Vaccine: X 24 (2025) 100647

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Enhanced safety surveillance of the adjuvanted respiratory syncytial virus vaccine among Italian older adults

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ARTICLE INFO

Keywords:
Respiratory syncytial virus
RSV
RSV vaccine
Arexvy
Safety
Elderly

ABSTRACT

An adjuvanted vaccine to prevent lower respiratory tract disease caused by respiratory syncytial virus (RSV) in older adults has recently become available. Post-authorization safety studies (PASSs) conducted under real-world conditions complement data obtained from clinical trials characterized by stringent eligibility criteria. The aim of this PASS study was to evaluate reactogenicity and safety of the novel RSVPreF3 OA, which is currently not included in the Italian immunization schedule. In 2024, adult individuals aged ≥60 years were invited to get vaccinated with a single dose of RSVPreF3 OA. Following vaccination, they were instructed to fill in a diary on the occurrence, grade and duration of local and systemic adverse events (AEs) during the first week post-vaccination. They were also encouraged to notify any other events occurring at any time post-vaccination. The exposure set included 453 adults. Of these, 398 individuals returned valid diaries. At least one solicited AE (generally lasted 1–3 days) was reported by 70.6 % (95 % CI: 65.9–75.0 %) of vaccinees. Injection-site pain was the far most prevalent (60.1 %; 95 % CI: 55.1–64.9 %) solicited AE. Among systemic AEs, malaise/fatigue, headache, arthralgia and myalgia occurred in >10 % of vaccinees, while fever was rare (0.3 %; 95 % CI: 0–1.4 %). Grade 3 severe AEs were registered in 3.5 % (95 % CI: 1.9–5.8 %) of vaccinees. Older age was associated with a lower likelihood of reporting AEs. During a median follow-up of 211 days, no unsolicited serious AEs were registered. This PASS study confirmed an acceptable safety and reactogenicity profiles of RSVPreF3 OA.

1. Introduction

Respiratory syncytial virus (RSV) is a common cause of both acute respiratory infections (ARIs) and lower respiratory tract disease (LRTD) in all population groups, including older adults [1,2]. For instance, it is believed that 5–15 % of all pneumonias diagnosed in the elderly during the winter are caused by RSV [3]. Although the burden of RSV in older adults is substantially underestimated [4,5], some data suggest [6,7] that the impact of RSV is similar to that of seasonal influenza.

In older adults, LRTD caused by RSV can be prevented by means of recently licensed vaccines [8]. Among these latter, recombinant RSV glycoprotein F stabilized in pre-fusion conformation (preF) vaccine for older adults (RSVPreF3 OA) is the only adjuvanted formulation. RSVPreF3 OA was first approved in 2023 [9,10] with the indication of the prevention of RSV-associated LRTD in individuals aged ≥60 years. In 2024, this indication was extended to adults aged 50–59 years who are at increased risk of the disease caused by RSV [11]. RSVPreF3 OA proved effective in the pivotal randomized controlled trial (RCT): cumulative vaccine efficacy against RSV-associated LRTD of a single RSVPreF3 OA dose was 82.6 % [96.95 % confidence interval (CI): 57.9–94.1 %) [12], 67.2 % (97.5 % CI: 48.2–80.0 %) [13] and (62.9 %; 97.5 % CI: 46.7–74.8 %) [14] across one, two and three RSV seasons, respectively. RSVPreF3 OA showed an acceptable safety profile with most adverse events (AEs) being mild-to-moderate in intensity, reactogenic in nature and occurring at the injection site. The rate of treatment-related serious adverse events (SAEs) was similar between the RSVPreF3 OA (0.1 %) and placebo (0.1 %) [12].

Although RCTs are considered the gold standard for assessing both

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https://doi.org/10.1016/j.jvacx.2025.100647
Received 10 February 2025; Received in revised form 22 April 2025; Accepted 22 April 2025
Available online 26 April 2025

vaccine efficacy and safety [15], stringent RCT exclusion criteria may impact representativeness and generalizability issues [16]. In this regard, post-authorization safety studies (PASSs) have been increasingly carried out with the goal of identifying, characterizing and quantifying safety hazards associated with an authorized product and confirming the safety profile of the product established during its clinical development [17]. The aim of this PASS study was to assess the reactogenicity, tolerability and safety of RSVPreF3 OA in a sample of Italian older adults aged ≥60 years, who country-wide were among the first users of this novel vaccine.

2. Methods

2.1. Study design and procedures

This PASS was designed as an enhanced active surveillance [18]. The study was conducted in Liguria (northern Italy) between February and September 2024. The vaccine RSVPreF3 OA (Arexvy, lot Y7H7S; GlaxoSmithKline Biologicals SA, Rixensart, Belgium) was purchased directly from the manufacturer and before its availability to public and private markets.

To recruit participants, we advertised the study in local media and distributed pamphlets to general practitioners (GPs). Adult volunteers were then presented with all principle study details and assessed for their eligibility. In particular, to be included in the study, individuals of both sexes had to be ≥60 years and be able to provide informed consent. Subjects were excluded from the study if they had allergies to any vaccine component. Subjects who had been vaccinated with any other vaccine in the preceding seven days, were eventually invited to receive RSVPreF3 OA one week later.

As per summary of the product characteristics (SmPC) [11], RSVPreF3 OA was administered intramuscularly in the deltoid region of the non-dominant arm. Following vaccination, individuals were monitored for immediate reactions. During this observation period, subjects were interviewed and relevant sociodemographic (age, sex, nationality, education level) and medical history (underlying health conditions, including smoking status and body mass index) data were collected. On the day of vaccination, all participants completed also a questionnaire aimed to assess attitudes towards RSV and RSV vaccination; these results can be assessed elsewhere [19].

The study was approved by the Ethics Committee of Liguria Region (n. 1/2024, id #13611). All subjects provided written informed consent.

2.2. Surveillance and analysis of adverse events

After vaccination, all subjects were provided with a paper-and-pencil diary, which aimed to prospectively register the presence (yes or no) of both pre-specified AEs (henceforth referred to as "solicited AEs") and any other non-listed AEs (henceforth referred to as "unsolicited AEs"), their grade [mild (grade 1); moderate (grade 2); severe (grade 3)] and days on which each reported AE occurred (from 0 to 7, where day 0 corresponds to the day of vaccination). Subjects were instructed to fill in the questionnaire on each day and return the latter in the most convenient modality. Subjects and their GPs were also encouraged to contact the research staff at any time post-vaccination to report any other AEs, including SAEs, that occurred after seven days or were not recorded in the questionnaire for any reason. The median follow-up (days between vaccination and December 31, 2024) was 211 (range 92–334) days. A SAE was defined as an AE resulted in death, persistent or significant disability or incapacity, was life-threatening or required hospitalization [20].

Solicited AEs comprised both local injection site (pain; swelling; erythema; pruritus) and systemic (fever ≥38 °C or feverishness <38 °C; chills; malaise/fatigue; muscle aches; joint pain; headache; nausea; vomiting; diarrhea; swollen lymph nodes; rash; generalized pruritus) reactions. Selection of the solicited AEs was based on the pivotal RCT of RSVPreF3 OA [12], SmPC [11] and previous PASS experience of our center [20–22].

Non-solicited AEs were described by vaccinees in an open field. The narrative was coded to the primary system organ class (SOC) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) v. 27.1.

2.3. Data analysis

The analysis of solicited and unsolicited AEs was performed on the safety set, which included all vaccinees who returned the completed questionnaire. The analysis of SAEs was based on the exposure set, which corresponded to the total number of doses administered. Cumulative percentages of individuals reporting ≥1 and specific AEs were expressed as proportions (%) with exact Clopper-Pearson's 95 % confidence intervals CIs. This analysis was performed overall, by AE grade, sex and age group (60–74 and ≥ 75 years). Duration of AEs in days was summarized as medians with interquartile ranges (IQRs), while the normally distributed variable of age was expressed as mean ± standard deviation (SD). Fisher's exact test was used to compare the frequency of AEs between sexes and age groups. Additionally, adjusted odds ratios (aORs) were estimated through a multivariable logistic regression model to investigate association between reactogenicity and demographic characteristics. In the model, the dependent variable was reporting ≥1 solicited AE, while independent variables were age, sex and their interaction.

All analyses were carried out in R stats packages v. 4.1.0 (R Core Team, Vienna, Austria) and Excel v. 2408 (Microsoft, Redmond, WA, USA).

3. Results

A total of 453 adults aged ≥60 years were vaccinated with a single dose of RSVPreF3 OA and formed the exposure set. Their mean age was 74.9 ± 8.0 years, 50.6 % (229/453) were males and most (89.2 %; 404/453) had ≥1 co-morbidity. In the preceding one week, no subjects had been exposed to other vaccines. A total of 400 (88.3 %) individuals returned their questionnaires on AEs. Subjects who returned the questionnaire and those who did not were similar in terms of age (74.4 ± 8.3 vs 76.2 ± 8.0 years) and sex (males 50.3 % vs 52.8 %). Of 400 questionnaires available, two (0.5 %) were excluded, as they contained both empty fields and careless responses (both presence and absence of the same AE were marked). Therefore, the safety set was composed of 398 individuals. Socio-demographic and clinical characteristics of the exposure and safety sets are reported in Table 1.

In the safety set, any solicited AE was reported by 70.6 % (281/398; 95 % CI: 65.9–75.0 %) of individuals. At least one local and systemic solicited AEs were reported by 64.1 % (255/398; 95 % CI: 59.1–68.8 %) and 40.7 % (162/398; 95 % CI: 35.8–45.7 %) of adults, respectively. As shown in Fig. 1, injection site pain was the most common (60.1 %) local AE, while the frequency of pruritus, swelling and erythema was <20 %. The most frequent systemic AE was malaise/fatigue reported by 23.1 % of adults. Headache, arthralgia and myalgia were reported by 14.6 %, 12.1 % and 11.8 % of individuals, respectively. Other systemic AEs were reported by <10 % of adults. Notably, only one (0.3 %) subject had fever ≥38 °C (Fig. 1, Appendix A).

Most solicited AEs were mild-to-moderate in intensity and lasted 1–3 days (Table 2). Indeed, any grade 3 solicited AE was reported by only 14 individuals (3.5 %; 95 % CI: 1.9–5.8 %).

Although males (67.5 %; 135/200) and females (73.7 %; 146/198) reported ≥1 solicited AE at similar proportions ($p = 0.19$), the frequency of injection site pain (65.2 % vs 55.0 %; $p = 0.041$), erythema (20.2 % vs 9.5 %; $p = 0.003$), headache (21.2 % vs 8.0 %; $p < 0.001$) and malaise/fatigue (27.3 % vs 19.0 %; $p = 0.057$) were more common among females. Compared with ≥75-year-olds, younger (60–74 years) adults reported ≥1 solicited AE more frequently [81.0 %(158/195) vs 60.6 %

Table 1
Characteristics of the exposure and safety sets.

Variable	Level	*n* (%)	
		Exposure set (*N* = 453)	**Safety set (*N* = 398)**
Sex	Male	229 (50.6)	200 (50.3)
	Female	224 (49.4)	198 (49.7)
Age, years	Mean (SD)	74.9 (8.0)	74.8 (8.0)
	60–74	220 (48.6)	195 (49.0)
	≥75	233 (51.4)	203 (51.0)
Education level	Primary school	58 (12.8)	51 (12.8)
	Lower secondary school	84 (18.5)	75 (18.8)
	Upper secondary/ vocational school	175 (38.6)	160 (40.2)
	University	128 (28.3)	109 (27.4)
	Not available	8 (1.8)	3 (0.8)
Nationality	Italian	440 (97.1)	387 (97.2)
	Foreigner	13 (2.9)	11 (2.8)
Smoking status	Never smoker	199 (43.9)	172 (43.2)
	Ex-smoker	205 (45.3)	184 (46.2)
	Current smoker	49 (10.8)	42 (10.6)
Body mass index, kg/m^2	<18.5	14 (3.1)	10 (2.5)
	18.5–24.9	221 (48.8)	194 (48.7)
	25.0–29.9	158 (34.9)	140 (35.2)
	≥30.0	60 (13.2)	54 (13.6)
Presence of co-morbidities	≥1	404 (89.2)	359 (90.2)
	Cardiovascular (incl. hypertension)	319 (70.4)	283 (71.1)
	Cardiovascular (excl. hypertension)	160 (35.3)	139 (34.9)
	Cerebrovascular	46 (10.2)	40 (10.1)
	Respiratory	125 (27.6)	110 (27.6)
	Diabetes	84 (18.5)	74 (18.6)
	Gastrointestinal	41 (9.1)	40 (10.1)
	Renal	23 (5.1)	22 (5.5)
	Autoimmune/rheumatic	29 (6.4)	26 (6.5)
	Asplenia	3 (0.7)	3 (0.8)
	Current cancer	11 (2.4)	9 (2.3)
	Past cancer	68 (15.0)	63 (15.8)

SD = standard deviation.

(123/203); $p < 0.001$]. The overall difference was driven by injection site pain (70.3 % vs 50.2 %; $p < 0.001$), feverishness (11.8 % vs 4.9 %; $p = 0.017$), malaise/fatigue (29.2 % vs 17.2 %; $p = 0.006$), myalgia (16.4 % vs 7.4 %; $p = 0.008$), headache (22.1 % vs 7.4 %; $p < 0.001$) and generalized pruritus (4.1 % vs 0.5 %; $p = 0.018$) (Appendix B). In the multivariable logistic regression analysis, each one-year increase in age was associated ($p < 0.001$) with an 8 % decrease in the odds (aOR 0.92; 95 % CI: 0.89–0.95) of reporting ≥1 AE, while the age-adjusted estimate for sex showed a 21 % increase (aOR 1.21; 95 % CI: 0.77–1.90) in AE reporting among women, which however was not significant ($p = 0.41$). No interaction between the age and sex was found.

Thirteen individuals (3.3 %; 95 % CI: 1.8–5.5 %) reported 14 (3.5 %; 95 % CI: 1.9–5.8 %) different unsolicited AEs. Among these, the PTs "productive cough", "rash" and "injection site pain" were specified by two individuals each (0.5 %). All other PTs were single (0.3 %) occurrences (Table 3).

Finally, during the follow-up period, no SAEs (0 %, 0/453; 95 % CI: 0–0.8 %) were reported by vaccinees or their GPs.

4. Discussion

In this PASS study, we investigated reactogenicity, tolerability and safety of the recently licensed RSVPreF3 OA vaccine under real-world conditions. Post-marketing surveillance studies are indeed essential to gain further insights into the vaccine safety, as such data obtained from RCTs, which are characterized by a strict set of eligibility criteria, may have suboptimal external validity. For instance, older adults with any confirmed or suspected immunosuppressive condition were systematically excluded from the RSVPreF3 OA pivotal RCT [12]. In our study, a substantial proportion of the first Italian RSVPreF3 OA vaccine users had some form of immunodeficiency and will be likely the primary target group for the future vaccination campaign. In this real-world setting, the safety profile of RSVPreF3 OA was judged acceptable with the majority of AEs reported at the level of injection site, reactogenic in nature, mild-to-moderate in intensity and short in duration.

The observed vaccine reactogenicity profile was generally comparable to the findings of several phase I–III RCTs of RSVPreF3 OA [12,23,24]. For instance, in the pivotal phase III study [12], a total of 71.9 % (95 % CI: 68.8–74.9 %) of vaccinees in the solicited safety population ($N = 879$) reported at least one solicited AE. In this study, this overall proportion was almost identical (70.6 %; 95 % CI: 65.9–75.0 %) in terms of both effect size and precision. Analogously, injection site pain was the far most frequent AE, which in our study accounted for 60.1 % (95 % CI: 55.1–64.9 %), while Papi et al. [12] reported a highly congruent percentage of 60.9 % (95 % CI: 57.5–64.1 %). Indeed, adjuvanted vaccine formulations are known to be associated with an increase in reactogenicity, especially at the level of injection site [25]. On the other hand, when considering the relative frequency of other single AEs, some differences emerged. For example, compared with the available phase I–III trials [12,23], participants in our survey reported a slightly higher frequencies of injection-site swelling (18.8 % vs 5.5–11 %) and erythema (14.8 % vs 7.5–14 %), but lower frequencies of fever (0.3 % vs 2.0 %), malaise/fatigue (23.1 % vs 33.6–35 %), myalgia (11.8 % vs 15–28.9 %), arthralgia (12.1 % vs 18.1–15 %) and headache (14.6 % vs 23–27.2 %). A number of concurrent factors may explain these differences. First, our study population was significantly older and had a higher prevalence of chronic conditions. Second, a geographical variation in reporting rates of AEs is well-known [26,27]. Third, the solicitation method used in the present study was likely different to methods used in the previous RCTs [28]. Finally, these differences may due to a pure chance [26]. Taken together, the observed differences underscore the utility of PASS studies in complementing experimental studies, also to enhance public confidence in vaccines.

With regard to severity, we found that only 3.5 % (95 % CI: 1.9–5.8 %) of vaccinees reported grade 3 events. This estimate is again in line with the pivotal RCT [12] that recorded a rate of 4.1 % (95 % CI: 2.9–5.6 %).

To date, only a few phase IV studies [29,30] evaluated safety and reactogenicity of RSVPreF3 OA. A recent United States (US) study reported results [29] of both the V-safe active and VAERS (Vaccine Adverse Event Reporting System) passive surveillance systems. In the V-safe study, in which 6402 adults ≥60 years were web surveyed on days 0–7 after vaccination with RSVPreF3 OA, the overall proportion of subjects reporting symptoms possibly related to RSVPreF3 OA was lower (48.6 %) than both our estimate (70.6 %) and that observed in the pivotal trial (71.9 %) [12]. The difference was primarily driven by a lower frequency of local reactions, which in the US study accounted for 43.9 %. Relative distribution of single AEs was generally similar to our findings with the injection site pain (41.3 %) and fatigue/tiredness (25.6 %) being the most common local and systemic reactions, respectively. Similarly to our estimates, severe injection site (1.4 %) and systemic (3.8 %) symptoms were uncommon. In the analysis of 2193 VAERS reports relative to the RSVPreF3 OA vaccine, most concerned (92.4 %) non-serious events, while the remaining 7.6 % were classified as SAEs. Among these latter, 13 reports met case definition of the Guillain-Barré syndrome (GBS) with an estimated reporting rate of 1.8 per million doses of RSVPreF3 OA. The estimated GBS reporting rate after vaccination with a bivalent non-adjuvanted RSV vaccine was 4.4

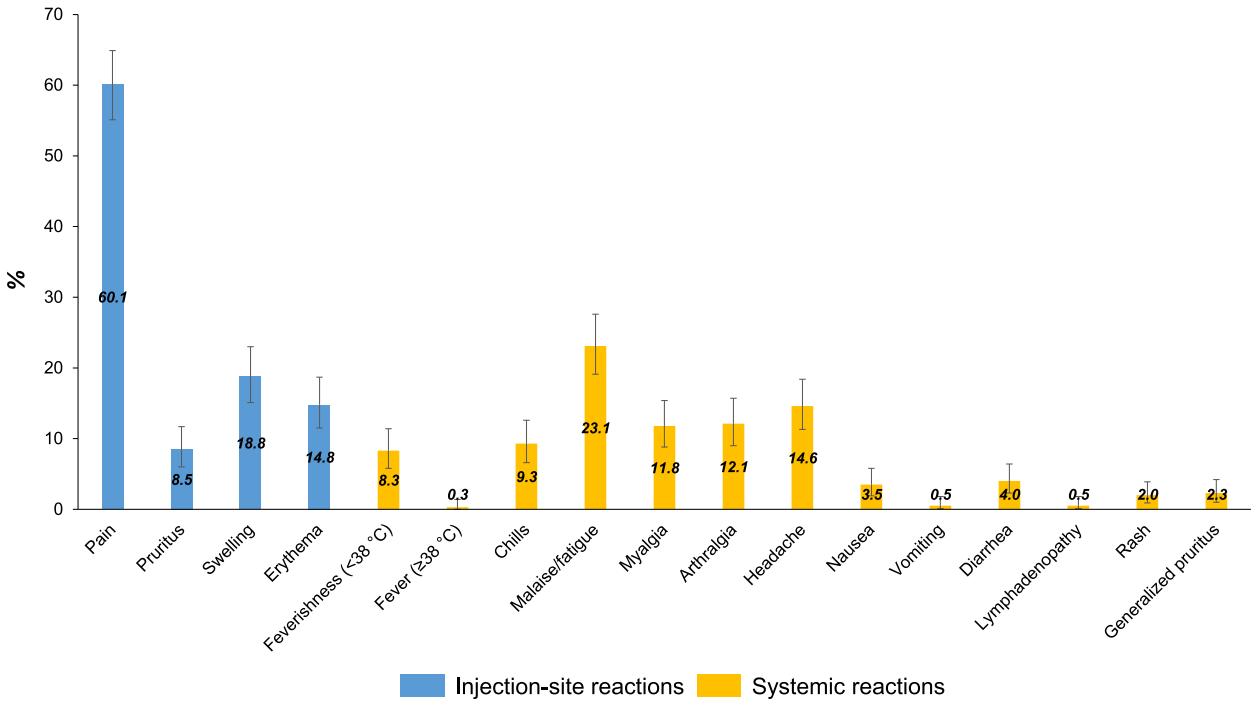

Fig. 1. Incidence of local and systemic solicited adverse reactions in the first seven days following vaccination with RSVPreF3 OA (N = 398).

Table 2
Duration and severity of solicited adverse reactions in the first seven days following vaccination with RSVPreF3 OA.

Adverse reaction		*N*	Grade, % (*n*)			Duration in days, median [IQR]
			1 (mild)	2 (moderate)	3 (severe)	
Local	Pain	210	75.7 (159)	21.4 (45)	2.9 (6)	2 [2–3]
	Pruritus	25	76.0 (19)	24.0 (6)	0 (0)	2 [1–3]
	Swelling[1]	65	80.0 (52)	18.5 (12)	1.5 (1)	2 [2–3]
	Erythema	48	56.3 (27)	39.6 (19)	4.2 (2)	2 [1–3]
Systemic	Fever/Feverishness[2]	34	97.1 (33)	2.9 (1)	0 (0)	1 [1–2]
	Chills	16	62.5 (10)	37.5 (6)	0 (0)	1 [1–2]
	Malaise/fatigue	49	57.1 (28)	36.7 (18)	6.1 (3)	2 [1–2]
	Myalgia	29	58.6 (17)	27.6 (8)	13.8 (4)	2 [1–3]
	Arthralgia	27	55.6 (15)	33.3 (9)	11.1 (3)	1 [1–3]
	Headache	33	63.6 (21)	27.3 (9)	9.1 (3)	1 [1–2]
	Nausea	10	50.0 (5)	50.0 (5)	0 (0)	1 [1–1]
	Vomiting	2	50.0 (1)	50.0 (1)	0 (0)	1[3]
	Diarrhea	9	66.7 (6)	33.3 (3)	0 (0)	1 [1–1]
	Lymphadenopathy	NA[4]	NA	NA	NA	1–4[5]
	Rash	5	20.0 (1)	80.0 (4)	0 (0)	3 [3–4]
	Generalized pruritus	5	60.0 (3)	40.0 (2)	0 (0)	3 [2–5]

IQR = interquartile range; NA = not available.
[1] Defined as <2 cm, 2–5 cm and >5 cm for grades 1, 2 and 3, respectively.
[2] Defined as <38 °C, 38–39 °C and >39 °C for grades 1, 2 and 3, respectively.
[3] Reported as single data point.
[4] Intensity of two events was missing.
[5] Reported as range.

per million doses. Both estimates were higher than the expected background rate in a vaccinated population. Despite this safety signal, the estimated benefits of RSV vaccination were judged to outweigh potential risks [29].

A smaller (N = 105) Polish study recently reported [30] some data on the safety of RSVPreF3 OA adult patients with high-risk heart failure. However, our results may be not fully comparable, as all individuals in the Polish study were co-administered RSVPreF3 OA with an inactivated standard-dose non-adjuvanted quadrivalent influenza vaccine. In any case, principal findings of that study were similar to ours. In particular, local pain and swelling in the first four days post-vaccination were reported by 75 % and 13 % of vaccinees, respectively. Among systemic reactions, fatigue (22 %), headache (10 %) and myalgia (9 %) were the most prevalent [30].

Following vaccination with RSVPreF3 OA, both sex and, especially, age appear to determine AE reporting. In this study, younger individuals were about three times more prone to report solicited AEs than older subjects. Other adjuvanted products like MF59-adjuvanted influenza vaccines [31] showed similar age-related patterns. The lower frequency of reactogenic AEs in older individuals may be explained by both higher tolerance gained with life experience and waning of some innate immune responses, such as lower post-vaccination levels of C-reactive

Table 3
Incidence of unsolicited adverse reactions in the first seven days following vaccination with RSVPreF3 OA ($N = 398$).

System Organ Class	Preferred term	% (*n*)	95 % CI
Respiratory, thoracic and mediastinal disorders	Productive cough	0.5 (2)	0.1–1.8
	Dyspnea	0.3 (1)	0.0–1.4
Skin and subcutaneous tissue disorders	Rash	0.5 (2)	0.1–1.8
Nervous system disorders	Headache	0.3 (1)	0.0–1.4
	Dizziness	0.3 (1)	0.0–1.4
General disorders and administration site conditions	Injection site pruritus	0.3 (1)	0.0–1.4
	Injection site pain	0.5 (2)	0.1–1.8
	Fatigue	0.3 (1)	0.0–1.4
Renal and urinary disorders	Dysuria	0.3 (1)	0.0–1.4
Gastrointestinal disorders	Gingivitis	0.3 (1)	0.0–1.4
	Gingival pain	0.3 (1)	0.0–1.4

CI = confidence interval.

protein and pro-inflammatory cytokines [25]. With regard to sex, women are well-known to report AEs more frequently: a recent meta-analysis on the reactogenicity of influenza vaccines [32] has estimated that compared with older males, the risk of reporting reactogenic local and systemic reactions in older females is increased by 43 % (95 % CI: 28–60 %) and 27 % (95 % CI: 20–34 %), respectively. In this study, the overall reporting rate was higher in women, but the difference was not significant. On the other hand, some single solicited AEs, such as erythema (20.2 % vs 9.5 %) and headache (21.2 % vs 8.0 %) were clearly skewed to female vaccinees. A Canadian study [33] has underlined that sex-specific differences in AE reporting are complex, depend on both biological (e.g., immunological and hormonal determinants) and behavioral (e.g., related to different health seeking behavior with a tendency to report more minor events) factors and differ between vaccine types.

This study has several limitations. The most important shortcoming is a limited sample size. On the one hand, the main study objective was to assess the frequency of a comprehensive set of solicited adverse reactions under real-world circumstances. For this purpose, we believe that the study succeeded and the results were sufficiently powered. Indeed, the precision (as measured by the width of 95 % CIs) of single proportions was similar to that reported by the pivotal RCT [12]. On the other hand, our sample size is clearly insufficient to detect rare AEs. It has been suggested [28] that passive surveillance of 3000 exposed individuals would allow detecting the occurrence of an AE associated to 0.1 % incidence. This may also explain no SAEs registered in our study. Second, although the diary return rate was relatively high (88.3 %) and the fact that adults who returned the diary and those who did not were comparable in terms of age and sex, the AE frequency in the latter group may be still different. As previously suggested [34], it is plausible that the non-responders experienced only mild and common AEs and deemed "cumbersome" to return the diary. In this regard, Assefa et al. [35] found that the response rate in active surveillance of AEs following immunization is higher for telephone interview (93 %) than for dairy cards (78 %). Third, the study may be subject to the volunteer bias, as the study population was composed of first-ever Italian recipients of the novel RSV vaccine. These individuals might be more health-conscious, more prone to preventive measures or more aware of RSV and consequently may have a different profile than the general population of adults aged ≥60 years. Fourth, although the passive surveillance had a median duration of seven months and could eventually capture the overwhelming majority of late-onset AEs, an active surveillance performed for a period longer than one week would provide useful insights into the frequency and patterns of late-onset AEs. Finally, since the reporting of AEs is a multifactorial phenomenon [36], our findings may be not fully generalizable to other settings. Future PASS research should be conducted in more diversified settings and using different data collection and solicitation methods.

In conclusion, this observational post-marketing study confirmed an acceptable safety and reactogenicity profile of the novel RSVPreF3 OA, which was similar to that recorded in the vaccine clinical development program. Although the sample size was limited and insufficient to capture rare AEs, no safety signals were identified.

CRediT authorship contribution statement

Alexander Domnich: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Andrea Orsi:** Writing – review & editing, Methodology. **Piero Luigi Lai:** Validation, Software, Data curation. **Elvira Massaro:** Validation, Investigation. **Carlo-Simone Trombetta:** Investigation, Data curation. **Julieta Pastorino:** Investigation. **Charlott Roihl:** Investigation. **Sara Tardito:** Investigation, Data curation. **Marianna Pianta:** Investigation. **Giancarlo Icardi:** Writing – review & editing, Supervision, Resources. **Donatella Panatto:** Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alexander Domnich provided consultancies and received speaker fees from CSL Seqirus, GSK and SD Biosensor and was previously (from 2016 to 2021) an employee of Seqirus S.r.L. Andrea Orsi provided consultancies and/or received speaker fees from CSL Seqirus, Moderna, Novavax and SD Biosensor. Giancarlo Icardi provided consultancies and/or received grants for conducting experimental and/or observational studies for GSK, Sanofi, MSD, CSL Seqirus and Pfizer. Donatella Panatto provided consultancies for Pfizer and CSL Seqirus and received grants for conducting observational studies from Sanofi, Pfizer, GSK and Viatris. 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.

Acknowledgements

The authors thank the following physicians for their support in the recruitment phase of the study: Barettoni Pier Francesco, Barilaro Giovanni, Bogliolo Francesco, Braido Fulvio, Canepa Vittorio, Cardini Marco, Carpi Antonella, Carraro Andrea, Crocetti Marta, Delucchi Simona, Ferrari Chiara, Frumento Virna, Gandolfo Augusto, Gavazzi Barbara, Gizzi Michele, Menicocci Elio, Messina Valeria, Miglio Luigi Pio, Migliorini Rossana, Moscatelli Paolo, Pennacchietti Carlotta, Pestarino Luca, Picciotto Rinaldo, Pisano Giovanni, Polese Marco, Rinosi Fabio, Roncan Bianca, Tardani Enrico.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100647.

Data availability

Data will be made available on request.

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