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Original Article

Active Surveillance of Adverse Events Following Immunization against Pandemic Influenza A (H1N1) in Korea

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SUMMARY: Surveillance of vaccine safety is one of the public health interventions used to investigate the causal relationship between vaccines and adverse events. Using active surveillance data, we aimed to compile a detailed summary describing the safety of the pandemic influenza A (H1N1) vaccine. Computer-assisted telephone interview was used to investigate adverse events for 9,000 subjects who had received non-adjuvanted vaccines between November 2009 and January 2010, and for 19,000 adults who received adjuvanted vaccines from January through March 2010. The participants were interviewed to obtain information about local and systemic adverse events. Among subjects who received the non-adjuvanted vaccine, 5.5% (n = 492) reported adverse events after vaccination, while 6.7% of those who received the adjuvanted vaccine reported adverse events. In the group receiving the adjuvanted vaccine, the highest reported rate of adverse events was among persons aged 19–49 years (9.1%, 577/6,329), followed by persons aged 50–64 years (7.2%, 485/6,718), and elderly persons aged 65 years and over (3.4%, 204/5,953). The implementation of this active surveillance study demonstrated the safety of both the adjuvanted and non-adjuvanted H1N1 vaccines.

INTRODUCTION

Although vaccination is one of the most effective public health measures for the control and prevention of communicable diseases, no vaccine is perfectly safe (1,2). A decrease in the perceived threat of vaccine-preventable diseases, due to the high vaccine coverage rate, has resulted in an increase in concerns regarding adverse events following immunization (AEFI) in the general public (3). Subsequently, when public confidence in vaccination is lost, herd immunity decreases because of the resulting decline in vaccine coverage, and outbreaks of vaccine-preventable diseases may occur (4). To avoid such consequences, monitoring vaccine safety is considered to be one of the most essential public health measures that can be implemented to maintain public confidence in vaccination programs (5).

Monitoring the safety of the influenza vaccine is especially important because of the inherent properties of the vaccine. First, the antigenic components of the influenza vaccine may change each season, since the immunity conferred in one season does not prevent infection by a different viral strain the next season. Thus, it is necessary to administer vaccines yearly (6). Second, in contrast to other vaccines, the primary target groups of the influenza vaccine are patients who have certain medical conditions that may elevate the risk of morbidity and mortality. This may result in an increase in the reporting rate of AEFIs (7). Lastly, timely detection of AEFIs in the setting of the pandemic influenza vaccination campaign is crucial, mainly because the majority of the population was exposed to the vaccine during implementation of the mass immunization program.

Multifaceted approaches have been used to achieve efficacious vaccine safety surveillance in many countries. Passive surveillance has detected under-recognized AEFIs and has enabled the collection of data that can be used to assess causality between the vaccine and adverse events (8). However, certain aspects of the passive reporting system, namely, low reporting rate, biased reports, and incomplete information, limit the quality of surveillance (9). To complement passive surveillance programs, active surveillance through either direct patient follow-up or database-linked methods may provide additional information and may lead to the detection of mild AEFIs that are not detectable through passive surveillance programs (10).

In Korea, the importance of AEFI surveillance was not widely recognized until 1994, when 5 deaths occurred that were thought to be related to the Japanese encephalitis vaccine (11). After the incident, a passive surveillance system was established, which included an electronic reporting system that allowed patients, their guardians, and their physicians to submit information. Comprehensive case investigations of AEFIs by the national regulatory authority, in conjunction with the National Vaccine Injury Compensation Program, were established as well. In 2001, the Infectious Diseases Prevention Act was revised to mandate that all

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healthcare personnel report particular AEFIs through the electronic surveillance system (12).

Although the AEFI reporting rate and related compensation claims have increased since 2005, the quality of the AEFI surveillance program in Korea is still limited by under-reporting, inadequate data provided by reporters, lack of the denominator data needed to accurately estimate rates, and lack of known background rates. In the United States, the dose-based AEFI reporting rate from 1991 to 2001 was 0.014% (11.4 reports per 100,000 net doses distributed) (9). In Korea, the number of AEFI cases reported through routinely operated passive surveillance systems was as low as 364 cases in 2005, 635 cases in 2006, 515 cases in 2007, and 407 cases in 2008, despite the fact that more than 16,000,000 doses of vaccines were distributed annually during these years. Clearly, establishment of an active surveillance program and collection of more detailed AEFI data is needed.

In October 2009, Korea launched an immunization campaign against the pandemic (H1N1) 2009 virus. The initial priority groups, including healthcare workers, essential service providers, and pregnant women, were vaccinated with a non-adjuvanted, monovalent vaccine manufactured by a domestic pharmaceutical company (Green Cross Corp., Seoul, Korea) (13). Subsequently, the target group was expanded to include children ranging from 6 months to 3 years of age, as well as preschool and school-aged children by late 2009 to 2010 (14). In conjunction with the monovalent vaccine produced by Green Cross Corporation, an emulsion-based adjuvant, MF59 (Novartis International AG, Basel, Switzerland) was administered to the general population above the age of 19, including the elderly over 65 years of age, and those with chronic health conditions (15).

With the implementation of such a large-scale immunization campaign, detailed vaccine safety monitoring is necessary, especially considering that the vaccines used in this campaign underwent accelerated registration procedures. To complement the routinely operated passive surveillance program, the Korea Centers for Disease Control and Prevention (KCDC) conducted active surveillance for the detection of adverse events following immunization against the pandemic (H1N1) 2009 virus. The aim of this study was to compile a detailed summary of the safety surveillance of monovalent, non-adjuvanted or adjuvanted influenza vaccines administered in Korea during the 2009–2010 season.

MATERIALS AND METHODS

A cross-sectional study was conducted from November 2009 through January 2010 to survey participants who had received non-adjuvanted vaccines and from January 2010 through March 2010 to survey participants who had received adjuvanted vaccines. Data concerning vaccine recipients were collected from the National Immunization Registry, and the participants were recruited using quota sampling to ensure adequate correspondence between groups for age and sex.

From October 28, 2009 through March 1, 2010, approximately 12,849,619 persons in Korea had received the H1N1 vaccine. This population comprised 10,531,885 persons who had received the non-adjuvanted vaccine and 2,317,734 persons who had received the adjuvanted vaccine. Nine thousand non-adjuvanted vaccine recipients and 19,000 adjuvanted vaccine recipients were selected by quota sampling. Surveys were conducted from November 2009 through January 2010 for the non-adjuvanted vaccine recipient group and from January 2010 through March 2010 for the adjuvanted vaccine recipient group. Participants in the non-adjuvanted vaccine group were classified according to their social group as well as their age: 2,000 subjects were less than 3 years old, 1,000 subjects were preschool-aged children, 3,000 subjects were school-aged children, and 3,000 subjects were adult-aged recipients. The adult group comprised 1,000 healthcare workers, 1,000 essential service providers, and 1,000 pregnant women. The participants in the adjuvanted vaccine group were classified according to their age: 6,329 recipients aged 19–49 years, 6,718 recipients aged 50–64 years, and 5,953 recipients over the age of 65 years. In addition, the adjuvanted group was further classified according to health status at the time of interview: 4,500 recipients were chronically ill and 14,500 recipients were previously healthy. Data from the Korea Health Insurance Review Agency were retrieved in order to determine whether the interviewee had a chronic illness. Participants were defined as having chronic illnesses if they had been previously diagnosed with diabetes mellitus, hypertension, chronic liver diseases, chronic heart diseases, or chronic lung diseases.

Recipients were selected if they (i) agreed to allow the collection and utilization of their personal information and (ii) signed an immunization administration record sheet. In order to enroll in the study, participants were asked to record both their home telephone number and cellular phone number on the immunization administration record sheet. A total of 3 telephone calls were made: the first call through the home telephone (45 s), and 2 subsequent trials through cellular telephones. Research & Research Corporation (Seoul, Korea) was commissioned by the KCDC to conduct interviews from a questionnaire developed after extensive consultation with researchers (Table 1). Computer-assisted telephone interview (CATI) with random dialing was used to interview the participants. Reports from parents or guardians were used for participants less than 3 years old and for preschool-aged children. The telephone interview involved 26 questions and lasted approximately 8 to 10 min. Informed consent was obtained during the call session. The questionnaire specifically sought information about the vaccination. For example, the participants were asked, ''Did you have any side effects you would attribute to the pandemic influenza vaccine?'' If the participant answered ''no,'' then no further questions were asked. Those who indicated that they had experienced adverse events were subsequently asked about the nature of the adverse events, including local events, such as redness, pain, and indurations, and systemic events, such as fever, chills, myalgia, arthralgia, general weakness, headache, syncope, nausea, and vomiting. The participants were also asked about the occurrence of urticaria, itchiness around eyes and mouth, respiratory difficulties, weakness in the lower extremities, diagnoses of Guillain-Barré syndrome (GBS), tremors in the extremities, and seizure-like symptoms.

For statistical analysis, the χ^2 test and Fisher's exact

Table 1. Questionnaire for computer-assisted telephone interview, translated from Korean

SQ1. Confirm the name of participant

SQ2. Have you (or child) received pandemic influenza A (H1N1) vaccine within 1 month?
(1) Yes (2) No (→ Excluded from analysis)

SQ3. Sex (→ Checked through CATI)
(1) Male (2) Female

SQ4. Age (→ Checked through CATI)
(1) 6–11 months (2) 1 ≤ age < 3 (3) 3 ≤ age < 6 (4) 7 ≤ age < 18 (5) 18 ≤ age < 65 (6) age ≤ 65

SQ5. Which city or province have you received your immunization?
(1) Seoul (2) Busan (3) Daegu (4) Incheon (5) Gwangju (6) Daejeon
(7) Ulsan (8) Gyeonggi (9) Gangwon (10) Chungbuk (11) Chungnam (12) Jeonbuk
(13) Jeonnam (14) Gyeongbuk (15) Gyeongnam (16) Jeju

SQ6. After the immunization, did the participant have any side effect that would attribute to pandemic influenza vaccine?
(1) Yes (2) No (→ Excluded from analysis)

SQ7. Was there any other vaccines did the participant received at the same time or within 1 month of the immunization against pandemic influenza?
(1) Yes (2) No

SQ8–24. After the immunization, which of the following problem did the participant had experienced?
SQ8. Redness (1) Yes (2) No
SQ9. Induration (1) Yes (2) No
SQ10. Pain (1) Yes (2) No
SQ11. Fever (1) Yes (2) No
SQ12. Chilling (1) Yes (2) No
SQ13. Myalgia (1) Yes (2) No
SQ14. Arthralgia (1) Yes (2) No
SQ15. General weakness (1) Yes (2) No
SQ16. Headache (1) Yes (2) No
SQ17. Syncope (1) Yes (2) No
SQ18. Urticaria (1) Yes (2) No
SQ19. Itching (1) Yes (2) No
SQ20. Respiratory difficulty (1) Yes (2) No
SQ21–1. If yes, when did the participant had respiratory difficulty?
(1) within 1 day (2) 1–2 days (3) 2–3 days (4) 3–4 days
SQ21–2. If yes, did the participant have diagnosed with asthma before immunization?
(1) Yes (2) No
SQ21–3. If yes, was the participant treated for respiratory difficulty?
(1) Yes (2) No
SQ21–4. If yes, was the participant diagnosed as anaphylaxis by physician?
SQ21. Numbness (1) Yes (2) No
SQ22. Tremor (1) Yes (2) No
SQ23. Seizure (1) Yes (2) No
SQ24. Lower extremities weakness (1) Yes (2) No

SQ25. How soon after the immunization given did the first symptom occurred? ( ) days

SQ26. Did the participant visit medical facility because of the symptom?
(1) No (2) office visit (3) hospital admission

CATI, computer-assisted telephone interview.

test were used to assess the association of adverse events with vaccine type, sex, age, and health status. A P value < 0.05 was considered statistically significant, and all statistical analyses were performed using Statistical Package for Social Sciences software, version 16.0 (SPSS, Chicago, Ill., USA).

RESULTS

Among the 9,000 participants who had received the non-adjuvanted vaccine, 5.5% (492/9,000) reported adverse events after vaccination (Table 2). When stratified by social groups, the highest reported rate for adverse events was among healthcare workers (9.9%, 99/1,000). This rate was more than twice that among preschool-aged children (4.0%, 40/1,000). The lowest reported rate was found in infants and young children less than 3 years old (2.0%, 39/2,000). This was followed by preschool-aged children, pregnant women (4.5%, 45/1,000), school-aged children (6.1%, 183/3,000), and essential service providers (8.6%, 86/1,000). Adverse events were more frequent among females than males

Table 2. Adverse events after the receipt of the influenza A (H1N1) 2009 monovalent vaccines

			Target population[1)]	Doses vaccinated[1)]	Survey subject	Reported adverse event	Predicted adverse event
						No. (%)	
Non-adjuvant[2)]	Social group	Children < 3 y	840,000/840,000	628,833/533,273	2,000	39 (1.95)	12,262/103,098
		Preschool-aged	1,370,000/1,370,000	1,117,271/932,518	1,000	40 (4.00)	44,691/37,301
		School-aged	6,150,000/434,000	6,167,033/407,321	3,000	183 (6.10)	376,189/24,847
		Healthcare worker	570,000	437,944	1,000	99 (9.90)	43,356
		Essential services	170,000	219,159	1,000	86 (8.60)	18,848
		Pregnant women	100,000	88,533	1,000	45 (4.50)	3,984
		Subtotal for adult-aged	840,000	745,636	3,000	230 (7.67)	57,165
	Sex	Male	NA	NA	3,930	185 (4.71)	NA
		Female			5,070	307 (6.06)	
	Total		11,844,000	10,531,885	9,000	492 (5.47)	575,743
Adjuvant	Age group (y)	19–49	NA	169,933	6,329	577 (9.12)	15,492
		50–64		145,323	6,718	485 (7.22)	10,491
		≥65	2,300,000	2,002,478	5,953	204 (3.43)	68,622
	Medical history	Chronic illness	1,820,000	965,594	4,500	404 (8.98)	86,689
		Previously healthy	NA	1,352,140	14,500	862 (5.94)	NA
	Sex	Male	NA	NA	8,281	379 (4.58)	NA
		Female			10,719	887 (8.28)	
	Total		NA	2,317,734	19,000	1,266 (6.67)	NA

[1)]: Vaccinations in Korea by August 13, 2010, 2 doses are given to children aged 6 months through 9 years, described as the first dose/second dose.
[2)]: Age-adjusted crude proportion of adverse events vaccination by direct standardization.
NA, not applicable.

(6.1%, 307/5,070 for females versus 4.7%, 185/3,930 for males; $P < 0.01$). From the 2,317,734 recipients who had received the adjuvanted vaccine, 19,000 were quota-selected for interview, and of these, 6.7% reported having experienced adverse events (1,266/19,000). When stratified by age group, the highest reported rate for adverse events was among persons aged 19–49 years (9.1%, 577/6,329), followed by persons aged 50–64 years (7.2%, 485/6,718). This was more than twice the rate found in elderly people over the age of 65 years (3.4%, 204/5,953). In the adjuvanted vaccine group, more adverse events were reported by females than by males (8.3%, 887/10,719 for females versus 4.6%, 379/8,281 for males; $P < 0.01$), and adverse events were more frequently reported by participants with chronic health conditions than by healthy participants (9.0%, 404/4,500 and 5.9%, 862/14,500, respectively; $P < 0.01$).

The time interval between vaccination with the non-adjuvanted vaccine and the onset of symptoms was reported for 492 participants. More than two-thirds of these participants (78.3%, 382/492) reported that they had experienced symptoms less than a day following vaccination, while 12.6% (62/492) reported that they had an adverse event within 2 days of vaccination. Sixty-nine out of 492 (14.0%) participants reported that they had visited outpatient-based healthcare services for their symptoms, and 3 reported being hospitalized after receiving the vaccine. These 3 participants subsequently recovered without any complications. For recipients of the adjuvanted vaccine, the time interval between vaccination and the onset of symptoms was reported for 1,266 participants. Seventy-five percent (949/1,266) reported that they had experienced symptoms less than a day after receiving the vaccine, while 18.0% (228/1,266) reported that they had experienced an adverse event within 2 days of vaccination. Two participants from the non-adjuvanted vaccine group and 1 from the adjuvanted vaccine group were hospitalized for more than 5 days following administration of the vaccine (1 with pneumonia, 1 with dehydration, and 1 for an underlying disease), though it was not determined whether the vaccine was the cause of these complications.

Among the 492 participants from the non-adjuvanted vaccine group who reported adverse events after vaccination, 1.8% (166/9,000) reported local injection-site events (Table 3). The most common local reactions included injection-site pain ($n = 83$), followed by redness ($n = 58$), and induration ($n = 55$). Occurrence of local-site redness and induration ($P < 0.008$ and $P = 0.024$, respectively) was significantly higher among preschoolers than among children less than 3 years old, school-aged children, and adults.

Among the 1,266 participants from the adjuvanted vaccine group who reported adverse events, 3.2% (615/19,000) experienced local adverse events, and, similar to the non-adjuvanted vaccine group, the most frequently reported adverse event was pain ($n = 418$), followed by induration ($n = 265$), and redness ($n = 141$). The occurrence of local adverse events was the highest among persons aged 19–49 years (334/6,329, 5.3%), followed by persons aged 50–64 years (203/6,718, 3.0%), and the elderly over the age of 65 years (78/5,953, 1.3%; $P < 0.01$).

Systemic adverse events occurred in 363 participants in the non-adjuvanted vaccine group. These included general weakness ($n = 178$), headache ($n = 171$), fever ($n = 139$), and chills ($n = 104$). The overall occurrence

Table 3. Local and systemic events after vaccination with non-adjuvanted and adjuvanted vaccines

	Non-adjuvant								Adjuvant					
				Adult-aged				Total	Age (y)			Medical history		Total
	Children < 3 years	Preschool-aged	School-aged	HCP	ESP	Pregnant women	Subtotal		19–49	50–64	≥65	Chronic illness	Previously healthy	
	n = 39 /2,000	*n* = 40 /1,000	*n* = 183 /3,000	*n* = 99 /1,000	*n* = 86 /1,000	*n* = 45 /1,000	*n* = 230 /3,000	*n* = 492 /9,000	*n* = 577 /6,329	*n* = 485 /6,718	*n* = 204 /5,953	*n* = 404 /4,500	*n* = 862 /14,500	*n* = 1,266 /19,000
Local events	7 (0.4)	21 (2.1)	68 (2.3)	23 (2.3)	28 (2.8)	19 (1.9)	70 (2.3)	166 (1.8)	334 (5.3)	203 (3.0)	78 (1.3)	181 (4.0)	434 (3.0)	615 (3.2)
Redness	5 (0.3)	11 (1.1)	29 (1.0)	3 (0.3)	4 (0.4)	6 (0.6)	13 (0.4)	58 (0.6)	73 (1.2)	53 (0.8)	15 (0.3)	50 (1.1)	91 (0.6)	141 (0.7)
Induration	3 (0.2)	14 (1.4)	23 (0.8)	7 (0.7)	5 (0.5)	3 (0.3)	15 (0.5)	55 (0.6)	165 (2.6)	78 (1.2)	22 (0.4)	81 (1.8)	184 (1.3)	265 (1.4)
Pain	4 (0.2)	12 (1.2)	36 (1.2)	11 (1.1)	9 (0.9)	11 (1.1)	31 (1.0)	83 (0.9)	251 (4.0)	125 (1.9)	42 (0.7)	127 (2.8)	291 (2.0)	418 (2.2)
Systemic events	32 (1.6)	21 (2.1)	129 (4.3)	84 (8.4)	65 (6.5)	32 (3.2)	181 (6.0)	363 (4.0)	302 (4.8)	321 (4.8)	136 (2.3)	255 (5.7)	504 (3.5)	759 (4.0)
Fever	23 (1.2)	12 (1.2)	56 (1.9)	21 (2.1)	18 (1.8)	9 (0.9)	48 (1.6)	139 (1.5)	76 (1.2)	63 (0.9)	33 (0.6)	52 (1.2)	120 (0.8)	172 (0.9)
Chilling	7 (0.4)	3 (0.3)	39 (1.3)	21 (2.1)	24 (2.4)	10 (1.0)	55 (1.8)	104 (1.2)	120 (1.9)	136 (2.0)	42 (0.7)	106 (2.4)	192 (1.3)	298 (1.6)
Myalgia	6 (0.3)	1 (0.1)	42 (1.4)	31 (3.1)	22 (2.2)	11 (1.1)	64 (2.1)	113 (1.3)	155 (2.4)	152 (2.3)	61 (1.0)	131 (2.9)	237 (1.6)	368 (1.9)
Arthralgia	4 (0.2)	2 (0.2)	25 (0.8)	17 (1.7)	12 (1.2)	3 (0.3)	32 (1.1)	63 (0.7)	97 (1.5)	103 (1.5)	46 (0.8)	79 (1.8)	167 (1.2)	246 (1.3)
GW	13 (0.7)	9 (0.9)	64 (2.1)	37 (3.7)	39 (3.9)	16 (1.6)	92 (3.1)	178 (2.0)	190 (3.0)	185 (2.8)	71 (1.2)	160 (3.6)	286 (2.0)	446 (2.3)
Headache	4 (0.2)	5 (0.5)	76 (2.5)	31 (3.1)	38 (3.8)	17 (1.7)	86 (2.9)	171 (1.9)	140 (2.2)	117 (1.7)	51 (0.9)	114 (2.5)	194 (1.3)	308 (1.6)
Syncope	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0)	2 (0.0)	2 (0)	2 (0)	0 (0)	1 (0)	3 (0)	4 (0)
Nausea/vomiting	6 (0.3)	6 (0.6)	57 (1.9)	0 (0)	0 (0)	11 (1.1)	11 (0.4)	80 (0.9)	74 (1.2)	59 (0.9)	16 (0.3)	66 (1.5)	83 (0.6)	149 (0.8)
Other symptoms														
Urticaria	8 (0.4)	2 (0.2)	12 (0.4)	3 (0.3)	1 (0.1)	4 (0.4)	8 (0.3)	30 (0.3)	12 (0.2)	12 (0.2)	5 (0.1)	11 (0.2)	18 (0.1)	29 (0.2)
Itching	3 (0.2)	3 (0.3)	7 (0.2)	2 (0.2)	0 (0)	2 (0.2)	4 (0.1)	17 (0.2)	29 (0.5)	33 (0.5)	14 (0.2)	31 (0.7)	45 (0.3)	76 (0.4)
Resp difficulty	1 (0.1)	0 (0)	0 (0)	2 (0.2)	2 (0.2)	3 (0.3)	7 (0.2)	8 (0.1)	4 (0.1)	13 (0.2)	7 (0.1)	11 (0.2)	13 (0.1)	24 (0.1)
Numbness	0 (0.0)	1 (0.1)	5 (0.2)	0 (0)	0 (0)	1 (0.1)	1 (0)	7 (0.1)	25 (0.4)	44 (0.7)	17 (0.3)	31 (0.7)	55 (0.4)	86 (0.5)
Tremor	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	25 (0.4)	11 (0.2)	3 (0.1)	14 (0.3)	25 (0.2)	39 (0.2)
Seizure	2 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	7 (0.1)	9 (0.1)	5 (0.1)	5 (0.1)	16 (0.1)	21 (0.1)
LE weakness	1 (0.1)	0 (0)	0 (0)	1 (0.1)	1 (0.1)	0 (0)	2 (0.1)	3 (0)	7 (0.1)	10 (0.1)	7 (0.1)	7 (0.2)	17 (0.1)	24 (0.1)

HCP, healthcare personnel; ESP, essential service providers; GW, general weakness; Resp, respiratory; LE, lower extremities.

of systemic events was the highest among healthcare personnel (84/1,000, 8.4%), followed by essential service providers (65/1,000, 6.5%), school-aged children (129/3,000, 4.3%), pregnant women (32/1,000, 3.2%), preschool children (21/1,000, 2.1%), and children less than 3 years old (32/2,000, 1.6%; $P < 0.01$). Occurrence of fever was high in children less than 3 years old (23/2,000, 1.2%; $P < 0.01$), whereas headache and nausea/vomiting occurred more often in school-aged children (76/3,000, 2.5%, and 57/3,000, 1.9% respectively; $P = 0.044$).

Among the 1,266 participants in the adjuvanted vaccine group, 759 reported systemic events. The most frequently reported systemic adverse event was general weakness ($n = 446$), followed by myalgia ($n = 368$), headache ($n = 308$), and chills ($n = 298$). Systemic adverse events were the most frequent among persons aged 50–64 years (321/6,718, 4.8%) and aged 19–49 years (302/6,329, 4.8%), followed by elderly persons over the age of 65 years (136/5,953, 2.3%; $P < 0.01$).

Only a small number of participants in the non-adjuvanted vaccine group reported experiencing urticaria (30/9,000, 0.3%) or itching (17/9,000, 0.2%). Out of the 8 participants who reported respiratory difficulties, 5 had symptom onset within a day of vaccination, and none had a previous history of airway hypersensitivity. In the adjuvanted vaccine group, 0.2% (29/19,000) reported urticaria, and 0.4% (76/19,000) reported experiencing a nonspecific itching sensation. Out of the 24 participants who had respiratory difficulties, 6 had symptom onset within a day of vaccination, and 4 had a previous history of airway hypersensitivity. None of the participants from either the non-adjuvanted vaccine group or adjuvanted vaccine group reported physician-diagnosed anaphylaxis or anaphylactic reaction.

In the non-adjuvanted vaccine group, 3 participants reported seizure-like symptoms, and another 3 reported weakness in the lower extremities. None of these cases were diagnosed as epilepsy or GBS. In the adjuvanted vaccine group, 24 participants reported weakness in the lower extremities, and 21 experienced seizure-like events, but again, none of these cases were diagnosed as GBS or epilepsy.

DISCUSSION

Through employment of an ad hoc active surveillance program, this study aimed to provide a detailed description of the AEFIs experienced by recipients of the pandemic (H1N1) 2009 vaccine. Safety issues inevitably arose as a result of the mass vaccination campaign in Korea. During the influenza season of 2009–2010, the Green Cross Corporation launched their newly produced seasonal influenza vaccines as well as the pandemic vaccines in Korea for the first time. Because the methods used to produce the traditional influenza vaccines and the pandemic influenza vaccines were identical, the adverse events associated with the new pandemic influenza vaccines were expected to be similar to those of the seasonal influenza vaccines (16). Earlier studies have concluded that the monovalent A (H1N1) vaccine has a safety profile similar to that of the seasonal influenza vaccine (17–19).

Consistent with a previous placebo-controlled study, our study found that the most frequently occurring local adverse event was pain at the injection site, which was typically mild and did not interfere with daily activities (20). In participants aged 65 years and over, other adverse events occurring locally at the injection site and systemic symptoms such as fever and general weakness were less frequently reported, coinciding well with earlier studies (21–23). The unexpectedly high frequency of adverse events experienced by healthcare personnel may have resulted from the unique perceptions and attitudes toward AEFIs that exist in this particular population (24). Additionally, it is possible that this group might have reported their adverse events more actively than other populations in this study. The non-adjuvanted vaccine was found to be safe for pregnant women, as suggested by other studies (25,26).

In many other countries, the purpose of active surveillance is to supplement the centrally operated routine surveillance of AEFIs, monitor the introduction of new vaccines, and detect specific AEFIs that are significantly associated with a particular vaccine (27). The Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system operated in the United States, detects early warning signals and generates hypotheses regarding new vaccines and potential AEFIs. However, the data collected contains biased information, and incidence rates and relative risks of AEFIs associated with particular vaccines cannot be calculated (28). During the 2009–2010 season, the Chinese government issued an adjunct active surveillance system that used diary cards and a random telephone survey, in conjunction with the routinely performed passive surveillance system, for reporting events associated with the monovalent influenza vaccine (29). Through active surveillance, additional data was gathered that strengthened our understanding of vaccine safety and encouraged vaccine recipients to report adverse events and to seek medical care.

There were several limitations of this study. First, reports from preschool-aged children and children less than 3 years old were obtained by interviewing parents, and therefore, symptoms such as pain or itching might have been under-reported. Second, the frequency of adverse events was not intended to be used to directly compare non-adjuvanted vaccine recipients and adjuvanted vaccine recipients, since the background populations of these 2 groups was different. More importantly, however, both vaccines were generally well tolerated, and serious adverse events were uncommon among the participants of this study.

In conclusion, the presently described active surveillance system was implemented in order to supplement the collection of adverse event data from routine passive surveillance system. Active surveillance of the pandemic influenza A (H1N1) 2009 vaccine demonstrated the safety of both adjuvanted and non-adjuvanted vaccines. Continuous monitoring of vaccine recipients is necessary to ensure the long-term safety of these vaccines, and may assist in the development of new policies to enhance the control of influenza and reduce its complications in Korea.

Conflict of interest None to declare.

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