HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 1, e1935170 (4 pages)
https://doi.org/10.1080/21645515.2021.1935170

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Improved post-marketing safety surveillance of quadrivalent inactivated influenza vaccine in Mexico using a computerized, SMS-based follow-up system

Miguel Betancourt-Cravioto[a], Patricia Cervantes-Powell[b], Roberto Tapia-Conyer[c], Shaleesa Ledlie[d], and Sonja Gandhi-Banga[d]

[a]Sociedad Mexicana de Salud Pública, CDMX, Mexico; [b]Medical Department, Sanofi Pasteur, CDMX, México; [c]Family Medicine, School of Medicine. National Autonomous University of Mexico, Mexico City, Mexico; [d]Epidemiology and Benefit-Risk Department, Sanofi Pasteur, Toronto, Ontario, Canada

ABSTRACT

Quadrivalent influenza vaccines (QIVs) are designed to prevent influenza disease caused by two influenza A viruses (H1N1 and H3N2) and both influenza B lineages. Risk-monitoring of QIVs to identify adverse events (AEs) is necessary as influenza vaccines are reformulated each year. We developed a new active surveillance system (*Sistema de Control de Vacunación*; SICOVA) to improve pharmacovigilance in Mexico. Participants (N = 2013) aged 0 – 96 years from nine sites across three influenza seasons (n = 1166 in 2015 – 2016; n = 633 in 2016 – 2017; and n = 214 in 2017 – 2018) agreed to receive text messages 1, 7, 28, and 42 days post-vaccination to know if they had experienced any AEs. The study was completed electronically by 1763 (87.6%) participants; manual follow-up was conducted for 250 participants whose reporting was incomplete. The overall AE rate was 9.09%. At least one AE was reported by 183 participants, of whom 131 (71.58%) did not require a medical visit and 52 (28.42%) needed medical attention, with none requiring hospitalization. Most AEs requiring medical attention occurred in children aged 0 – 5 years (n = 22, 42.31%) and adults aged 31 – 35 years (n = 5, 9.62%). These results are consistent with the established safety profile of Fluzone® Quadrivalent, and show that SICOVA can facilitate surveillance and increase AE reporting in Mexico.

ARTICLE HISTORY
Received 12 February 2021
Revised 5 May 2021
Accepted 21 May 2021

KEYWORDS
Influenza vaccines; vaccination; safety; post-marketing safety surveillance; seasonal influenza; risk management plan; adverse events; pharmacovigilance; immunization

Introduction

Influenza is an acute, highly contagious respiratory disease caused by influenza A or B viruses, resulting in 3 to 5 million cases of severe illness and 290,000 to 650,000 deaths worldwide every year.[1] The disease spreads mainly through respiratory droplets, and is accompanied by fever, and other systemic symptoms ranging from mild fatigue to respiratory failure, and sometimes death. The highest risk of complications occurs in children younger than 2 years, adults aged 65 years or older, pregnant women, and people with underlying chronic health conditions.[2] Vaccination is the most effective method of controlling seasonal influenza outbreaks. Influenza vaccination is recommended by the WHO for children 6 months to 5 years of age, adults with chronic health conditions, pregnant women, and elderly individuals over 65 years of age.[1,2] Because circulating viruses undergo frequent genetic and antigenic changes, yearly vaccination is essential at the start of each influenza season to optimize protection.

Influenza vaccines are reformulated based on annual WHO recommendations,[3] making regular benefit-risk monitoring necessary. Seasonal influenza vaccines also present several challenges to post-marketing surveillance systems, due to the large populations immunized within a short period of time every year, and the availability of several influenza vaccine products in the market. Since these vaccines are administered to large populations of healthy people, they must conform to a high safety standard. Post-marketing safety surveillance is conducted to identify adverse events (AEs) and potential safety signals for further investigation.[4]

Post-marketing safety surveillance of vaccines has largely relied on passive or spontaneous reporting of AEs from patients and healthcare providers. However, passive surveillance systems have the drawback of low sensitivity and underreporting of AEs.[5] Despite these challenges, passive surveillance is generally chosen by healthcare systems due to the ease of implementation. However, active, participant-centered monitoring of AEs is now recognized as an important and valuable component of post-marketing safety surveillance.[6] Automated SMS-based reporting systems are increasingly used to facilitate active post-marketing surveillance of vaccines.[7–9] This approach to surveillance has the advantages of monitoring patient groups in near real-time, and recording and addressing safety incidents in a timely manner, leading to improved public trust in the role of vaccines in preventing disease.

Sanofi Pasteur produces a quadrivalent influenza vaccine (QIV) (Fluzone Quadrivalent®) against two subtype A and two lineage B influenza viruses.[10] QIV is currently licensed in 27 countries, including the United States, Canada, and Mexico for the active immunization of individuals aged 6 months and older. The Federal Commission for the Protection against Sanitary Risks (*Comisión Federal para la Protección contra*

CONTACT Sonja Gandhi-Banga sonja.banga2@sanofi.com Epidemiology & Benefit Risk, Sanofi Pasteur, 1755 Steeles Ave W, Toronto, ON M2R 3T4, Canada.

Riesgos Sanitarios; COFEPRIS) approved the use of QIV in Mexico in June 2014 (License authorization 146M2014SSA[11]).

We have developed a new *ad hoc* surveillance system (*Sistema de Control de Vacunación*; SICOVA) to improve pharmacovigilance of QIV in Mexico. SICOVA is a centrally managed, easily accessible, digital vaccination control system to manage participant registration at each clinical site, generate a subject database for export and analysis, send SMS messages to collect information on AEs, and record AEs in participants receiving the QIV. SICOVA is operated based on a password-differentiated access system dependent on pre-defined user profiles. Here we describe an active surveillance procedure using an automated short message service (SMS) text messaging system to rapidly collect information on AEs occurring after QIV administration in the Mexican population aged 6 months and older.

Methods

This was a 3-year post-marketing, observational, pharmacovigilance study conducted in Mexico from 2015 – 2018. Target recruitment was 2000 participants. Nine clinical sites participated in 2015 – 2016 (Cuautitlán Izcalli, Estado de México; Monterrey, Nuevo León; Naucalpan de Juárez, Estado de México; two sites in México City, México City; two sites in León, Guanajuato; Guadalajara, Jalisco; Querétaro, Querétaro), five of these sites participated in 2016 – 2017, and three participated in 2017 – 2018. Individuals aged ≥6 months who received routine influenza vaccine at study centers were invited to participate in the study. Participants were enrolled from 10 October 2015 to 30 April 2016; 14 October 2016 to 9 January 2017; and 2 November 2017 to 10 April 2018. The inclusion criteria considered all subjects from 6 months of age, who had received Fluzone® quadrivalent, had a mobile phone able to receive and send SMS messages, and had signed informed consent form (ICF) (in case of participants aged ≤7 years, the ICF was signed by parents or guardians; participants aged 7 – 17 years were required to give informed assent). The Mexico Center for Clinical Research *"Comité Bioético para la Investigación Clínica* (CBIC)*"* approved the study and issued a study approval letter in Spanish to all participating clinical sites. The primary objectives were to describe the AEs occurring after QIV administration in Mexican participants aged ≥6 months using an automated SMS text messaging system, and to identify any serious and non-serious adverse events that occur after the QIV administration.

Participants ≥36 months of age received one or two 0.5 mL-doses of QIV, with each dose containing 15 µg hemagglutinin (HA) of each antigen, whereas children between 6 – 35 months of age received one or two 0.25 mL-doses of QIV, with each dose containing 7.5 µg HA of each antigen, according to vaccination record. All participants were registered on SICOVA to monitor post-vaccination AE reports. SMS messages were sent to all participants (and in case of children, to their parents) to know if they had experienced any post-vaccination reactions. SMS messages were sent on days 1, 7, 28, and 42 after vaccination; participants who received two doses of the vaccine were followed-up until day 42 after the vaccination date of the second dose. Once a message was received by the participant, he or she was required to respond by SMS using the following options: F0, "No events"; F1, "I experienced an adverse event but I didn't go to the doctor"; F2, "I experienced an adverse event and I went to the doctor"; or F3, "I experienced an adverse event and I was hospitalized". An F0 report required no further action from the study monitoring team. When a participant response was F1, F2, or F3, the study physician was informed of the AE. The study physician then initiated a manual follow-up with the participant to evaluate the AE, submitted the pharmacovigilance report to the study monitoring team within 24 hours. The pharmacovigilance report was then registered in the Sanofi Pasteur pharmacovigilance database and submitted to the Mexican healthcare authorities.

Statistical analyses were descriptive and included data from all participants. All participants were included in the analysis, regardless of completion of electronic follow-up. The study monitoring team ensured that the lack of response from a participant was not due to onset of severe AEs.

Results

A total of 2013 individuals participated in the study (1166 participants in 2015 – 2016; 633 participants in 2016 – 2017; and 214 participants in 2017 – 2018) (Table 1). The participants' age range was 0 – 96 years, and average age was 27 years. More women than men participated in the study in all three seasons (55.44% female overall). Electronic follow-up was completed in 1763 (87.6%) participants. A direct follow-up was carried out by the study monitoring team for the 250 participants whose electronic follow-up was incomplete. None of these participants experienced an AE.

A total of 183 participants reported at least one AE across the three influenza seasons. Of these, 131 (71.58%) participants did not find it necessary to visit the doctor and 52 (28.42%)

Table 1. Demographics of study participants by influenza season.

	2015–16 (N = 1166)		2016–17 (N = 633)		2017–18 (N = 214)		Overall (N = 2013)	
Background	n	%	n	%	n	%	n	%
Average age (y)	27		28		20		27	
Sex								
Male	540	46.31	264	41.71	93	43.46	897	44.56
Female	626	53.69	369	58.29	121	56.54	1116	55.44
AEs after a previous administration of the influenza vaccine	19	1.63	3	0.47	1	0.47	23	1.14
Pregnant	11	0.94	7	1.11	0	–	18	0.89
Breastfeeding	9	0.77	3	0.47	0	–	12	0.60
Chronic conditions								
Neurological disease	21	1.80	5	0.79	3	1.40	29	1.44
Cardiovascular disease	38	3.26	17	2.69	5	2.34	60	2.98
Metabolic disease	35	3.00	21	3.32	4	1.87	60	2.98
Liver disease	1	0.09	0	–	0	–	1	0.05
Chronic kidney disease	5	0.43	4	0.63	1	0.47	10	0.50
Chronic pulmonary disease	34	2.92	15	2.37	6	2.80	55	2.73
Immunodeficiency	5	0.43	3	0.47	1	0.47	9	0.45
Obesity	25	2.14	8	1.26	2	0.93	35	1.74
Allergy	33	2.83	18	2.84	3	1.40	54	2.68
Treatment with medications	158	13.55	71	11.22	17	7.94	246	12.22

Abbreviations: AEs, adverse events.

Table 2. Participants reporting at least one AE by type and season, 2015–2018.

	Overall (N = 2013)	
	n	%
Participants reporting ≥1 AE[#]		
0 – 5 y	47	2.33
6 – 17 y	30	1.49
18 – 64 y	95	4.72
Total participants reporting at least 1 AE	183	9.09
Did not require medical visit*	131	6.51
Required outpatient treatment	52	2.58
Hospital admission	0	-

Abbreviations: AEs, adverse events; *indicates individuals who experienced >1 AE but did not require a medical visit; [#]There were 11 (0.55%) participants aged >65 years who reported ≥1 AE.

participants felt the need for medical attention (Table 2). The group with the fewest participants reporting ≥1 AE was the ≥65-year age group across all three seasons, with only 11 reporting overall (0.55%). When the AE frequency was compared across seasons, occurrence of AEs that did not result in a visit to the doctor was 7.03% during the first season (2015 – 2016) and 2.80% during the third season (2017 – 2018).

Based on the AEs reported, the overall rate of AEs was 9.09% across the three seasons. Based on the age at AE occurrence, 25.7% of AEs occurred in children 0 – 5 years of age, and 33.3% AEs in adults 31 – 50 years of age. Most AEs requiring medical attention occurred in children 0 – 5 years of age (N = 22, 42.31%) and adults 31 – 35 years of age (N = 5, 9.62%). One of 18 women who reported being pregnant at the time of vaccination reported an AE. This AE did not require a medical visit. None of the 12 women who were breastfeeding at the time of vaccination reported an AE.

There were only 43 participants with chronic conditions who reported AEs. Approximately 75% of the AEs reported by those with chronic conditions did not require a medical visit. AEs requiring a medical visit were reported by participants with chronic pulmonary disease (n = 5) and allergies (n = 3).

Discussion

An automated text messaging system can facilitate easy access to data by both the participant and the healthcare facility, and has been successfully used in increasing participant engagement and AE reporting in Australia (SmartVax or Vaxtracker tools in the AusVaxSafety active surveillance program).[6,9,12,13] The AusVaxSafety surveillance system relies on data automatically obtained from providers or healthcare clinics using the SmartVax data monitoring platform, and sends text messages to all patients who have been vaccinated, and invites them to seek or share AE information as part of routine patient care. Pilot studies have been conducted to test the feasibility of using this approach in post-marketing safety surveillance in Cambodia to circumvent the absence of a functional pharmacovigilance system (71.7% response rate), and in the US.[14,15]

The pharmacovigilance system currently in place throughout Mexico utilizes passive surveillance where AE notifications are sent to various governmental agencies. Since 1991, passive surveillance has been conducted by various collaborating government institutions in Mexico such as the COFEPRIS and the *Centro Nacional para la Salud de la Infancia y la Adolescencia* (CeNSIA) using the Monitoring System of Adverse Events Supposedly Attributable to Vaccination or Immunization (ESAVI).[16] The CeNSIA is formally responsible for the collection, analysis and dissemination of results.[17] However, AEs are seldom reported in Mexico, although a fully operational system is in place.

Between 2003 and 2007 the reporting rate of AEs following influenza immunization to CeNSIA was 0.1 per 100,000 doses distributed; over 50% were classified as mild events.[18] During the 2009 – 2010 influenza season the reporting rate increased to 0.74 events per 100,000 doses distributed with almost 70% classified as mild events.[17] In 2014, COFEPRIS reported that the most commonly reported AEs after administration of QIV influenza vaccines in adults were mild including injection site pain, muscle pain, headache, and fatigue.[18]

SMS-based reporting systems were tested for AE reporting in Mexico for the first time in 2009. A pilot study was conducted by the Ministry of Health during the 2009 H1N1 pandemic that used a nationwide SMS system to invite influenza vaccine recipients to complete a survey assessing influenza illness and related symptoms. This approach achieved a response rate of 5.8%.[19] SICOVA was introduced as a novel surveillance method in Mexico, and presents a new automated system that allows registration and follow-up of individuals after vaccination. This system makes remote monitoring of participants and AEs reporting accessible and easy for both the healthcare provider and the vaccinee. The use of SICOVA showed promising response rates as successful electronic follow-up was achieved in over 87% of participants, and thus represents a form of improved surveillance that has the potential to increase the rate of AE reporting. In the current study, the rate of participants that experienced at least 1 AE was 9.09%, of which over 70% did not require medical attention. As compared to the reporting rates observed through standard passive surveillance in Mexico, the use of the improved SMS system was able to capture a higher proportion of AEs.

The main limitations of this study include lack of information on the AEs reported, and details regarding their severity and duration. Although the main purpose of SICOVA was to conduct electronic follow-up and record the outcomes of AEs, and the system was not designed to include information on AEs, it could be improved by including simple questions regarding AE details or by conducting manual follow-up with those who report an AE. During the first year of data collection, technical difficulties were experienced when attempting to follow-up with some participants and manual follow-up had to be enlisted; these technical issues were subsequently resolved and did not recur in the following seasons. Further, selection bias may occur when enrolling participants as those attending private vaccination sites may be more affluent, younger, and reside in urban areas.[14] For example, when SMS surveillance was conducted in Cambodia, difficulties were encountered in some rural settings as some individuals were not familiar with sending SMSs. However, SMS-improved surveillance still appears to be relatively inexpensive and simple to implement. Few elderly participants aged >65 years took part in this study

as reflected by the young average age (<30 years) across the three influenza seasons (Table 2). This could be due to the technological requirement to respond to SMS messages about experiencing an AE.[20] As such, SMS reporting systems may not be as suited to the older population. Thus, the study results may be more generalizable to younger populations. Other common limitations of surveillance systems include the under-reporting of common and expected AEs, and subjective reporting of some outcomes of vaccine safety (e.g., fever, malaise); therefore, the AEs reported in this study cannot be compared to those reported in clinical trials.

The results presented in this study are consistent with the established safety profile of Fluzone® QIV and other influenza vaccines. Automated SMS-based reporting via a digital platform can facilitate sustainable monitoring of AEs in real-time, contribute to early identification of potential safety issues, and strengthen the pharmacovigilance system in Mexico.

Acknowledgments

The authors would like to thank the Fluzone QIV09 Study Team: Adriana Romero Rosales (Sanofi Pasteur, México, Ciudad de México), Felipe Aguilar Ituarte, Georgina Delgado Gómez, Cesar Adrian Martinez Longoria, Rodrigo Romero Feregrino, Raul Gutierrez Suarez, Javier M Castellanos Martinez, Rafael Hernandez Magaña, Pedro Galindo Jiménez, and Nicolas Paredes Melesio for their work. Medical writing assistance was provided by Dr. Surayya Taranum (4Clinics, Paris, France) and funded by Sanofi Pasteur.

Disclosure of potential conflicts of interest

S. B. and P. C.-P. are employed by Sanofi Pasteur and may hold shares and/or stock options in the company. M. B-C and R. T-C. received research support from Sanofi Pasteur during this study. S. L., M. B.-C., and R. T-C. were consultants for Sanofi Pasteur.

Funding

This study was funded by Sanofi Pasteur.

ORCID

Patricia Cervantes-Powell http://orcid.org/0000-0001-9173-9000

References

1. WHO. Influenza (Seasonal). [accessed 2020 May 12]. https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal).
2. WHO. Vaccines against influenza WHO position paper - November 2012. Wkly Epidemiol Rec 2012;87:461–76.
3. WHO. WHO recommendations on the composition of influenza virus vaccines. [accessed 2020 May 12]. https://www.who.int/influenza/vaccines/virus/recommendations/en/.
4. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, Wassilak SG. The vaccine adverse event reporting system (VAERS). Vaccine. 1994;12:542–50. doi:10.1016/0264-410X(94)90315-8.
5. Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. Active surveillance for adverse events following immunization. Expert Rev Vaccines. 2014;13:265–76. doi:10.1586/14760584.2014.866895.
6. Cashman P, Macartney K, Khandaker G, King C, Gold M, Durrheim DN. Participant-centred active surveillance of adverse events following immunisation: a narrative review. Int Health. 2017;9:164–76. doi:10.1093/inthealth/ihx019.
7. Westphal DW, Williams SA, Leeb A, Effler PV. Continuous active surveillance of adverse events following immunisation using SMS technology. Vaccine. 2016;34:3350–55. doi:10.1016/j.vaccine.2016.05.015.
8. Regan AK, Blyth CC, Mak DB, Richmond PC, Effler PV. Using SMS to monitor adverse events following trivalent influenza vaccination in pregnant women. Aust N Z J Obstet Gynaecol. 2014;54:522–28. doi:10.1111/ajo.12266.
9. Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K. Active SMS-based influenza vaccine safety surveillance in Australian children. Vaccine. 2017;35:7101–06. doi:10.1016/j.vaccine.2017.10.091.
10. Pasteur S. Fluzone quadrivalent: influenza virus vaccine quadrivalent types A and B (split virion). Product Monograph. 2019 [accessed 2020 May 12]. http://products.sanofi.ca/en/fluzone-qiv.pdf.
11. Secretaría de Salud. Ficha Technica Fluzone Quadrivalent. [accessed 2020 July 01 https://www.gob.mx/cms/uploads/attachment/file/243174/146M2014.pdf.
12. Leeb A, Regan AK, Peters IJ, Leeb C, Leeb G, Effler PV. Using automated text messages to monitor adverse events following immunisation in general practice. Med J Aust. 2014;200:416–18. doi:10.5694/mja13.11166.
13. Cashman P, Moberley S, Dalton C, Stephenson J, Elvidge E, Butler M, Durrheim DN. Vaxtracker: active on-line surveillance for adverse events following inactivated influenza vaccine in children. Vaccine. 2014;32:5503–08. doi:10.1016/j.vaccine.2014.07.061.
14. Baron S, Goutard F, Nguon K, Tarantola A. Use of a text message-based pharmacovigilance tool in Cambodia: pilot study. J Med Internet Res. 2013;15:e68. doi:10.2196/jmir.2477.
15. Stockwell MS, Broder K, LaRussa P, Lewis P, Fernandez N, Sharma D, Barrett A, Sosa J, Vellozzi C. Risk of fever after pediatric trivalent inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine. JAMA Pediatr. 2014;168:211–19. doi:10.1001/jamapediatrics.2013.4469.
16. Secretaría de Salud. Manual de Eventos Supuestamente Atribuibles a la Vacunación o Inmunización. [accessed 2020 May 12]. https://www.gob.mx/cms/uploads/attachment/file/287240/ESAVI_2014.pdf.
17. Vidal P, Reyna J, Saldana P, Richardson VL. Events temporarily associated with anti-influenza A (H1N1) vaccination in Mexico. Arch Med Res. 2011;42:627–32. doi:10.1016/j.arcmed.2011.10.007.
18. Secretaría de Salud. Eventos Temporalmente Asociados a Vacunación. Manual de Procedimientos Técnicos. [accessed 2020 May 12]. http://www.salud.gob.mx/unidades/cdi/documentos/manualetav.pdf.
19. Lajous M, Danon L, Lopez-Ridaura R, Astley CM, Miller JC, Dowell SF, O'Hagan JJ, Goldstein E, Lipsitch M. Mobile messaging as surveillance tool during pandemic (H1N1) 2009, Mexico. Emerg Infect Dis. 2010;16:1488–89. doi:10.3201/eid1609.100671.
20. Kuerbis A, van Stolk-cooke K, Muench F. An exploratory study of mobile messaging preferences by age: middle-aged and older adults compared to younger adults. J Rehabil Assist Technol Eng. 2017;4:2055668317733257. doi:10.1177/2055668317733257.