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journal homepage: www.elsevier.com/puhe

Short Communication

Rapid assessment of enhanced safety surveillance for influenza vaccine

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ARTICLE INFO

Article history:
Received 3 May 2018
Received in revised form
30 November 2018
Accepted 19 December 2018
Available online 13 February 2019

Keywords:
Vaccine safety
Influenza
Vaccine
Adverse events
Surveillance
Immunization information system

ABSTRACT

Objectives: The enhanced safety surveillance for seasonal influenza vaccines established by the European Medicines Agency is required each season. Therefore, a registry capable of rapidly detecting and evaluating potential new safety concerns is needed. The aim of the study is to demonstrate the effectiveness of the vaccine information system of the Valencia region to make a rapid assessment of the influenza vaccine safety and describe the safety of the two vaccine types used in the 2017/2018 season.
Study design: It is a population-based descriptive study.
Methods: Adverse events following immunization reports collected from 23rd October 2017 to 15th March 2018 were analyzed.
Results: A total of 55 adverse events for influenza vaccine were reported in season 2017/2018 with a reporting rate (RR) of 0.77 per 10,000 administered doses. Injection site reactions had a RR of 0.30 and 0.47 per 10,000 for subunit and adjuvanted vaccines, respectively. Differences per vaccine, sex, and risk group did not reach statistical significance.
Conclusions: Reported events of the two influenza vaccine types used were similar than in other seasons and consistent with their safety profiles.

Introduction

Seasonal influenza vaccines present several specific challenges for pharmacovigilance (mass immunization in a short period, the inclusion of pregnant women vaccination in target groups, etc). Therefore, the strategy for enhanced safety surveillance, established by the European Medicines Agency (EMA),[1] should be applied to detect a potential increase in reactogenicity and allergic events that are intrinsic to the product, in near real time in the earliest vaccinated cohorts.

Immunization information systems (IISs) have proved to be useful in many vaccine-related fields, including analysis and evaluation of vaccine safety.[2]

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https://doi.org/10.1016/j.puhe.2018.12.013
0033-3506/

The vaccine information system (SIV) is the IIS of the Valencia region, an autonomous community or region of Spain located in the south-eastern part of the country, with a population of 5 million inhabitants, more than 1 million children and around 4 million adults (slightly over 10% of the Spanish population).

SIV was established as the registry for the immunizations carried out in the region. It allows to rapidly detect and evaluate the safety profile of administered vaccines.

The aim of the study is to demonstrate the effectiveness of the SIV to make a rapid assessment of the influenza vaccine safety and describe the safety of the two vaccine types used in the 2017/2018 season.

Methods

SIV provides a population-based nominal record established for the registry of immunizations and the report and surveillance of adverse events following immunization (AEFI). SIV includes other functionalities useful for the stakeholders involved. All the information is based on real time.

Over 64,000 healthcare workers from all the public health centers, including primary care centers and hospitals (around 1350) and more than 780 private centers of the 24 health areas of the Valencia region have access to the SIV. Citizens also have secure online access to consult their vaccination records.

SIV is integrated into the health systems of the region, so nominal immunization data could be linked to the information contained in other health record databases (medical history, hospital discharge records, pharmacovigilance, epidemiological, and microbiological surveillance system).

SIV of the Valencia region has previously proven its potential in the immunization safety monitoring.[3]

A descriptive study of AEFI reports of vaccinated population against influenza in the Valencia region has been performed. All influenza AEFI reports registered by the health centers of the Valencia region were analyzed. AEFI reports were collected during the influenza vaccination campaign and 45 days after the ending of the vaccination (23rd October 2017 to 15th March 2018).

All personal data were anonymized.

From each AEFI report, we analyzed the following: age, sex, risk group, adverse events (AEs) (recorded as per the medical dictionary for regulatory activities (MedDRA) classification and System Organ Class (SOC)[4], type of influenza vaccine (subunit and adjuvanted), and date of vaccination, AE, and notification.

The AE of interest as per the strategy for enhanced safety surveillance for seasonal influenza vaccines in the European Union[1] were fever, vomiting and nausea, malaise, headache, irritability (for under 5-year-old vaccinees), crying (for under 5-year-old vaccinees), decreased appetite, injection site reactions, rash, myalgia/arthralgia, and events indicative of allergic and hypersensitivity reactions.

The vaccine-specific reporting rate (RR) was calculated for each influenza vaccine type, subunit and adjuvanted (indicated in 65 years and older), age group (6 months–5 years, 6–12 years, 13–17 years, ≥ 18–65 years, and > 65 years), sex, and AE as the number of reports per 10,000 doses administered. As the data correspond to the whole population, and not a sample, the 95% confidence interval was not required.

The denominator by sex and age was obtained from the population information system of the Valencia region (SIP).

Results

During the study period, a total of 27 AEFI reports and 710,018 doses administered (540,430 subunit influenza vaccine and 169,588 adjuvanted) were recorded in SIV. AEFI came from 12 of the 24 health areas of the Valencia region and 20 centers reported (14 primary care centers, five hospitals, and one private center).

Two AEFI reports had incomplete data (type of AE or date of the AE were not included in the report), so finally, 25 AEFI reports were evaluated with a RR of 0.35 per 10,000 doses. By sex, nine reports were on men (RR 0.28), and 16, on women (RR 0.41).

Nine of the reports corresponded to persons with chronic pulmonary (including asthma) or cardiovascular disorders (RR 0.26), seven corresponded to persons with renal disease, with morbid obesity, who were immunocompromised, or with diabetes (RR 0.67), six to healthcare workers (RR 1.94), two to caregivers and contacts of those at risk (RR 1.06), and one with no risk (RR 0.33). There were not AEFI reports on pregnant women.

Influenza AEFIs were registered in SIV with a median of 3.5 days (range 0–98) after the AE occurrence. Most AE developed on the same vaccination day (median 0 days, range 0–13).

Characteristics of the AE

A total of 55 AEs were included in the reports (mean of 2.2 AE per AEFI report), 37 were reported in women (67.27%); 21 (38.18%) in patients with chronic pulmonary (including asthma) or cardiovascular disorders, 13 (23.64%) in persons with renal disease, with morbid obesity, who were immunocompromised, or with diabetes, and 13 (23.64%) in healthcare workers. Thirty-eight (69.1%, RR 0.70) of the AEs corresponded to the subunit influenza vaccine, and 17, (30.9%, RR 1.00) to the adjuvanted influenza vaccine. Twenty-nine (52.7%, RR 0.41) of the events were classified as general disorders and administration site conditions.

For the AEs of interest required by the EMA (see Table 1), injection site reactions had a rate of 0.30 per 10,000 administered doses for the subunit vaccine and 0.47 for the adjuvanted vaccine; by age group, a rate of 3.06 was reported for the 6–12 years group (subunit vaccine). Allergic/hypersensitivity events represented a rate of 0.09 (subunit vaccine) and 0.06 (adjuvanted vaccine) per 10,000 doses. There were two anaphylaxis cases reporting six AEs (10.9%), as per the standardized MedDRA queries.

Discussion

The SIV is an effective and integrated tool for the assessment of vaccine safety. It allows a rapid detection of safety signals to activate the pharmacovigilance response.[3]

Table 1 – Reported adverse events by age group and type of vaccine in the Valencia region of influenza season 2017/2018.

Adverse event	6 months to 5 years		6–12 years		13–17 years		18–65 years		>65 years		Total	
	Subunit	Adjuvanted	Subunit	Adjuvanted	Subunit	Adjuvanted	Subunit	Adjuvanted	Subunit	Adjuvanted	Subunit	Adjuvanted
Fever	0		0		0		2 (0.09)	0	1 (0.03)	1 (0.06)	3 (0.06)	1 (0.06)
Vomiting	0		0		0		0	0	0	0	0	0
Nausea	0		0		0		0	0	0	0	0	0
Malaise	0		0		0		1 (0.05)	0	0	0	1 (0.02)	0
Headache	0		0		0		1 (0.05)	0	1 (0.03)	1 (0.06)	2 (0.04)	1 (0.06)
Irritability[a]	0										0	
Crying[a]	0										0	
Decrease appetite	0		0		0		0	0	0	1 (0.06)	0	1 (0.06)
Injection site reactions	0		3 (3.06)		0		11 (0.50)	2 (4.90)	2 (0.07)	6 (0.36)	16 (0.30)	8 (0.47)
Rash	0		0		0		1 (0.05)	0	2 (0.07)	1 (0.06)	3 (0.06)	1 (0.06)
Myalgia	0		0		0		1 (0.05)	0	1 (0.03)	1 (0.06)	2 (0.04)	1 (0.06)
Arthralgia	0		0		0		0	0	0	1 (0.06)	0	1 (0.06)
Allergic/hypersensitivity reactions	0		0		0		5 (0.23)	0	0	1 (0.06)	5 (0.09)	1 (0.06)
Other	0		0		1 (1.81)		5 (0.23)	0	0	2 (0.12)	6 (0.11)	2 (0.12)
Total	0		3 (3.06)		1 (1.81)		27 (1.24)	2 (4.90)	7 (0.24)	15 (0.91)	38 (0.70)	17 (1.00)

Doses administered: 6 months to 5 years, 8776 (subunit); 6–12 years, 9797 (subunit); 13–17 years, 5514 (subunit); 18–65 years 218,473 (subunit) and 4079 (adjuvanted); >65 years, 297,870 (subunit) and 165,509 (adjuvanted).
Reporting rate per 10,000 administered doses.
Shadowed area: vaccine not indicated/information not required.
[a] For under 5-year-old.

Regarding the specific monitoring of the seasonal influenza vaccine safety (that varies in composition by brand and season), SIV has demonstrated to generate high quality data on real time.

SIV is a population-based register that meets the requirements of the IIS.[2] It was set up in 2002. All registered residents of the Valencia region have a unique identification number that is linked to the SIV. Vaccinations and AEFI are recorded in SIV by healthcare workers and can be consulted on real time. Over 98% of AEFIs notified in the Valencia region are reported through SIV.[3] The sensitivity and specificity of SIV for influenza vaccination status were estimated to be 90% and 99%, respectively.[5]

The RR registered in this influenza season was similar to that of the 2016/2017 season (0.40). The highest RR corresponded to women and to the healthcare workers as in other influenza vaccination campaigns.[6,7]

The highest RR corresponded to the MedDRA SOC general disorders and administration site conditions, such as pain or erythema at the point of injection. All of them are described as very frequent (>1/10) and frequent (<1/10,>1/100) in the summary of the product characteristics of the vaccines.

There were two anaphylaxis reports (6 AEs).[4,8] There was one event related to the subunit vaccine, and one, to the adjuvanted vaccine. These vaccinees that suffer allergic or hypersensitivity reactions had received influenza vaccine in previous seasons with no reports of allergic events. One of the objectives of the enhanced safety surveillance for seasonal influenza vaccines was the monitoring of these types of events, probably associated to the intrinsic safety profile of the product. The incorporation of the new influenza strains for 2017 season may have carried a higher allergen component in the manufacturing processes. However, these findings need to be confirmed by national and international data before broader hypotheses can be drawn. An increase in the number of allergic-related events were described in Australia for the 2015 season where an increase in generalised allergy-related AEFI, across all used vaccine brands, supports evidence of variable reactogenicity arising from influenza vaccine strain variations.[9]

The recognized limitations of passive surveillance, including unquantifiable underreporting, potential reporting biases, align to the benefit of approaches for signal detection. Besides, reports on AEFIs collected through SIV overcome some of the deficiencies of passive surveillance systems such as insufficient information on cases reported, subjected to stimulated reporting or absence of denominator data.[10] SIV presents a suitable tool for enhanced safety surveillance of seasonal influenza vaccines.

Author statements

Ethical approval

Ethical approval was not required. This study is part of the protocol of the AEFI surveillance for the influenza vaccine carried out by the health authority every season.

Funding

No funding has been received.

Competing interests

None declared.

Author contributions

AM.A-R and A.P-A performed data analyses and wrote the manuscript. AM.A-R, A.P-A, and J.M-T interpreted the results. E.P-V, J.D-D, JA.L-R and A.S-F reviewed and provided valuable comments to the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. European Medicines Agency (EMA). *Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU*. April 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165492.pdf. [Accessed 1 April 2018].
2. Derrough Tarik, Olsson Kate, Gianfredi Vincenza, Simondon Francois, Heijbel Harald, Danielsson Niklas, et al. Immunisation Information Systems – useful tools for monitoring vaccination programmes in EU/EEA countries, 2016. *Euro Surveill* 2017;**22**(17). pii=30519, https://doi.org/10.2807/1560-7917.ES.2017.22.17.30519.
3. Alguacil-Ramos AM, Muelas-Tirado J, Garrigues-Pelufo TM, Portero-Alonso A, Diez-Domingo J, Pastor-Villalba E, et al. Surveillance for adverse events following immunization (AEFI) for 7 years using a computerised vaccination system. *Publ Health* 2016;**135**:66–74.
4. Medical Dictionary for Regulatory Activities (MedDRA). [Accessed 1 Apr 2018].Available from: https://www.meddra.org/.
5. Puig-Barberà J, García-de-Lomas J, Díez-Domingo J, Arnedo-Pena A, Ruiz-García M. Limón-Ramírez R. Influenza vaccine effectiveness in preventing influenza A(H3N2)-related hospitalizations in adults targeted for vaccination by type of vaccine: a hospital-based test-negative study, 2011-2012 A(H3N2) predominant influenza season, Valencia, Spain. *PLoS One* 2014;**9**(11):e112294. https://doi.org/10.1371/journal.pone.0112294 PMID: 25392931.
6. Portero Alonso A, Alguacil Ramos AM, Sanchis Ferrer A, Pastor Villalba E, López Maside A, Miralles Espí MT, et al. *Prevención y vigilancia de la gripe en la Comunidad Valenciana. Temporada 2016/17. [Prevention and surveillance of influenza in the Valencia region. Season 2016/17]. Informe de Salud nº150. Generalitat*. Conselleria de Sanidad Universal y Salud Pública; 2017.
7. Alguacil-Ramos AM, Garrigues-Pelufo TM, Muelas-Tirado J, Portero-Alonso A, Pérez-Panadés J, Fons-Martínez J. Seguridad de las vacunas antigripales en grupos de riesgo: análisis de las sospechas de reacciones adversas notificadas en Comunidad Valenciana entre 2005 y 2011 [Safety of influenza vaccines in risk groups: analysis of adverse events following immunization reported in Valencian Community from 2005 to 2011]. *Rev Española Quimioter* 2015;**28**(4):193–9.
8. Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and

guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; 1;**25**(31):5675–84.

9. Clothier Hazel J, Crawford Nigel, Russell Melissa A, Buttery Jim P. Allergic adverse events following 2015 seasonal influenza vaccine, Victoria, Australia. *Euro Surveill* 2017;**22**(20):pii=30535. https://doi.org/10.2807/1560-7917.ES.2017.22.20.30535.
10. Bricout H, Chabanon AL, Souverain A, Sadorge C, Vesikari T, Caroe TD. Passive enhanced safety surveillance for Vaxigrip and Intanza 15 μg in the United Kingdom and Finland during the northern hemisphere influenza season 2015/16. *Euro Surveill* 2017;**22**(18):pii=30527. https://doi.org/10.2807/1560-7917.ES.2017.22.18.30527.