HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 2, 2261689
https://doi.org/10.1080/21645515.2023.2261689

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BRIEF REPORT

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Three seasons of enhanced safety surveillance of a cell culture-based quadrivalent influenza vaccine

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ABSTRACT

The objective of this paper is to summarize annual enhanced safety surveillance activity across three seasons (2019/20–2021/22) for cell culture-based quadrivalent influenza vaccine (QIVc; Flucelvax® Tetra) in all age groups. This activity was conducted in primary care setting in Genoa (Italy) during the seasons 2019/20, 2020/21 and 2021/22. All adverse events registered within the first seven days following immunization were analyzed by season, type, age group and seriousness. Over three seasons, 3,603 QIVc exposures were recorded within the enhanced passive safety surveillance activity. No safety signals were identified. The overall reporting rates of individual case safety reports for the seasons 2019/20, 2020/21 and 2021/22 were 1.75%, 0.48% and 0.40%, respectively. The average number of adverse events per individual case safety report was similar (range 3.3–3.8 adverse events per case report) across the three seasons. Most adverse events were reactogenic in nature. The rate of adverse events was similarly low in all age groups. Enhanced passive safety surveillance activity is a feasible approach for the post-marketing monitoring of seasonal influenza vaccines. Within its limitations, results of this study support the favorable safety profile of QIVc. These safety data could further bolster public trust in influenza vaccines with the goal to increase vaccination uptake in all target groups.

ARTICLE HISTORY
Received 20 June 2023
Revised 4 September 2023
Accepted 19 September 2023

KEYWORDS
Influenza; cell-based influenza vaccine; Flucelvax® Tetra; enhanced safety surveillance; safety; adverse event

Introduction

Seasonal influenza is responsible for a large global burden of disease, with approximately one billion cases each year, of which 290,000–650,000 result in death.[1] Influenza vaccination is an important public health means for reducing the global burden of disease.[2] Pregnant women, young children, older adults, subjects with underlying medical conditions and healthcare workers have been identified as principal target populations for annual immunization.[1]

The currently available seasonal influenza vaccines differ by several characteristics, including virus inactivation patterns (live attenuated, inactivated split virion or subunit), antigen content (standard dose of 15 μg per strain vs high dose of 60 μg per strain) and presence or absence of adjuvants. In the US and most European countries like Italy, all the above-described vaccines are quadrivalent, containing two influenza A strains A(H1N1)pdm09 and A(H3N2) and two B strains belonging to lineages Victoria and Yamagata.[3,4] While most influenza vaccines are still produced in eggs, recent advances have brought alternative egg-free production platforms, such as cell culture and recombinant technologies.[5] Advantages of these technologies include a lack of reliance on large-scale egg supply, scalability and use of closed-system bioreactor manufacturing processes that reduce risk of contamination.[6] However, the most important benefit of the cell-based vaccines is the prevention of egg-adaptive mutations, which can arise during serial egg passages.[7] Egg-adaptive mutations frequently alter vaccine antigenicity properties and have been proposed to be an important driver of the suboptimal vaccine effectiveness, especially against influenza A(H3N2).[8,9] The available systematic evidence suggests that in some seasons cell-based influenza vaccines may be more effective than egg-based analogs.[10]

Contrary to other pharmaceuticals, vaccines are mostly given to large numbers of healthy individuals and therefore continuous post-marketing monitoring of their safety is essential.[11] Seasonal influenza vaccines have at least three distinctive features compared to other vaccines: (i) their formulation may change every season (up to twice a year) to keep pace with the evolving virus population; (ii) influenza vaccination campaigns take place in a well-defined and relatively short time window and (iii) availability of several vaccine brands utilizing different manufacturing technologies, which may have different safety profiles.[3,4,12,13] These aspects further enhance the need for near-real-time safety surveillance activities to be able to rapidly identify safety signals and enable re-assessment of the benefit – risk ratio of the authorized seasonal influenza vaccines. In this regard, the European Medicine Agency (EMA) has issued requirements for annual enhanced safety surveillance to be performed throughout the post-marketing life cycle of approved influenza vaccines in the European Union.[14] In particular, the

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Supplemental data for this article can be accessed on the publisher's website at https://doi.org/10.1080/21645515.2023.2261689.

main goal of the enhanced safety surveillance is to promptly detect any significant increase in the frequency or severity of a pre-defined list of local, systemic, or allergic adverse events of interest, indicating potentially more serious risks.[14]

In Italy, a cell culture-based quadrivalent influenza vaccine (QIVc; Flucelvax® Tetra, CSL Seqirus Inc, Summit, NJ, US) has been available since the 2019/20 influenza season.[15] Despite several phase III randomized clinical trials have suggested a good safety profile of QIVc, which is similar to standard egg-based vaccines, no enhanced safety surveillance data for QIVc have been available.[16] The objective of this paper is to summarize annual enhanced safety surveillance activity conducted during three consecutive seasons (from 2019/20 to 2021/22) for QIVc in all age groups.

Methods

Overall surveillance design and setting

EMA requires all marketing authorization holders that commercialize influenza vaccines in Europe to set up enhanced safety surveillance of their products. The EMA guideline underlines that marketing authorization holders should explore whether existing influenza sentinel surveillance networks may effectively coordinate the pharmacovigilance activities.[14] The present enhanced safety surveillance was therefore coordinated by the Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT; Genoa, Italy), which is an interregional influenza surveillance network, and was conducted in the metropolitan city of Genoa. The interim guidance issued by EMA outlines three options for carrying out enhanced safety surveillance, namely active surveillance, passive surveillance, and data mining/use of electronic record data.[14] The choice among the three options should be justified and agreed with the EMA or relevant local competent authorities. Accordingly, CSL Seqirus, which manufacturers and commercializes QIVc, included enhanced passive safety surveillance (EPSS) in its routine pharmacovigilance activities. Some of the benefits of the data collection through the EPSS are: (i) increased vaccinee's awareness of reporting adverse events (AEs); (ii) facilitation of the reporting by providing vaccinees with contact information for signaling AEs and (iii) improvement of quality of the individual case safety reports (ICSRs).[17] In Europe, the EPSS approach has been adopted for other influenza vaccines, including MF59-adjuvanted subunit, split virion standard-dose and high-dose formulations.[17–21]

This report describes results of the EPSS conducted during three consecutive northern hemisphere influenza seasons (2019/20, 2020/21 and 2021/22). The EPSS protocol was compliant with the interim EMA guidelines.[14] For each season, we aimed to include at least 1,000 routine exposures to QIVc, which is a commonly used sample size in EPSS.[17–21] In particular, by vaccinating 1,000 individuals, the cumulative Poisson law probability of observing at least one AE is >99.9%.

EPSS is a routine pharmacovigilance activity, as the decision to vaccinate is part of routine clinical care and the choice of influenza vaccine type or brand (including QIVc) is solely at the discretion of the vaccinating physicians. Protocols for the EPSS activity were approved by the Ethics Committee of Liguria Region (resolutions 222/2019 and 346/2020).

Exposure to the cell culture-based quadrivalent influenza vaccine

QIVc is an inactivated non-adjuvanted standard-dose (15 μg of hemagglutinin per strain) subunit vaccine that contains surface antigens (hemagglutinin and neuraminidase) of four strains, which are regularly updated according to the World Health Organization's recommendations for the northern hemisphere influenza season.[22] In particular, during the surveillance period of three consecutive seasons both the A (H1N1)pdm09 and A(H3N2) strains changed each year. B/Victoria vaccine strain changed for the 2020/21 season, whilst the B/Yamagata QIVc strain remained unchanged for all three seasons (Table S1). QIVc is manufactured from influenza viruses propagated in the Madin-Darby canine kidney cell culture. Vaccinees were enrolled according to the age indication of QIVc, which for the 2021/22 season changed from adults and children ≥9 years to adults and children ≥2 years.[23]

During the three seasons, ten general practitioners and four primary care pediatricians, who take part of the CIRI-IT network, routinely administered QIVc at their practices. Before the start of each vaccination campaign, all physicians were trained on all relevant aspects of the EPSS. Following immunization, each vaccinee or his/her legal representative were encouraged by their physicians to report any AE in general and, in particular, those occurring in the first seven days. The time window of seven days is specifically required for inactivated vaccine formulations.[14] Each vaccinee was then provided with a standardized and uniquely numbered vaccination card that reported influenza vaccine brand (Flucelvax® Tetra) and associated batch number, date of vaccination and contact details to report AEs. The main purpose of vaccination cards is to facilitate spontaneous AE reporting by vaccinees to the pharmacovigilance team. The number of vaccination cards distributed corresponds to the total exposure (denominator for the reporting rate calculation).

Data collection and analysis

An ICSR was created when at least one AE was reported for a vaccine recipient and served as the primary source data. ICSRs were collected and processed by trained personnel at a toll-free call center, the phone number for which was provided on vaccination cards, through a structured standardized interview based on the Council for International Organizations of Medical Sciences I form on suspect adverse reaction reports.[24] This form is recommended by the EMA guideline on good pharmacovigilance practices.[23] The interview aimed to systematically collect the following information: verbatim description of the AEs experienced, their onset, severity and outcome, vaccination card number, vaccinee's demographics, past and present health-related conditions, and concomitant medications.

For the purpose of EPSS, each ICSR had to meet the following eligibility and validity criteria: (i) reported to the call center within the EPSS activity; (ii) AE occurrence within the first seven days post-vaccination; (iii) at least one identifiable

reporter; (iv) at least one identifiable vaccine recipient; (v) at least one suspected AE (without inferring causality); (vi) at least one suspected vaccine. Ineligible ICSRs were excluded from the EPSS main analysis but were included in the continuous routine surveillance of QIVc data in the CSL Seqirus global safety database. Moreover, the ineligible ICSRs were included in a *post-hoc* sensitivity analysis conducted to verify any significant increase in the number of AEs with respect to the base case.

Vaccinee's reported verbatim narrative was translated into English and coded to the preferred terms using the current (at the time of each seasonal EPSS) version of the Medical Dictionary for Regulatory Activities (MedDRA). ICSRs were then reviewed by the CSL Seqirus Pharmacovigilance and Risk Management Team according to standard good pharmacovigilance practice.[25] For the analysis presented in the current report, CSL Seqirus shared all verbatim ICSRs with the CIRI-IT team.

The AEs received within EPSS were analyzed and classified as one of the following: (i) reactogenic AEs of interest; (ii) events of interests monitored for the periodic safety update reports and (iii) other events that were not classified into the former two categories. As per EMA guidelines,[14] the pre-specified list of reactogenic AEs of interest included systemic events, such as fever, nausea, vomiting, malaise, headache, decreased appetite, myalgia, arthralgia, irritability and crying (for children aged less than five years), injection site reactions such as pain, erythema, induration and swelling, and events indicative of allergic and hypersensitivity reactions (including rash and ocular symptoms). All AEs were also classified by seriousness (serious vs non-serious). Serious AEs were defined as those that resulted in death, persistent or significant disability or incapacity, were life-threatening or required hospitalization.

Statistical analysis

Rates of ICSRs and individual AEs of interest were reported as percentages with exact Clopper-Pearson's 95% confidence intervals (CIs). Rates were described overall, by their seriousness and age groups (2–8/9–17, 18–64 and ≥65 years of age) and compared with their expected frequency, as per the regularly updated summary of product characteristics of QIVc.[26] Fisher's exact test was used to compare reporting rates across the seasons. The exact binomial test was used to test the null hypothesis of the equal sex distribution of ICSRs. Statistical analysis was performed in R stats packages v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Distribution of vaccination cards coincided with the beginning of national immunization campaigns and most doses were administered between mid-October and November of each season. As per protocol, in each season at least 1,000 vaccination cards were distributed, and most exposures occurred in working-age adults (Table 1).

The frequency of ICSRs diminished ($p = .002$) over time with reporting rates of 1.75%, 0.48% and 0.40% documented during the seasons 2019/20, 2020/21 and 2021/22, respectively.

Table 1. Overall exposure to the cell culture-based quadrivalent influenza vaccine, by age group and season.

	Influenza season, n (%)		
Age groups, years	2019/20	2020/21	2021/22
2/9–17[a]	95 (9.22)	214 (20.74)	257 (25.67)
18–64	652 (63.30)	577 (55.91)	502 (50.15)
≥65	283 (27.48)	241 (23.35)	242 (24.18)
Total	1030 (100)	1032 (100)	1001 (100)

[a]9–17 years for the seasons 2019/20 and 2020/21 and 2–17 years for the influenza season 2021/22.

However, in the 2019/20 season, 8 out of 18 ICSRs did not meet the eligibility criteria and were therefore excluded. All non-valid ICSRs were registered during the 2019/20 season and their characteristics are reported in Table S2.

Most ICSRs concerned working-age adults. Conversely, during the three seasons there was only one ICSR registered in the pediatric age group (Table 2). With regard to sex, most (84.7%, $p = .004$) ICSRs were reported for women, especially during the first two seasons (2019/20: 9/10; 2020/21: 5/5; 2021/22: 2/4).

The average number of AEs (any AE) per ICSR analyzed was similar across the three seasons (2019/20: 3.5, 35/10; 2020/21: 3.8, 19/5; 2021/22: 3.3, 13/4) and most of these were considered reactogenic AEs of interest. As shown in Table 3, the most common systemic reactogenic AEs of interest were fever, malaise and headache, while injection site swelling and erythema were the most common local events. Across the three seasons, no cases of the pre-specified reactogenic AEs of decreased appetite, myalgia and rash occurred. When analyzed by age group, all rates of all reactogenic AEs of interest were below the corresponding expected rates, as per QIVc summary of product characteristics (Table 3).[26]

Two ICSRs regarded hypersensitivity reactions. The first occurred in a 43-year-old female who reported dry mouth, tongue erythema and a stretching sensation around her mouth (coded as oral discomfort) a few hours after being administered QIVc, all judged non-serious. The vaccinee reported no systemic events. From her medical history, the patient was allergic to some foods and recalled experiencing a similar sensation after previous episodes of food allergy. The patient recovered from all events within 12 hours. The causality assessment was confounded by food the patient ate that day. The second ICSR was reported by a consumer/non-healthcare professional (neither patient nor healthcare worker) and regarded a woman of unknown age who developed an allergic reaction (swollen tongue, lip swelling, swelling face, dyspnea, tachycardia, vomiting, hand erythema, cold sweats, tinnitus and paresthesia) approximately one hour after exposure to QIVc. From her past history, she had undergone surgery for metastatic thyroid cancer and at the time of QIVc receipt was on levothyroxine replacement treatment. The patient had never been vaccinated against influenza. Following sublingual administration of betamethasone sodium citrate, her symptoms started to abate and the patient was transferred to an emergency department, where the corticosteroid therapy was continued. The patient recovered from all events on the same day and was discharged directly from the emergency department. The event satisfied the Brighton Collaboration criteria with level 1 diagnostic

Table 2. Number and reporting rates of illegible individual case safety reports in subjects immunized with the cell culture-based quadrivalent influenza vaccine, by age group and season.

	Frequency of individual case safety reports in each season					
	2019/20		2020/21		2021/22	
Age groups, years	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Any	10/1030	0.97 (0.47–1.78)	5/1032	0.48 (0.16–1.13)	4/1001	0.40 (0.11–1.02)
2/9–17[a]	0/95	0 (0–3.81)	1/214	0.47 (0.01–2.56)	0/257	0 (0–1.43)
18–64	8/652	1.23 (0.53–2.40)	2/577	0.35 (0.04–1.25)	2/502	0.40 (0.05–1.43)
≥65	2/283	0.71 (0.09–2.53)	0/241	0 (0–1.52)	2/242	0.83 (0.10–2.95)
Unknown	0/1030	0 (0–0.36)	2/1032	0.19 (0.02–0.70)	0/1001	0 (0–0.37)

[a]9–17 years for the influenza seasons 2019/20 and 2020/21 and 2–17 years for the influenza season 2021/22.

Table 3. Number and reporting rates of reactogenic adverse events of interest in individuals of all ages immunized with the cell culture-based quadrivalent influenza vaccine, by season and age group.

			2019/20		2020/21		2021/22	
Type	Reactogenic adverse event of interest	Expected frequency[26]	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
All ages								
Systemic	Fever	≥0.1% <1%[a]	3	0.29 (0.06–0.84)	1	0.10 (0.00–0.54)	*1*	*0.10 (0.00–0.56)*
	Nausea	≥1% <10%[a]	2	0.19 (0.02–0.70)	0	0 (0–0.36)	0	0 (0–0.37)
	Vomiting	≥10% <1%[a]	1	0.10 (0.00–0.54)	*1*	*0.10 (0.00–0.54)*	0	0 (0–0.37)
	Malaise/fatigue	≥10%[a]	3	0.29 (0.06–0.84)	0	0 (0–0.36)	1	0.10 (0.00–0.56)
	Headache	≥10%[a]	3	0.29 (0.06–0.84)	0	0 (0–0.36)	0	0 (0–0.37)
	Arthralgia	≥1% <10%[a]	0	0 (0–0.36)	0	0 (0–0.36)	*1*	*0.10 (0.00–0.56)*
Local	Pain	≥10%[a]	2	0.19 (0.02–0.70)	0	0 (0–0.36)	0	0 (0–0.37)
	Erythema	≥10%[a]	1	0.10 (0.00–0.54)	1	0.10 (0.00–0.54)	1	0.10 (0.00–0.56)
	Induration	≥10%[a]	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
	Swelling	Unknown	3	0.29 (0.06–0.84)	1	0.10 (0.00–0.54)	1	0.10 (0.00–0.56)
Allergic	Hypersensitivity	Unknown	0	0 (0–0.36)	*1*[c]	*0.10 (0.00–0.54)*	0	0 (0–0.37)
	Swollen face	Unknown	0	0 (0–0.36)	*1*[c]	*0.10 (0.00–0.54)*	0	0 (0–0.37)
	Lip swelling	Unknown	0	0 (0–0.36)	*1*[c]	*0.10 (0.00–0.54)*	0	0 (0–0.37)
	Swollen tongue	Unknown	0	0 (0–0.36)	*1*[c]	*0.10 (0.00–0.54)*	0	0 (0–0.37)
	Dry mouth	Unknown	0	0 (0–0.36)	1[d]	0.10 (0.00–0.54)	0	0 (0–0.37)
	Tongue erythema	Unknown	0	0 (0–0.36)	1[d]	0.10 (0.00–0.54)	0	0 (0–0.37)
	Oral discomfort	Unknown	0	0 (0–0.36)	1[d]	0.10 (0.00–0.54)	0	0 (0–0.37)
	Pruritus	Unknown	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Children (2/9–17 years)[e,f]								
Local	Erythema	≥10%	0	0 (0–3.81)	1	0.47 (0.01–2.58)	0	0 (0–1.43)
	Induration	≥10%	0	0 (0–3.81)	1	0.47 (0.01–2.58)	0	0 (0–1.43)
Working-age adults (18–64 years)[f]								
Systemic	Fever	≥0.1% <1%	2	0.31 (0.04–1.10)	1	0.17 (0.00–0.96)	*1*	*0.20 (0.01–1.10)*
	Nausea	≥1% <10%	2	0.31 (0.04–1.10)	0	0 (0–0.64)	0	0 (0–0.73)
	Vomiting	≥10% <1%	1	0.15 (0.00–0.85)	1	0.17 (0.00–0.96)	0	0 (0–0.73)
	Malaise/fatigue	≥10%	2	0.31 (0.04–1.10)	0	0 (0–0.64)	0	0 (0–0.73)
	Headache	≥10%	2	0.31 (0.04–1.10)	0	0 (0–0.64)	0	0 (0–0.73)
Local	Pain	≥10%	2	0.31 (0.04–1.10)	0	0 (0–0.64)	0	0 (0–0.73)
	Erythema	≥10%	1	0.15 (0.00–0.85)	0	0 (0–0.64)	1	0.20 (0.01–1.10)
	Swelling	Unknown	3	0.46 (0.09–1.34)	1	0.17 (0.00–0.96)	1	0.20 (0.01–1.10)
Allergic	Dry mouth	Unknown	0	0 (0–0.56)	1[d]	0.17 (0.00–0.96)	0	0 (0–0.73)
	Tongue erythema	Unknown	0	0 (0–0.56)	1[d]	0.17 (0.00–0.96)	0	0 (0–0.73)
	Oral discomfort	Unknown	0	0 (0–0.56)	1[d]	0.17 (0.00–0.96)	0	0 (0–0.73)
	Pruritus	Unknown	1	0.15 (0.00–0.85)	0	0 (0–0.64)	0	0 (0–0.73)
Older adults (≥65 years)[f]								
Systemic	Fever	≥0.1% <1%	1	0.35 (0.01–1.95)	0	0 (0–1.52)	0	0 (0–1.51)
	Malaise/fatigue	≥10%	1	0.35 (0.01–1.95)	0	0 (0–1.52)	1	0.41 (0.01–2.28)
	Headache	≥10%	1	0.35 (0.01–1.95)	0	0 (0–1.52)	0	0 (0–1.51)
	Arthralgia	≥1% <10%	0	0 (0–1.30)	0	0 (0–1.52)	*1*	*0.41 (0.01–2.28)*

[a]Expected frequency refers to adult individuals, as the most representative age group.
[b]Expected frequency refers to young children.
[c]All events occurred in the same individual A.
[d]All events occurred in the same individual B.
[e]9–17 years for the season 2019/20 and 2020/21 and 2–17 years for the season 2021/22.
[f]Age-specific reporting rates for the 2020/21 season may be underestimated since the age of vaccinee was unknown in 2 of 5 individual safety case reports. Serious adverse events are evidenced in italics.

certainty of anaphylaxis. This AE was judged serious and related to QIVc.

Other AEs (i.e., those non-classifiable as reactogenic AEs of interest or events of interests monitored for the periodic safety update reports) were less frequently reported with the reporting rates of single AEs ≤ 0.2% (Table 4).

The proportion of ICSRs with at least one serious AE was 11.1%, 20.0% and 25.0% for the 2019/20, 2020/21 and 2021/22

Table 4. Number and reporting rates of other adverse events (non-classifiable as reactogenic adverse events of interest or events of interests monitored for the periodic safety update reports) in individuals of all ages immunized with the cell culture-based quadrivalent influenza vaccine, by season.

	2019/20 (*N* = 1030)		2020/21 (*N* = 1032)		2021/22 (*N* = 1001)	
Adverse event	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Abdominal pain upper	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Chills	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Cough	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Diarrhea	2	0.19 (0.02–0.70)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Feeling abnormal	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Feeling cold	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Hypotension	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Influenza	*2*	*0.19 (0.02–0.70)*	0	0 (0–0.36)	0	0 (0–0.37)
Herpes zoster	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Pain [aching body]	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Pruritus [not at vaccination site]	2	0.19 (0.02–0.70)	0	0 (0–0.36)	0	0 (0–0.37)
Trigeminal neuritis	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Blister	1	0.10 (0.00–0.54)	0	0 (0–0.36)	0	0 (0–0.37)
Tachycardia	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Dyspnea	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Tinnitus	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Erythema [not at vaccination site]	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Cold sweat	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Paresthesia	0	0 (0–0.36)	1	0.10 (0.00–0.54)	0	0 (0–0.37)
Pain in extremity	0	0 (0–0.36)	0	0 (0–0.36)	2	0.20 (0.02–0.72)
Throat irritation	0	0 (0–0.36)	0	0 (0–0.36)	1	0.10 (0.00–0.56)
Rhinorrhea	0	0 (0–0.36)	0	0 (0–0.36)	1	0.10 (0.00–0.56)
Feeling of body temperature	0	0 (0–0.36)	0	0 (0–0.36)	1	0.10 (0.00–0.56)
Paralysis	0	0 (0–0.36)	0	0 (0–0.36)	*1*	*0.10 (0.00–0.56)*
Foot fracture	0	0 (0–0.36)	0	0 (0–0.36)	*1*	*0.10 (0.00–0.56)*
Ligament sprain	0	0 (0–0.36)	0	0 (0–0.36)	*1*	*0.10 (0.00–0.56)*

Serious adverse events are evidenced *in italics*.

seasons, respectively ($p = .58$). During the first season, two serious ICSRs were identified by the MedDRA preferred term as "Influenza." In the context of symptom onset of one and two days after QIVc administration, respectively, vaccination failure was not biologically plausible as insufficient time had passed for a complete immune response to develop, and the reported events were likely ascribable to influenza-like symptoms. The third serious ICSR was registered in the 2020/21 season and concerned the case of anaphylaxis described earlier. Another serious ICSR was recorded in the 2021/22 season and involved a 66-year woman, who a day after vaccination with QIVc developed paralysis of a tibialis anterior muscle, ankle sprain associated with arthralgia and metatarsal fracture due to the difficulties caused by the paralysis. At the time of follow-up, the patient was recovering from all the events. Causality of the events was assessed as not related to the vaccine due to biological implausibility. Additionally, the patient's concurrent conditions included Parkinson's disease, which confounded causality assessment of the paralysis.

In a sensitivity analysis, in which non-valid ICSRs were included, the overall number of AEs increased by 65.7% (from 35 to 58) and this increase regarded mostly reactogenic AEs of interest like fever, malaise (from 0.29% to 0.49% for both), malaise and injection site pruritus (from 0.10% to 0.29%). However, all AEs were constantly below the expected rates (<0.5% for all) (Table S3).

Discussion

This report is the first to describe the enhanced safety surveillance of QIVc, which is required by the EMA,[14] across three consecutive influenza seasons. In particular, the present EPSS did not identify any safety signal that could alter the benefit-risk profile of QIVc and therefore supports a favorable safety profile for QIVc, which was consistent across the three seasons and all age groups. Most AEs reported were judged reactogenic in nature and non-serious, which is in line with both the current summary of product characteristics and data from QIVc clinical development.[16,26,27] These data align with periodic safety update reports (CSL Seqirus data on file) submitted to regulatory agencies. Analogously, the rate of serious AEs was relatively low and most of these latter were judged unrelated to QIVc. This finding is in line with a study on active post-marketing surveillance of the safety of QIVc administered to Italian healthcare workers ($n = 775$) during the 2019/20 influenza season. The study documented only one (0.13%) serious AE, which was judged unrelated to QIVc.[28] More generally, our results endorse the usefulness of spontaneous surveillance activities conducted with the main aim of safety signal detections and hypothesis generating. Indeed, although different in nature, the US Vaccine Adverse Event Reporting System (VAERS) was able to successfully identify a safety signal of febrile seizures in young children vaccinated with an egg-based trivalent influenza vaccine.[29–31]

Compared with the 2019/20 influenza season, the overall AE reporting rate was significantly lower during more recent 2020/21 and 2021/22 seasons. An analogous reduction has been reported by other pharmacovigilance studies on influenza vaccines conducted in different countries.[21,32,33] For instance, the EPSS activity of other CSL Seqirus influenza vaccines (trivalent and quadrivalent influenza vaccines adjuvanted with MF59®) showed that compared with earlier seasons (2015/16: 0.5%; 2016/17: 0.7%; 2017/18: 0.5%),[17] the rate of ICSRs among Italian older adults was 5–7 times lower (0.1%)

during the 2021/22 season.[32] A similar trend was observed in the Italian monitoring system of AEs following vaccination with any available influenza vaccine (most of which, however, were egg-based): from 2019/20 to 2020/21 the overall reporting rate dropped from 20 to 3.9 per 100,000 doses administered.[34,35] In the same manner, a Finnish EPSS of an egg-based quadrivalent influenza vaccine noted a two-fold decrease (from 5.96% to 2.88%) in the ICSR reporting rate from 2019/20 to 2020/21.[21] As during the study period the manufacturing process of QIVc did not undergo significant changes, it is likely that the decrease in AE reporting was not driven by changes in the safety profile of QIVc, but by some external influence. One possible explanation for the observed decrease could be effects of the COVID-19 pandemic. On the other hand, it appears that the COVID-19 pandemic had an impact on reporting only non-serious AEs. Indeed, although non-significant ($p = .58$) for a small number of cases, we observed a relative increase in the proportion of serious AEs, which was in countertrend to the overall reporting. In this regard, the above-mentioned Italian vaccinovigilance platform[34,35] reported a stable notification rate of serious AEs, suggesting a higher population awareness to report this type of events. Furthermore, a comprehensive time-series analysis of the Pfizer's safety database (700,362 spontaneous reports of all Pfizer's medicines) has demonstrated that the overall decline in reporting observed during the first pandemic waves was country-specific and driven mainly by healthcare workers (as opposed to consumers) and non-serious AEs.[36] In any case, the EPSS activity on QIVc in the next seasons will shed light on longer safety trends.

Across the three seasons, most AEs were reported by female vaccinees. Overall, it seems that women are involved in more AE reporting, especially for non-serious AEs.[37,38] It has been estimated that approximately 70% of all ($n = 15,871$) VAERS reports on influenza vaccines submitted between December 1, 2020 and October 8, 2021 regarded women.[39] This gender-related gap may be explained by a true increase in the reactogenicity of influenza vaccines in women, but more likely, by a higher propensity of females to report AEs.[37,38] Taken together, these data indicate that healthcare professionals should put an extra effort on raising awareness of reporting AEs following vaccination of men.

The main inherent limitation of the EPSS is that AEs are reported spontaneously (and not gathered actively) and therefore are subject to some under-reporting. On the other hand, vaccinees taking part in EPSS were encouraged by their GPs to signal all AEs, which is expected to have increased the overall reporting rate. Indeed, during the 2019/20[34] and 2020/21[35] influenza seasons, the rates of AEs following any marketed influenza vaccine reported by the Italian Medicines Agency were up to 123 times lower than in the current EPSS. The second shortcoming is the lower exposure to QIVc of the pediatric population, especially during the 2019/20 season. This, however, reflects a very low influenza vaccination coverage rate among Italian children.[40] Future post-marketing safety surveillance studies should specifically focus on pediatric population, especially young children. Third, rates of spontaneous AE reporting differ significantly among countries.[41,42] This implies that our results may be not fully transferrable to other contexts and any between-country comparison must be viewed with caution. In this regard, a living continuously updated systematic review on all aspects of the safety of QIVc is warranted.

In conclusion, this EPSS of AEs following vaccination with QIVc did not identify any safety signal and confirmed the favorable safety profile of QIVc established in the summary of product characteristics. EPSS is a feasible safety signal detection method that can be conducted on the annual basis. These safety data could further bolster public trast in influenza vaccines and aid to increase influenza vaccination uptake in all principal target groups.

Acknowledgments

The authors thank all EPSS participants and GPs of the CIRI-IT network (Avanzino Giuseppe, Bosco Edmondo, Mangini Paola Maria, Messina Valeria, Percivale Mauro, Pirino Roberto, Aprile Emilia, Bosco Trentino, D'Errico Giovanni Battista, Fiume Damiano, Lippolis Orazio, Lo Russo Nicola Antonio, Marcellino Gaetano, Mastronuzzi Tecla) who helped to carry out EPSS during the 2019/2020, 2020/2021 and 2021/2022 influenza seasons. The authors thank Stefano Mosca for his IT support.

Disclosure statement

Maria Piedrahita-Tovar is a full-time employee of CSL Seqirus, a pharmaceutical company that manufactures and markets influenza vaccines, including Flucelvax® Tetra. Alexander Domnich was previously a full-time employee of Seqirus s.r.l. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AD is medical doctor at IRCCS San Martino Polyclinic Hospital. DA, PLL, AO, GI, DP are members of the scientific committee of CIRI-IT, which received a grant for the EPSS. MPT is employed by CSL Seqirus.

Funding

This work was supported by CSL Seqirus under grant RZA 29385/2020.

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Contribution and authorship

Conceptualization: M.P.-T., D. P. and G.I.; methodology: D.A., P.L.L., M. P.-T. and D. P.; formal analysis: A.D. and M.P.-T.; investigation: D.A., P. L.L., M.O., A.O. and D. P.; resources: M.P.-T. and G.I.; writing – original draft preparation: A.D.; writing – review and editing: all authors; project administration: M.P.-T. and D. P. All authors have read and approved the final version of the manuscript.

Data availability statement

All relevant raw data are within the manuscript and associated supporting information.

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