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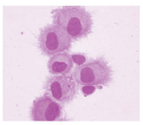

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RESEARCH PAPER

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Enhanced passive safety surveillance of a trivalent and a quadrivalent influenza vaccine in Denmark and Finland during the 2018/2019 season

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ABSTRACT

The European Medicines Agency requires Enhanced Passive Safety Surveillance (EPSS) for all seasonal influenza vaccines. Here, we report the EPSS results for the trivalent inactivated influenza vaccine (IIV3; Vaxigrip®) and the quadrivalent inactivated influenza vaccine (IIV4; VaxigripTetra™) during the 2018/19 influenza season in Denmark and Finland. The primary objective was to estimate the rates of suspected adverse reactions (ARs) occurring within 7 days following routine vaccination. Between October and November 2018, 1000 safety report cards (SRCs) for IIV3 were distributed in Denmark, and 996 SRCs for IIV4 were distributed in Finland. Participants were instructed to report any ARs by telephone or e-mail using the information provided on the SRC. All participants vaccinated with IIV3 were aged ≥18 years. Most participants vaccinated with IIV4 (95.5%) were aged 18 – 65 years, 2.2% were aged 6 months to 17 years, and 2.3% were aged >65 years. Fifty-five ARs were reported by 12 participants (1.2%) vaccinated with IIV3 and 162 ARs were reported by 53 participants (5.3%) vaccinated with IIV4. The most frequent ARs were vaccination site pain and fever for IIV3, and vaccination site pain, vaccination site inflammation, myalgia, and headache for IIV4. The 2018/19 AR rates for IIV3 were comparable to 2017/18 rates. The 2018/19 AR rates for IIV4 were higher than those in 2017/18 but were still lower than the expected AR rates listed in the IIV4 Summary of Product Characteristics. In conclusion, the 2018/19 EPSS showed no clinically significant change from the expected safety profiles of IIV3 and IIV4 vaccines.

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Introduction

Vaccination is the most effective way to control seasonal influenza and annual vaccination is recommended by the World Health Organization to at-risk groups including pregnant women, children aged <5 years, the elderly, and individuals with chronic health conditions.[1] Seasonal influenza vaccines present specific challenges for pharmacovigilance, which include mass immunization in large populations over a short and fixed period of time. To keep an optimal match between influenza vaccine formulation and the circulating seasonal influenza viral strains, a new vaccine has to be developed each year. In response to these challenges, the European Medicines Agency (EMA) requires enhanced safety surveillance for all seasonal influenza vaccines to rapidly detect and evaluate a significant increase in frequency or severity of adverse reactions (including local, systemic, or allergic reactions) in near real-time at the start of each seasonal influenza season, before the peak of vaccination occurs. Whereas routine pharmacovigilance is required in all countries where the vaccine is authorized, enhanced safety surveillance must be conducted each year in EU countries, preferably at the start of the vaccination season, and continue until a sufficient amount of vaccine exposure and safety data have been collected.

Enhanced passive safety surveillance (EPSS) is one of the surveillance designs recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).[2] Unlike active surveillance, which involves active follow-up of vaccinees who agreed to participate in the follow-up surveillance, passive safety surveillance relies on safety data collected spontaneously from vaccinees. Therefore, EPSS combines routine surveillance with clinical services that encourage patients and health-care professionals to report adverse events.[3] This can help reduce underreporting of adverse events, which usually occurs in routine pharmacovigilance systems.[3-5] Safety concerns may be indicated by increased rates of reactogenicity or allergic events compared to those expected or measured from the previous year's EPSS for a given vaccine. Therefore, EPSS acts as an early warning system by indicating a potential for more serious risks as vaccination uptake increases.

Sanofi Pasteur has produced a trivalent inactivated influenza vaccine (IIV3; Vaxigrip®) since 1968 and a quadrivalent inactivated influenza vaccine (IIV4; VaxigripTetra™) since 2016.[6] Both IIV3 and IIV4 are intramuscularly administered, split-virion vaccines and are indicated in Europe for individuals aged 6 months and older. The results from EPSS in previous seasons have been published for IIV3[7-9] and for IIV4.[9]

Here, we describe the EPSS results for IIV3 and IIV4 in the Northern Hemisphere for the 2018/19 influenza season and compare them with the 2017/18 season results.

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Patients and methods

Study design

This was a multicenter, non-interventional, EPSS study conducted in October and November 2018. EPSS of IIV3 was performed at 10 routine clinical care sites in Denmark and EPSS of IIV4 was performed at 8 routine clinical care sites in Finland. The EPSS aimed to include all age groups in line with the recommended indication for each vaccine. No sensitive data about the participants were collected including patient identification and confidential data. The primary objective was to estimate the rates of suspected adverse reactions (ARs) occurring within 7 days following routine vaccination with IIV3 (Vaxigrip, also called Inactivated Influenza Vaccine [split virion] BP; Sanofi Pasteur) or IIV4 (VaxigripTetra, also called Quadrivalent influenza vaccine [split virion, inactivated]; Sanofi Pasteur) during the Northern Hemisphere 2018/19 influenza season. Secondary objectives were to estimate reporting rates of suspected ARs by age group; estimate the rates of serious suspected ARs; and to compare the reporting rates of suspected ARs either with those recorded in the 2017/18 Northern Hemisphere influenza season, or with the IIV3 or IIV4 Summary of Product Characteristics (SmPC). The study was conducted in accordance with the Declaration of Helsinki, Good Epidemiological Practice, and the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance.[10-12] Ethics committee approval and informed consent were not required because the EPSS relied on routine pharmacovigilance and voluntary spontaneous reporting.

Vaccine formulations

The 2018/19 vaccine strains used for IIV3 were A/Michigan/45/2015 (H1N1) pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and B/Colorado/06/2017-like virus (B/Victoria lineage). IIV4 included these three strains plus B/Phuket/3073/2013-like virus (B/Yamagata lineage).

Study conduct and data collection

The study conduct and method of data collection used for this EPSS have been reported previously.[9] Briefly, health-care professionals distributed SRCs to the participants vaccinated with IIV3 or IIV4 (or for participants aged <18 years, to their parents or legal guardians), and recorded the vaccination information for each participant (participant identifier, age group, country, site, vaccine brand and batch, date of vaccination) using an electronic data capture system (eClinicalOS, Clinical Leader, PA, US). Participants were instructed to report any suspected ARs, especially those occurring in the first 7 days, via an e-mail address or by calling a dedicated local toll-free telephone number provided on the SRC. ARs reported by each participant were documented by a structured telephone interview or by follow-up e-mail. All events reported spontaneously by participants or health-care professionals were considered as suspected ARs (i.e., vaccine-related) unless the participants stated that they believed the events were unrelated to the vaccine or that a causal relationship could be excluded. No causality assessment was requested from the vaccinees or health-care professionals. We assumed that if participants did not report ARs, they did not experience an AR or AEI, although it is recognized that not all participants who experience an AR or AEI report it to their HCP. The EPSS began at the start of routine influenza vaccination for the 2018/19 influenza season at the study sites, and ended when 1000 SRCs per vaccine had been distributed (+2 weeks for subject reporting) or 2 months after the first vaccinations (including 6 weeks for SRC distribution + 2 weeks for subject reporting), whichever came first.

Sample size

The EU interim guidance for seasonal influenza vaccines requires that EPSS detects common ARs (frequency ≥1%).[2] Therefore, to provide a > 99% probability of reporting ≥1% of a given common AR, 1000 SRCs for each vaccine were to be distributed. As this was passive safety surveillance, no prespecified number of ARs was defined for individual age groups.

Statistical analysis

The rates of ARs and adverse events of interest (AEIs) for each vaccine were calculated at the end of the surveillance period by dividing the number of participants who reported ARs or AEIs and the total number of ARs or AEIs reported, by the number of SRCs distributed. ARs were coded with Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 21.1). AEIs, as listed in the PRAC guidance,[2] are serious or non-serious noteworthy events to the vaccine for which ongoing monitoring and further investigation may be required. Two-sided 95% confidence intervals (CIs) were calculated as described previously[8] using SAS® version 9.4 (SAS Institute, Cary, NC, USA). AR rates reported in 2018/19 were compared with the rates reported in the previous EPSS for the 2017/18 influenza season, which was conducted in the UK and Ireland.[9] Comparisons assessed if the AR rates were greater or not than the upper limit of the 95% CI for the rates reported in the 2017/18 influenza season.[9] Analyses were descriptive and no confirmatory hypothesis testing was performed.

Results

Exposure data

Between October 1 and October 30, 2018, 1000 SRCs for IIV3 were distributed by 10 health-care professionals in Denmark. In Finland, between October 3 and November 14, 2018, 996 SRCs for IIV4 were distributed by eight health-care professionals (Table 1). The EPSS covered one batch of IIV3 and three batches of IIV4. All participants vaccinated with IIV3 were ≥18 years of age, and most (79.5%) were older than 65 years. Most of the participants vaccinated with IIV4 (95.5%) were aged 18 – 65 years. Twenty-two of the IIV4 recipients (2.2%) were aged 6 months to 17 years and 23 (2.3%) were aged >65 years.

Table 1. Overall frequencies of suspected adverse reactions (ARs) and adverse events of interest (AEIs) occurring within 7 days by vaccine and age group.

		Participants reporting ≥1 AR		#ARs		Participants reporting ≥1 AEI[a]		#AEIs[a]	
	Safety report cards recorded	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
IIV3									
18 – 65 y	205	2	1.0 (0.1 – 3.5)	8	3.9 (1.7 – 7.5)	2	1.0 (0.1 – 3.5)	7	3.4 (1.4 – 6.9)
>65 y	795	9	1.1 (0.4 – 1.9)	19	2.4 (1.4 – 3.7)	5	0.6 (0.2 – 1.5)	10	1.3 (0.6 – 2.3)
Total	1000	11	1.1 (0.5 – 1.8)	27	2.7 (1.8 – 3.9)	7	0.7 (0.2 – 1.2)	17	1.7 (1.0 – 2.7)
IIV4									
6 mo–5 y	7	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)
6 – 12 y	10	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)
13 – 17 y	5	1	20.0 (0.5 – 71.6)	2	40.0 (5.3 – 85.3)	1	20.0 (0.5 – 71.6)	1	20.0 (0.5 – 71.6)
18 – 65 y	951	25	2.6 (1.6 – 3.7)	66	6.9 (5.4 – 8.8)	24	2.5 (1.5 – 3.5)	42	4.4 (3.2 – 5.9)
>65 y	23	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)	0	0.0 (–)
Total[b]	996	28	2.8 (1.8 – 3.8)	76	7.6 (6.1 – 9.5)	27	2.7 (1.7 – 3.7)	47	4.7 (3.5 – 6.2)

Abbreviations: CI, confidence interval; IIV3, trivalent split-virion inactivated influenza vaccine; IIV4, quadrivalent split-virion inactivated influenza vaccine; –, not calculated

[a]AEIs were defined according to the Pharmacovigilance Risk Assessment Committee[2]

[b]Total ARs and AEIs post-IIV4 vaccination include additional events reported by two participants with no safety report card numbers and of unknown age group.

Safety data

IIV3

Fifty-five ARs were reported by 12 participants (1.2%) vaccinated with IIV3 over the EPSS period (Table 2). All ARs with known time to onset (27/55, 49.1%) occurred within 7 days of vaccination (Table 1), with most (20/27, 74.1%) occurring on the same day or the day after vaccination. All ARs with known duration resolved (19/55, 34.5%), half of them within 3 days of onset (10/19, 52.6%).

The reported ARs included 26 adverse events of interest (AEIs), the most frequent of which were vaccination site pain and pyrexia. Most of the AEIs were mild (42.3%) or moderate (23.1%) in severity (Table 3). The most frequent suspected ARs not considered AEIs (n = 29) were cough, influenza-like illness, and oropharyngeal pain. Eight suspected serious ARs were reported by an 82-year-old male participant. The participant experienced cough, influenza-like illness, and sneezing 2 days following vaccination, and also reported pneumonia, fever, malaise, poor sleep quality, and micturition urgency. He underwent a course of antibiotics for pneumonia and subsequently recovered from all ARs. As medical confirmation of the ARs and the participant's medical profile were not available, the relation of the ARs to the vaccine could not be established. AR and AEI rates for IIV3 during the 2018/19 season were generally comparable to those reported during the previous influenza season in the UK and Ireland (Table 2).

IIV4

One hundred and sixty-two ARs were reported in 53 participants (5.3%) vaccinated with IIV4 (Table 2). Most of the ARs with known time to onset (79/162, 48.8%) occurred within 7 days of vaccination (76/79, 96.2%) (Table 1), usually on the same day or the day after vaccination (60/79, 75.9%). All ARs with known duration (58/162, 35.8%) resolved, most of them within 3 days of onset (43/58, 74.1%).

ARs were reported in two participants among the 10 aged 6 – 12 years (tenderness indicative of myalgia in both cases), in one participant among the 5 aged 13 – 17 years (headache, rhinitis, and nasal congestion), and in 46 participants among the 951 adults aged 18–65 years. No ARs were reported in the 7 children aged 6 months to 5 years or in the 23 adults >65 years participating in the study.

The reported ARs included 96 AEIs, most frequently pain and inflammation at the vaccination site, myalgia, and headache (Table 2). Most of the AEIs with known severity were mild in intensity (30/61; 49.2%) (Table 3). The most frequent suspected ARs not considered AEIs were pain, pain in the arm or hand, and fatigue that could not be localized to a part of the body. No serious ARs were reported after vaccination with IIV4.

The proportion of participants reporting ARs following IIV4 vaccination was higher than that reported in the previous 2017/18 EPSS (vaccinee reporting rate: 5.3% [95% CI: 3.9 – 6.7%] in 2018/2019 vs. 2.1% [95% CI: 1.2 – 3.0%] in 2017/2018; Table 2). Likewise, more ARs were reported than in the previous season (AR reporting rate: 16.3% [95% CI: 14.0 – 18.7%] in 2018/2019 vs. 5.9% [95% CI: 4.5 – 7.5%] in 2017/2018). The AEIs reported more frequently than in the previous EPSS (i.e., at a rate above the upper limit of the 95% CI in 2017/18) were myalgia, pain, and inflammation at the vaccination site. However, the frequency categories determined from the reported AEIs (common [≥1% to 10%]) did not differ from those documented in the SmPC for IIV4 (very common [≥10%]).[13] The rates of the other AEIs and ARs not considered AEIs were comparable, albeit often slightly elevated, to those reported in 2017/18. As the EPSS did not detect any safety signal, estimation of suspected AR reporting rates per batch was not conducted.

Discussion

Safety surveillance is important at the start of seasonal influenza vaccination campaigns to detect increases in reactogenicity and other potential new safety concerns. For both IIV3 and IIV4, at least half the ARs with known time to onset occurred within 7 days of vaccination, and all ARs with known duration resolved, most of them within 3 days of onset. For both vaccines, the most frequently reported ARs included myalgia, mild and transient injection site reactions, headache, and fever, each

Table 2. Frequencies of all adverse reactions (ARs) and adverse events of interest (AEIs) for IIV3 and IIV4 reported during the 2018/19 EPSS and comparison with the frequencies reported during the 2017/18 EPSS.

	IIV3					IIV4				
	2018/19 (N = 1000)		2017/18[a] (N = 1005)			2018/19 (N = 996)		2017/18[a] (N = 957)		
ARs	n	% (95% CI)	n	% (95% CI)	Above 2017/18 rate[b]	n	% (95% CI)	n	% (95% CI)	Above 2017/18 rate[b]
Participants reporting ≥1 suspected AR	12	1.2 (0.5 – 1.9)	14	1.4 (0.7 – 2.1)	No	53	5.3 (3.9 – 6.7)	20	2.1 (1.2 – 3.0)	Yes
Participants reporting ≥1 AEI	11	1.1 (0.5 – 1.8)	10	1.0 (0.4 – 1.6)	No	48	4.8 (3.5 – 6.2)	16	1.7 (0.9 – 2.5)	Yes
Suspected ARs	55	5.5 (4.2 – 7.1)	40	4.0 (2.9 – 5.4)	Yes	162	16.3 (14.0 – 18.7)	56	5.9 (4.5 – 7.5)	Yes
AEIs[c]	26	2.6 (1.7 – 3.8)	17	1.7 (1.0 – 2.7)	No	96	9.6 (7.9 – 11.6)	25	2.6 (1.7 – 3.8)	Yes
Pyrexia	4	0.4 (0.1 – 1.0)	0	0.0 (0.0 – 0.4)	No	6	0.6 (0.1 – 1.1)	2	0.2 (0.0 – 0.8)	No
Headache	3	0.3 (0.1 – 0.9)	3	0.3 (0.1 – 0.9)	No	8	0.8 (0.3 – 1.4)	7	0.7 (0.2 – 1.3)	No
Malaise	2	0.2 (0.0 – 0.7)	2	0.2 (0.0 – 0.7)	No	3	0.3 (0.1 – 0.9)	2	0.2 (0.0 – 0.8)	No
Arthralgia	1	0.1 (0.0 – 0.6)	1	0.1 (0.0 – 0.6)	No	4	0.4 (0.1 – 1.0)	1	0.1 (0.0 – 0.6)	No
Myalgia	2	0.2 (0.0 – 0.7)	0	0.0 (0.0 – 0.4)	No	10	1.0 (0.4 – 1.6)	2	0.2 (0.0 – 0.8)	Yes
Vaccination site erythema	1	0.1 (0.0 – 0.6)	0	0.0 (0.0 – 0.4)	No	3	0.3 (0.1 – 0.9)	0	0.0 (0.0 – 0.4)	No
Vaccination site inflammation	0	0.0 (0.0 – 0.4)	6	0.6 (0.1 – 1.1)	No	11	1.1 (0.5 – 1.8)	3	0.3 (0.1 – 0.9)	Yes
Vaccination site pain	4	0.4 (0.1 – 1.0)	1	0.1 (0.0 – 0.6)	No	18	1.8 (1.0 – 2.6)	1	0.1 (0.0 – 0.6)	Yes
Vaccination site reaction	3	0.3 (0.1 – 0.9)	0	0.0 (0.0 – 0.4)	No	4	0.4 (0.1 – 1.0)	1	0.1 (0.0 – 0.6)	No
Other ARs[c]										
Chills	0	0.0 (0.0 – 0.4)	0	0.0 (0.0 – 0.4)	No	4	0.4 (0.1 – 1.0)	0	0.0 (0.0 – 0.4)	No
Fatigue	2	0.2 (0.0 – 0.7)	1	0.1 (0.0 – 0.6)	No	5	0.5 (0.2 – 1.2)	3	0.3 (0.1 – 0.9)	No
Influenza-like illness	3	0.3 (0.1 – 0.9)	1	0.1 (0.0 – 0.6)	No	4	0.4 (0.1 – 1.0)	1	0.1 (0.0 – 0.6)	No
Pain[d]	0	0.0 (0.0 – 0.4)	0	0.0 (0.0 – 0.4)	No	6	0.6 (0.1 – 1.1)	2	0.2 (0.0 – 0.8)	No
Pain in arm or hand	0	0.0 (0.0 – 0.4)	1	0.1 (0.0 – 0.6)	No	5	0.5 (0.2 – 1.2)	2	0.2 (0.0 – 0.8)	No
Nasopharyngitis	1	0.1 (0.0 – 0.6)	1	0.1 (0.0 – 0.6)	No	3	0.3 (0.1 – 0.9)	2	0.2 (0.0 – 0.8)	No
Rhinitis	0	0.0 (0.0 – 0.4)	0	0.0 (0.0 – 0.4)	No	3	0.3 (0.1 – 0.9)	0	0.0 (0.0 – 0.4)	No
Dizziness	1	0.1 (0.0 – 0.6)	1	0.1 (0.0 – 0.6)	No	3	0.3 (0.1 – 0.9)	2	0.2 (0.0 – 0.8)	No
Sleep disorder	0	0.0 (0.0 – 0.4)	1	0.1 (0.0 – 0.6)	No	4	0.4 (0.1 – 1.0)	0	0.0 (0.0 – 0.4)	No
Cough	5	0.5 (0.2 – 1.2)	2	0.2 (0.0 – 0.7)	No	1	0.1 (0.0 – 0.6)	2	0.2 (0.0 – 0.8)	No
Oropharyngeal pain	3	0.3 (0.1 – 0.9)	2	0.2 (0.0 – 0.7)	No	3	0.3 (0.1 – 0.9)	3	0.3 (0.1 – 0.9)	No

Abbreviations: AEI, adverse event of interest; CI, confidence interval; IIV3, trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine
[a]EPSS was conducted in the UK and Ireland for IIV3 and in the UK for IIV4 in 2017/2018
[b]If the 2018/19 percentage is greater than the upper limit of the 95% CI of 2017/18
[c]ARs and AEIs are shown only if they were reported by ≥3 participants vaccinated with IIV3 or IIV4 in 2018/19
[d]Pain that could not be localized to a particular part of the body

Table 3. Severity of adverse events of interest (AEIs) for IIV3 and IIV4 during the Northern Hemisphere 2018/19 influenza season.

		AEI severity, n (%)			
Vaccine	Total AEIs	Mild	Moderate	Severe	Unknown
IIV3	26	11 (42.3)	6 (23.1)	4 (15.4)	5 (19.2)
IIV4	96	30 (31.3)	18 (18.8)	13 (13.5)	35 (36.5)

Abbreviations: IIV3, trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine

of which is frequently reported for these and other influenza vaccines.[6,14-17] One subject vaccinated with IIV3 reported several serious suspected ARs, including influenza-like illness 2 days after being vaccinated and pneumonia at an unknown date. Although the time to onset might be compatible with a role of IIV3, as no other information was reported including patient medical history and laboratory data, causality of the vaccine was evaluated as not assessable, and that other etiology (bacterial or viral) should be evoked.

The 2018/19 EPSS showed comparable AR rates after IIV3 vaccination, but the overall AR rates after IIV4 vaccination were higher than those detected in the 2017/18 EPSS.[9] Despite being above the previous year, the reporting rates for IIV4 were still lower or close to the expected AR rates from clinical trial data listed in the IIV4 SmPC.[13] Moreover, no serious ARs, and no clinically significant changes in reporting pattern by AR type, frequency, or severity were observed during the surveillance period.

There were several differences between the 2018/19 and the 2017/18 EPSS that may account for the increased overall AR reporting rate for IIV3, and the generally higher AR rates for IIV4 observed. First, the previous 2017/18 EPSS for IIV4 was conducted in the UK rather than in Finland and mainly in older participants (70% were older than 65 years),[9] whereas in the 2018/19 EPSS almost all participants were 18 – 65 years of age. This is consistent with the product reference information which states that ARs are generally less frequent in the older adults than in children and adults.[13] Second, in Finland, vaccines are a topic frequently covered by the Finnish media,[18] and confidence in vaccines has been decreasing,[19] both of which may have stimulated reporting to levels above the previous year's EPSS. Third, the 2017/18 EPSS relied on phone call reporting alone, whereas both phone call and e-mail reporting were available to participants in the current EPSS. E-Mail reporting is likely to have stimulated AR reporting for IIV4 as it represented 66% of total reporting. As the IIV4 was recently licensed and still under additional monitoring, reporting potential ARs by e-mail or phone call was also actively encouraged in the package insert. This might have provided an additional prompt for IIV4 recipients to report ARs.

The design of this EPSS had a number of strengths. The method of data collection enabled safety concerns to be rapidly detected during the vaccination campaigns. Moreover, as shown for other enhanced surveillance designs,[20] the EPSS likely increased reporting rates in passive surveillance systems by actively encouraging participants to report ARs, and by communicating why this is important. The possibility to report ARs by e-mail in the 2018/19 EPSS, which was not available in the previous EPSS for these vaccines, also helped reduce potential underreporting.

The limitations of this EPSS may include under-reporting (where only a fraction of the total number of ARs occurring after vaccination are reported) or differential reporting (where serious ARs or ARs with shorter time onset post-vaccination are more likely to be reported than non-serious ARs with longer time onset) because AR reporting remained spontaneous.[3,16,21,22] Additionally, as EPSS relies on routine vaccination according to national recommendations, there were no enrollment quotas for the different age groups and younger vaccine recipients and IIV4 recipients aged over 65 years were poorly represented. Finally, although e-mail notification may have encouraged AR reporting, the quality of the data collected from e-mails was often poor despite close follow-up, and participants often did not respond to follow-up e-mails to complete data collection. More efficient methods of data collection are under investigation for future EPSS studies.

In conclusion, the 2018/19 EPSS results did not suggest any clinically significant change in what is known or expected for IIV3 and IIV4. This information supports the safety profile of these two vaccines and should help build or maintain public confidence in influenza vaccination.

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