and 74,920, respectively (Fig. 1). To focus on GBS, the most frequently reported neurological AE, we classified GBS as "case." Finally, 1,836 cases in the VAERS and 17 cases in the KAERS were included (Fig. 2).

After controlling for confounders by 1:10 exact matching method and considering sex, age group, and onset season variables, there was a slight difference between the VAERS and KAERS data after influenza vaccination (Table 3). After matching, the adjusted RORs for reporting the incidence of GBS following influenza vaccines in the VAERS and KAERS databases were 3.57 (95% CI, 3.16–4.03) and 3.09 (95% CI, 0.83–11.45), respectively (Table 4). Additionally, the VAERS data showed that GBS cases were more frequently reported after live-attenuated vaccination than after inactivated vaccination (adjusted ROR, 2.30; 95% CI, 1.74–3.05).

In the subgroup analysis of each age group in the VAERS data, ROR for GBS incidence in all age groups were statistically significant and the highest ROR was detected in the 0–3 years age group (adjusted ROR, 8.76; 95% CI, 5.14–14.93) (Table 5). Since only 17 cases in the KAERS database were included, it was not possible to perform subgroup analysis.

4. Discussion

To the best of our knowledge, this is the first study comparing >10 years of influenza vaccination-related AE reports from the US and South Korean AE databases. In addition, this study focused on evaluating the association between influenza vaccination and the development of GBS, a serious AEFI [1], using a case/non-case approach that effectively controlled the reported variables [29,30]. Currently, the South Korean government is actively expanding the target groups for free influenza vaccination [9], and thus, concerns regarding SAEs are increasing. Further, based on previous studies showing that the incidence of GBS varies based on geographical location [31], this study provides useful scientific evidence for safety signals of AE reporting, especially focusing on GBS, to implement a safe vaccine policy by comparing two

Table 2
Comparison of neurological AEs by the type of influenza vaccines from VAERS and KAERS between 2005 and 2017.

Neurological AEs	VAERS									KAERS								
	AE pairs, n (%)		*p*-value	AE pairs, n (%)		*p*-value	AE pairs, n (%)		*p* value	AE pairs, n (%)		*p*-value	AE pairs, n (%)		*p*-value	AE pairs, n (%)		*p*-value
	Tri-valent	Quadrivalent		Inactivated	Live		Egg based	Cell based		Tri-valent	Quadrivalent		Inactivated	Live		Egg based	Cell based	
GBS	916 (61.4)	126 (36.0)	<0.01	986 (57.3)	56 (47.1)	<0.01	1,023 (56.7)	19 (52.8)	<0.01	76 (29.8)	3 (33.3)	<0.01	79 (31.3)	0 (0.0)	–	77 (29.6)	2 (50.0)	<0.01
Facial paralysis	44 (3.0)	49 (14.0)	0.60	93 (5.4)	0 (0.0)	–	86 (4.8)	7 (19.4)	<0.01	37 (14.5)	1 (11.1)	<0.01	37 (14.7)	1 (8.3)	<0.01	37 (14.2)	1 (25.0)	<0.01
Narcolepsy	27 (1.8)	5 (1.4)	<0.01	19 (1.1)	13 (10.9)	0.29	32 (1.8)	0 (0.0)	–	10 (3.9)	0 (0.0)	–	4 (1.6)	6 (50.0)	0.53	10 (3.8)	0 (0.0)	–
Miller Fisher syndrome	33 (2.2)	2 (0.6)	<0.01	29 (1.7)	6 (5.0)	<0.01	35 (1.9)	0 (0.0)	–	1 (0.4)	0 (0.0)	–	1 (0.4)	0 (0.0)	0.65	1 (0.4)	0 (0.0)	–
Nerve injury	142 (9.5)	9 (2.6)	<0.01	148 (8.6)	3 (2.5)	<0.01	150 (8.3)	1 (2.8)	<0.01	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Nerve palsy	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Neuritis, excluding GBS/ neuropathy	35 (2.3)	10 (2.9)	<0.01	43 (2.5)	2 (1.7)	<0.01	45 (2.5)	0 (0.0)	–	9 (3.5)	1 (11.1)	0.01	10 (4.0)	0 (0.0)	–	10 (3.8)	0 (0.0)	–
Dysesthesia/paresthesia	17 (1.1)	0 (0.0)	–	17 (1.0)	0 (0.0)	–	17 (0.9)	0 (0.0)	–	40 (15.7)	0 (0.0)	–	40 (15.9)	0 (0.0)	–	40 (15.4)	0 (0.0)	–
Encephalitis/encephalopathy	108 (7.2)	11 (3.1)	<0.01	103 (6.0)	16 (13.4)	<0.01	119 (6.6)	0 (0.0)	–	21 (8.2)	3 (33.3)	<0.01	21 (8.3)	3 (25.0)	<0.01	24 (9.2)	0 (0.0)	–
Myelitis	16 (1.1)	2 (0.6)	<0.01	18 (1.0)	0 (0.0)	–	18 (1.0)	0 (0.0)	–	9 (3.5)	1 (11.1)	0.01	10 (4.0)	0 (0.0)	–	10 (3.8)	0 (0.0)	–
Meningitis/meningism	22 (1.5)	5 (1.4)	<0.01	20 (1.2)	7 (5.9)	0.01	27 (1.5)	0 (0.0)	–	3 (1.2)	0 (0.0)	–	3 (1.2)	0 (0.0)	–	3 (1.2)	0 (0.0)	–
Seizure/convulsion	131 (8.8)	131 (37.4)	<0.01	246 (14.3)	16 (13.4)	<0.01	253 (14.0)	9 (25.0)	<0.01	49 (19.2)	0 (0.0)	–	47 (18.7)	2 (16.7)	<0.01	48 (18.5)	1 (25.0)	<0.01
Total	1,491	350		1,722	119		1,805	36		255	9		252	12		260	4	

AE, adverse event; GBS, Guillain–Barré syndrome; VAERS, Vaccine Adverse Events Reporting System; KAERS, Korean Adverse Events Reporting System.

Table 3
Characteristics of GBS case and non-GBS case reports before and after matching from VAERS and KAERS databases between 2005 and 2017.

Characteristics	VAERS						KAERS					
	Before matching			After matching			Before matching			After matching		
	n (%)		*p*-value	n (%)		*p*-value	n (%)		*p*-value	n (%)		*p*-value
	Cases	Non-cases		Cases	Non-cases		Cases	Non-cases		Cases	Non-cases	
Sex			<0.01			1			<0.01			1
Male	978 (53.3)	724,421 (39.2)		978 (53.3)	9,780 (53.3)		11 (64.7)	6.659 (33.4)		11 (64.7)	110 (64.7)	
Female	858 (46.7)	1,123,127 (60.8)		858 (46.7)	8,580 (46.7)		6 (35.3)	13,288 (66.6)		6 (35.3)	60 (35.3)	
Age group (years)			<0.01			1			<0.01			1
0–3	92 (5.0)	451,506 (24.4)		92 (5.0)	920 (5.0)		0 (0.0)	5,833 (29.2)		0 (0.0)	0 (0.0)	
4–6	53 (2.9)	200,418 (10.8)		53 (2.9)	530 (2.9)		0 (0.0)	648 (3.2)		0 (0.0)	0 (0.0)	
7–12	73 (4.0)	151,709 (8.2)		73 (4.0)	730 (4.0)		0 (0.0)	475 (2.4)		0 (0.0)	0 (0.0)	
13–18	190 (10.3)	176,579 (9.6)		190 (10.3)	1,900 (10.3)		0 (0.0)	412 (2.1)		0 (0.0)	0 (0.0)	
19–44	459 (25.0)	352,182 (19.1)		459 (25.0)	4,590 (25.0)		8 (47.1)	8,037 (40.3)		8 (47.1)	80 (47.1)	
45–64	519 (28.3)	284,318 (15.4)		519 (28.3)	5,190 (28.3)		4 (23.5)	3,317 (16.6)		4 (23.5)	40 (23.5)	
>65	450 (24.5)	230,836 (12.5)		450 (24.5)	4,500 (24.5)		5 (29.4)	1,225 (6.1)		5 (29.4)	50 (29.4)	
Onset Season			<0.01			1			0.67			1
Spring	187 (10.2)	333,461 (18.0)		187 (10.2)	1,870 (10.2)		1 (5.9)	967 (4.8)		1 (5.9)	10 (5.9)	
Summer	239 (13.0)	399,977 (21.6)		239 (13.0)	2,390 (13.0)		0 (0.0)	1,841 (9.2)		0 (0.0)	0 (0.0)	
Fall	848 (46.2)	650,976 (35.2)		848 (46.2)	8,480 (46.2)		5 (29.4)	4,120 (20.7)		5 (29.4)	50 (29.4)	
Winter	373 (20.3)	319,889 (17.3)		373 (20.3)	3,730 (20.3)		2 (11.8)	2,870 (14.4)		2 (11.8)	20 (11.8)	
Unknown	189 (10.3)	143,245 (7.8)		189 (10.3)	1,890 (10.3)		9 (52.9)	10,149 (50.9)		9 (52.9)	90 (52.9)	

GBS, Guillain–Barré syndrome; VAERS, Vaccine Adverse Events Reporting System; KAERS, Korean Adverse Events Reporting System.

Table 4
Case/non-case approach for GBS following influenza vaccination before and after matching from VAERS and KAERS databases between 2005 and 2017.

	Before matching			After matching		
	ROR multivariate[†]	95% CI limits		ROR multivariate[†]	95% CI limits	
		Lower	Upper		Lower	Upper
Influenza vaccination						
In VAERS	3.71	3.31	4.16	3.57	3.16	4.03
In KAERS	2.42	0.67	8.80	3.09	0.83	11.45
Live attenuated influenza vaccination						
In VAERS	2.02	1.57	2.61	2.30	1.74	3.05

CI, confidence interval; GBS, Guillain–Barré syndrome; VAERS, Vaccine Adverse Events Reporting System; KAERS, Korean Adverse Events Reporting System; ROR, reporting odds ratio.
[†] Adjusted according to sex, age group, and onset season.

Table 5
Subgroup analysis associated with factors for GBS following influenza vaccination: sex, age group, and onset season from VAERS database between 2005 and 2017.

	VAERS					
	Before matching			After matching		
	ROR	95% CI limits		ROR multivariate[†]	95% CI limits	
		Lower	Upper		Lower	Upper
Sex						
Male	3.52	3.02	4.10	3.35	2.85	3.94
Female	3.99	3.37	4.73	3.86	3.23	4.62
Age group (years)						
0–3	8.62	5.34	13.92	8.76	5.14	14.93
4–6	4.02	2.10	7.68	3.84	1.92	7.67
7–12	2.39	1.32	4.31	2.12	1.14	3.97
13–18	2.08	1.39	3.10	2.01	1.32	3.08
19–44	3.07	2.47	3.83	2.88	2.28	3.63
45–64	4.61	3.65	5.81	4.56	3.57	5.84
>65	4.17	3.31	5.26	4.19	3.28	5.34
Onset season						
Spring	4.50	2.97	6.83	4.41	2.73	7.12
Summer	1.92	1.14	3.23	1.90	1.08	3.33
Fall	3.04	2.57	3.59	2.96	2.49	3.53
Winter	5.20	4.17	6.49	5.03	3.98	6.35

CI, confidence interval; GBS, Guillain–Barré syndrome; ROR, reporting odds ratio.
VAERS, Vaccine Adverse Events Reporting System.
[†] In the subgroup analysis by sex, adjusted according to age group and onset season, in the subgroup analysis by age group, adjusted according to sex and onset season, and in the subgroup analysis by onset season adjusted according to sex and age group.

nationwide AE reporting systems of representative areas of America and Asia. As the importance of comprehensive safety management is increasing, our findings can help monitor safety issues on influenza immunization worldwide and contribute making pharmacovigilance system by providing special aids for countries that do not yet have an AE reporting system.

Results of the comparison between the VAERS and KAERS databases demonstrated that the proportions of sex, age group, and year of reporting were different. These differences were considered related to differences in the timing of implementation and target age group of national vaccine policies in the US and South Korea. However, the proportion of neurological AEs between the two databases were similar, with GBS being the most commonly reported neurological AE after influenza vaccination in both databases. There was a discrepancy in the composition of neurological AEs between the two databases. The ratio of GBS/non-GBS neurological AE was 0.4 (79/185) in the KAERS database, whereas that in the VAERS database it was 1.3 (1,042/799) (Table 2). This could be attributed to the influence of country-specific medical patterns to ascertain neurological disorders [32]. These neurological disorders usually have similar early symptoms, such as peripheral muscle weakness and tingling; thus, it is not easy to accurately distinguish and diagnose them [33]. However, treatment and prognosis differ according to each diagnosis [33], which can also affect the direction of the implementation of the vaccine policy. Therefore, it is necessary to use internationally agreed diagnostic criteria, such as ICD-10th code [34] and the Brighton Collaboration, to accurately diagnose neurological disorders [35].

In this study, we analyzed whether the type of influenza vaccine affects the reporting patterns of neurological AEs. With the advent of live-attenuated, quadrivalent, and cell-cultured vaccines, there have been discussions about how these influenza vaccines compared to conventional vaccines (such as inactivated, trivalent, and egg-based vaccines) affect the development of neurological AEs. In particular, as influenza itself is a major cause of GBS [4] and live-attenuated vaccines have not been approved for use in children aged <2 years owing to safety concerns such as wheezing [36], there has been an increasing interest in the safety of live-attenuated vaccines. Our descriptive analysis (Table 2) showed no differences in the frequency of GBS reports among all neurological AEs between inactivated (57.3%) and live-attenuated vaccines (47.1%) in the VAERS data. However, results from the logistic regression after matching by sex, age group, and onset season showed more frequent GBS reports after administration of live-attenuated vaccines than after administration of inactivated vaccines (adjusted ROR 2.30; 95% CI, 1.74–3.05) (Table 4), which differs from the results obtained in previous studies [37–40]. From 2013 to 2016, the CDC did not recommend live-attenuated vaccines

[41], which lead to a reduction in AE reports. Hence, the effects of live-attenuated vaccines on GBS occurrence were difficult to observe in this study.

Spontaneous and voluntary AE reporting data have an intrinsic limitation, i.e., the inability to ascertain the causality of an AE owing to differences in the amount and quality of information collected in each case [42–44]. Nevertheless, disproportionality analysis can detect a safety signal when a specific AE is reported in a higher number than expected [28], thus allowing the safety signal to be monitored more closely in other healthcare databases and systems. Results from the disproportionality analysis showed that the most common safety signals were either pain or swelling at the injection site, which were predictable (**Supplementary** Table 3). Further, neurological AEs, such as muscle weakness and paresthesia, were detected in both databases. In addition, GBS was analyzed as the safety signal in the VAERS data. All the top 20 safety signals detected were on the influenza vaccine labels in the US and South Korea.

To confirm the association between influenza vaccination and GBS reporting as an AEFI, we used an advanced disproportionality analysis method known as the case/non-case approach. This method could control confounders in matching and multivariate logistic regression. Results from the case/non-case approach after matching showed that the ROR for GBS with influenza vaccination was significantly high in both the databases (VAERS: adjusted ROR, 3.57; 95% CIs 3.16–4.03 and KAERS: adjusted ROR, 3.09; 95% CI, 0.83–11.45). Although the association between influenza vaccination and the incidence of GBS is still controversial and there is no clear evidence on the biological mechanisms [16,17], we need to closely monitor and manage GBS events after influenza vaccination.

Previous studies have found that influenza infection itself leads to a higher risk of GBS than influenza immunization [4,45,46]. However, since the VAERS and KAERS data only include AE reports after influenza immunization, we could not directly compare the risk between influenza infection and immunization in this study. Although this study shows that GBS is the most frequently reported AEFI for influenza and that influenza vaccination is more likely to cause GBS than other vaccinations, it does not mean that influenza vaccination should be avoided or that influenza vaccinations lead to a higher risk of GBS than no vaccination. In this study, sex-specific analysis on GBS reporting showed that the frequency of AE reports was higher in males than in females in both databases, which is in line with the results of a previous study [15]. However, the results of the case/non-case approach show that GBS reporting was not affected by sex (**Supplementary** Table 4). GBS occurs more frequently in men than in women [31], but sex differences in the development of GBS after vaccination against influenza are controversial [47]. For example, Burwen found that males enrolled in the Medicare program reported more GBS than females after influenza immunization, but the combined results of all sexes were not statistically significant [48]. Using hospital discharge data of four states in the US, Lasky et al. observed no differences in GBS development between sexes ($p = 0.65$) [49]. Thus, to assess sex differences in GBS reporting, a comprehensive study using various combined datasets is needed.

This study has some limitations. First, as mentioned above, the two databases selected in this study, the VAERS and KAERS, are collections of voluntary reports from people who experience AEs. Therefore, some AE reports lacked crucial information required for diagnosis. Moreover, even a large number of specific AE reports after vaccination does not mean such AEs are caused by the vaccine. Second, the two databases used in this study use different AE coding systems (MedDRA in the VAERS vs. WHO-ART in the KAERS). Although we created a system to transfer AE terms between the two databases (**Supplementary** Table 2), there is still a possibility of unexpected non-systematic errors. For example, it is hard to perfectly remove potential misclassification errors among peripheral neurological diseases because of their similarities in symptoms and they may be different by geographical regions in the world [31]. Third, although we adjusted for confounders such as age group, sex, and onset season in the logistic regression, we could not control for influenza infection itself, which is a cause of GBS [4,45]. Fourth, although trends in GBS reporting are likely to be affected by the type of circulating viruses over the years [46], our study focused on GBS as an AEFI. Fifth, since follow-up reports were not open source, they could not be included in this study; hence, we could not track changes in diagnosis of GBS in the follow-up reports. Thus, we may have underestimated or overestimated the incidence of GBS. Therefore, the results should be interpreted with caution.

We found that GBS was the most commonly reported neurological AEFI for influenza and that people vaccinated with live-attenuated vaccines in the US reported more cases of GBS than those receiving other vaccine types. Additionally, as shown in the case/non-case analysis, we noted that the potential risk for the development of GBS with influenza vaccination was high. Thus, there is a need to proactively monitor the occurrence of GBS, and future population-based long-term epidemiological studies should be conducted to determine causality with live-attenuated influenza vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.06.038.

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