Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: www.tandfonline.com/journals/khvi20

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To cite this article: Zhuocheng Bao , Weixi Gao , Xiao Yu , Liqing Chai & Yuxiang Liu (2025) Post-marketing safety monitoring of RSV vaccines: A real-world study based on the Vaccine Adverse Event Reporting System (VAERS), Human Vaccines & Immunotherapeutics, 21:1, 2550857, DOI: 10.1080/21645515.2025.2550857

To link to this article: https://doi.org/10.1080/21645515.2025.2550857

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2550857
https://doi.org/10.1080/21645515.2025.2550857

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RESEARCH ARTICLE

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Post-marketing safety monitoring of RSV vaccines: A real-world study based on the Vaccine Adverse Event Reporting System (VAERS)

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ABSTRACT

Two protein subunit vaccines – RSVPreF3 (Arexvy, GSK) and RSVpreF (Abrysvo, Pfizer) – and one mRNA RSV vaccine, mRNA-1345 (mRESVIA, Moderna), have been approved. Post-marketing surveillance is crucial for evaluating the safety of RSV vaccines. We reviewed VAERS reports on RSV vaccines, using the Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) to identify safety signals. Our analysis incorporated severity, time-to-onset, subgroup, and sensitivity analyses to enhance key findings. After analyzing 5,147 RSVPreF3, 2,734 RSVpreF, and 35 mRNA-1345 reports, 91, 103, and 8 positive PT signals were found, respectively. Among serious reports, both RSVPreF3 and RSVpreF were associated with 9 important medical events (IMEs), including immune thrombocytopenia, which was also classified as a designated medical event (DME). Three pregnancy-related IME signals–hemorrhage in pregnancy, fetal death, and fetal hypokinesia – were reported for RSVpreF. Descriptive analysis of time-to-onset complemented the overall safety profiling, and sensitivity analysis offered further support for the observed disproportional reporting trends in certain adverse events (AEs). Our study utilized real-world data from large-scale spontaneous reporting systems to detect AEs that were disproportionately reported following RSV vaccination, thereby generating early safety signals to inform hypothesis development and support clinical awareness.

ARTICLE HISTORY
Received 8 May 2025
Revised 7 August 2025
Accepted 14 August 2025

KEYWORDS
Respiratory syncytial virus (RSV); vaccine safety; pharmacovigilance; Vaccine Adverse Event Reporting System (VAERS); adverse event

Background

Respiratory syncytial virus (RSV) is an enveloped RNA virus and a major cause of lower respiratory tract infections (LRTIs) and mortality worldwide, particularly in infants and the elderly.[1–3] In 2019, RSV was responsible for approximately 101,400 deaths among children under the age of 5, accounting for 2% of global childhood mortality.[4] RSV also caused 33 million cases of lower respiratory tract infections in this age group, with 3.6 million requiring hospitalization. In high-income countries, RSV led to 5.2 million infections, 470,000 hospitalizations, and 33,000 deaths among adults aged 60 and older.[3] The case fatality rate for hospitalized elderly patients can reach as high as 7.1%, with even higher mortality in patients with comorbidities, reaching up to 11.7%. Owing to the lack of specific antiviral therapies, vaccination is critical to prevent RSV infection in vulnerable populations. In the 1960s, the first RSV vaccine (a formalin-inactivated vaccine) was discontinued after it caused enhanced respiratory/RSV disease (ERD), leading to decades of suspension of RSV vaccine trials and indirectly resulting in stringent safety evaluations for all subsequent RSV vaccine candidates.[5] Current vaccine research is focused on the RSV F protein, particularly its pre-fusion (preF) conformation, which contains key neutralizing epitopes. Compared to other viral proteins, the neutralizing subunit of preF is highly conserved across different RSV serotypes, making it an ideal target for vaccine development.[6] However, stabilizing the preF protein remains a challenge, as it is prone to conformational changes that may

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21645515.2025.2550857

reduce vaccine efficacy. Given that the preF antigen may induce a focused immune response, the current emphasis of RSV vaccine research is on understanding the mechanisms of stabilizing the preF antigen and maintaining its stability.[7]

In June 2023, the Advisory Committee on Immunization Practices (ACIP) recommended clinical decision-making regarding RSV vaccination for adults aged 60 and older.[8] This followed the U.S. Food and Drug Administration's (FDA) approval of two RSV vaccines, RSVpreF and RSVPreF3, for this age group. Additionally, RSVpreF was approved in August 2023 for use in pregnant women between 32 and 36 weeks of gestation, marking the first RSV vaccine authorized for pregnant individuals.[9] In May 2024, the FDA approved a third vaccine, mRNA-1345. All three vaccines utilize the RSV PreF protein as the immunogen. In Phase III clinical trials, a single dose of RSVpreF (Abrysvo, Pfizer) showed an efficacy of 88.9% in preventing symptomatic LRTI, while RSVPreF3 (Arexvy, GSK) and mRNA-1345 (mRESVIA, Moderna) demonstrated efficacy rates of 82.6% and 83.7%, respectively.[10–12] However, clinical trial data and post-marketing observational data for RSVPreF3 and RSVpreF vaccines have indicated an increased risk of developing Guillain-Barre Syndrome (GBS) following vaccination.[13] In June 2024, the Centers for Disease Control and Prevention (CDC) and ACIP updated their RSV vaccination guidelines, excluding adults aged 60–74 without RSV risk factors from the recommendation.[14] In January 2025, the FDA required a warning regarding GBS in the prescribing information for both RSVPreF3 and RSVpreF to ensure vaccine safety, highlighting the need for further data to identify and evaluate potential rare side effects.[15] These measures aim to establish more targeted and safer vaccination strategies.

Given that clinical trials are conducted under controlled conditions with strict inclusion and exclusion criteria, they may not fully reflect the complexities encountered in real-world clinical practice (e.g., healthy user bias).[16] Therefore, ongoing post-marketing surveillance of RSV vaccines is crucial for assessing their long-term safety and identifying rare or unexpected adverse events (AEs). The Vaccine Adverse Event Reporting System (VAERS) is a widely used passive reporting system for monitoring potential pharmacovigilance signals in real-world settings.[17] This study aims to evaluate the post-marketing safety of RSV vaccines, analyze VAERS reports, and offer preliminary insights to inform future safety assessments.

Methods

Data source and data processing

VAERS, managed jointly by the CDC and the FDA, is a nationwide voluntary system designed to monitor the post-market safety of vaccines approved in the United States.[17] VAERS collects reports of AEs from vaccine manufacturers, healthcare providers, patients, caregivers, and other relevant sources. These reports are initially submitted in free-text (plain text) format, typically containing unstructured narrative descriptions of symptoms, diagnoses, and clinical outcomes. Subsequently, trained personnel at the CDC and FDA code the submitted information using standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA). While MedDRA is organized into five hierarchical levels, ranging from System Organ Classes (SOCs) to individual terms, the VAERS system applies coding exclusively at the Preferred Term (PT) level. Recognizing that these terms do not necessarily represent a confirmed medical diagnosis is essential. A single VAERS report may include multiple PTs and SOCs. In our analysis, each PT was mapped to its Primary SOC as defined by MedDRA (version 27.1), in accordance with standard pharmacovigilance practice. For PTs associated with multiple SOCs, only the Primary SOC was used to ensure consistent classification and to avoid double counting in SOC-level aggregation.

We conducted a search of VAERS data for reports related to RSVPreF3 (May 3, 2023–March 28, 2025), RSVpreF (May 31, 2023–March 28, 2025), and mRNA-1345 (May 31, 2024–March 28, 2025). Each VAERS report is assigned a unique report ID to ensure the reporter's anonymity and data traceability. To avoid duplication, multiple reports or symptoms associated with the same VAERS ID are merged into a single entry.[18] Reports include information such as age, sex, vaccine manufacturer, vaccination date, symptom descriptions, healthcare visits, mortality, and relevant medical history. VAERS is a routine safety monitoring program that does not require Institutional Review Board (IRB) approval or informed consent.

Study design and signal mining

Disproportionate analyses based on a 2 × 2 table (designed as a case/non-case study) were conducted to quantify the association between the RSV vaccine and AEs (Additional file 1: Table S1).[19] This analysis calculated the ratio of occurrences of the target AE between the target vaccine (cases) and all other vaccines (non-cases). A significant safety signal is indicated when the frequency of the target AE is higher with the target vaccine compared to all other vaccines. This method is widely used in pharmacovigilance for signal detection in large spontaneous reporting databases.

Standard algorithms for disproportionate analysis include the Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) (Additional file 2: Table S2). The advantage of the ROR is that it can correct for biases arising from the small number of event reports in specific categories. BCPNN excels at integrating multi-source data and performing cross-validation.[20,21] The Information Component (IC) was calculated using a BCPNN approach. IC025, defined as the lower bound of the 95% credibility interval, was used for signal detection. This study combined both algorithms to enhance the detection of reliable safety signals. When both algorithms meet the predefined criteria, a minimum of five reports is required to confirm a positive signal for RSVPreF3 and RSVpreF. In contrast, at least three reports are sufficient for mRNA-1345.

Serious vs. non-serious reports

According to the definition provided in the Code of Federal Regulations, reports can be classified as serious or non-serious. Specifically, cases that describe death, life-threatening conditions, hospitalization or prolonged existing hospitalization, permanent disability, congenital anomaly or birth defect must be classified as serious reports.[22] For serious reports, VAERS personnel require follow-up medical records for further review, except for those submitted by vaccine manufacturers, which are subject to a separate follow-up procedure.[17] Reports that do not meet these criteria are classified as non-serious. It is important to note that some reports may include multiple outcomes (e.g., a report may describe hospitalization, life-threatening conditions, and subsequently death). In such cases, we classified the report as "serious" if any of the outcomes met the seriousness criteria. We analyzed serious and non-serious reports to assess the severity of the identified safety signals.

Time-to-onset analysis and cumulative incidence

Time-to-onset (TTO) is the interval between RSV vaccine administration (VAX_DATE) and the onset of AEs (ONSET_DATE). As part of our data preprocessing, we excluded records containing missing, inconsistent, or implausible date information (e.g., onset dates preceding vaccination dates) to ensure the validity of the TTO analysis. The final dataset used for TTO analysis included only reports with complete and internally consistent temporal information, as reflected in Table 4. Descriptive analyses were conducted to summarize the TTO distribution, including median, quartiles, minimum, and maximum values. Additionally, for GBS – a serious and clinically meaningful neurological AE – Kaplan – Meier curves were plotted to visualize cumulative reporting incidence over time, and log-rank tests were employed to compare differences between RSVPreF3 and RSVpreF.

Sensitivity analysis

Sensitivity analysis using safety data from single-vaccine administrations enhances the accuracy of monitoring vaccine-related AEs. This approach eliminates the confounding effects of co-administration, allowing for a more precise evaluation of each vaccine's risks and providing more substantial evidence for public health decisions. Accordingly, we performed an in-depth analysis of the safety data for individual RSV vaccine administrations, focusing on serious reports.

Results

Descriptive analysis

During the study period, a total of 17,579 AEs related to RSVPreF3, 10196 AEs related to RSVpreF, and 132 AEs related to mRNA-1345 were identified in the VAERS database, affecting 5,147, 2,734, and 35 patients, respectively, with the clinical characteristics of these patients outlined in Table 1. Among the available demographic data, the majority of AE reports for all three RSV vaccines were from females (RSVPreF3: 3,424 reports, 66.5%; RSVpreF: 1,706 reports, 62.4%; mRNA-1345: 25 reports, 71.4%), and the median ages of the patients were 72 years (IQR: 66–77) for RSVPreF3, 70 years (IQR: 62–77) for RSVpreF, and 68 years (IQR: 60–76) for mRNA-1345. The median time from vaccination to AE onset was 0 days (IQR: 0–1) for RSVPreF3, 1 day (IQR: 0–3) for RSVpreF, and 1 day (IQR: 0–2) for mRNA-1345. Furthermore, in the majority of the reports, the RSV vaccine was administered alone, without co-administration of other vaccines during the same vaccination visit: RSVPreF3 (4299 reports, 83.5%), RSVpreF (2257 reports, 82.6%), and mRNA-1345 (25 reports, 71.4%). Notably, regarding the severity of AE reports, RSVpreF had a higher proportion of severe cases (408 reports, 14.9%) compared to RSVPreF3 (290 reports, 5.6%) and mRNA-1345 (4 reports, 11.4%), with 29 deaths reported for RSVpreF, 41 for RSVPreF3, and 1 for mRNA-1345.

Disproportionality analyses

Upon removing PT as a potential indication for RSV vaccines, we identified 91 positive PT signals for RSVPreF3, 103 for RSVpreF, and 8 for mRNA-1345 in the VAERS database (Additional file 3: Table S3). Interestingly, several statistical PT signals not currently listed in the FDA-approved product labels were identified – 40 for RSVPreF3, 37 for RSVpreF, and 1 for mRNA-1345 – and these exploratory findings are hypothesis-generating and may merit further investigation, particularly for events with biological plausibility or clinical relevance.

The top three most commonly reported PT signals for RSVPreF3 were injection site pain (639 reports), injection site erythema (553 reports), and pain (466 reports). For RSVpreF, the top three were headache

Table 1. Characteristics of VAERS reports following the administration of the RSV vaccine.

Characteristic	RSVPreF3 (Arexvy; GlaxoSmithKline)	RSVpreF (Abrysvo; Pfizer)	mRNA-1345 (mRESVIA; Moderna)
All reports	5147	2734	35
Sex, n (%)			
Female	3424 (66.5%)	1706 (62.4%)	25 (71.4%)
Male	1276 (24.8%)	720 (26.3%)	9 (25.7%)
Unknown	447 (8.7%)	308 (11.3%)	1 (2.9%)
Median age[a] (IQR), years	72 (66–77)	70 (62–77)	68 (60–76)
Median TTO[a] (IQR), days	0 (0–1)	1 (0–3)	1 (0–2)
RSV vaccine used alone, n (%)	4299 (83.5%)	2257 (82.6%)	25 (71.4%)
Serious[b]/non-serious statusn, n (%)			
Non-serious	4857 (94.4%)	2326 (85.1%)	31 (88.6%)
Serious, non-death	249 (4.8%)	379 (13.9%)	3 (8.6%)
Serious, death	41 (0.8%)	29 (1.1%)	1 (2.9%)
Vaccine doses, n (%)			
1	2397 (46.6%)	1393 (51.0%)	15 (42.9%)
2	318 (6.2%)	58 (2.1%)	2 (5.7%)
3	–	3 (0.1%)	–
5	2 (0.0%)	4 (0.1%)	–
7+	2 (0.0%)	–	–
Unknown	2428 (47.2%)	1276 (46.7%)	18 (51.4%)
Reporting year, n (%)			
2023	2009 (39.0%)	908 (33.2%)	–
2024	2670 (51.9%)	1504 (55.0%)	24 (68.6%)
2025 Q1*	468 (9.1%)	322 (11.8%)	11 (31.4%)

IQR: interquartile range, TTO: time-to-onset, n: number of cases.
[a]Age (RSVPreF3: 1151, 22.4%; RSVpreF: 923, 33.8%; mRNA-1345: 3, 8.6%) and time-to-onset (TTO) (RSVPreF3: 1198, 23.3%; RSVpreF: 653, 23.9%; mRNA-1345: 8, 22.9%) data are either missing or unknown.
[b]A report is considered serious based on the Code of Federal Regulations (21 CFR) definition if one or more of the following are reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.
*The first quarter of 2025.

(231 reports), fatigue (221 reports), and pain in extremity (182 reports). For mRNA-1345, the top three were arthralgia (5 reports), headache (5 reports), and pain (5 reports).

To explore differences in AE reporting between RSVPreF3 and RSVpreF, we conducted a comparative disproportionality analysis by calculating RORs and 95% confidence intervals for 54 shared positive PTs, using RSVpreF as the reference group (Figure 1). Given the limited number of reports for mRNA-1345, it was excluded from this analysis. RSVPreF3 demonstrated higher reporting proportions for several AEs related to local immune or inflammatory responses, including injection site pain, injection site erythema, pain, injection site swelling, injection site pruritus, injection site warmth, injection site bruising, injection site reaction, injection site rash, injection site nodule, erythema, skin warmth, and pain in extremity. In contrast, reports of GBS, a neurological condition, were more frequently reported with RSVpreF. These findings demonstrate variations in spontaneous reporting patterns and are intended solely for hypothesis generation, without implying causality.

Serious vs. Non-serious reports

The small number of reports for mRNA-1345 resulted in its data being removed from the analysis. We performed a disproportionality analysis to identify positive PT signals for RSVPreF3 and RSVpreF in

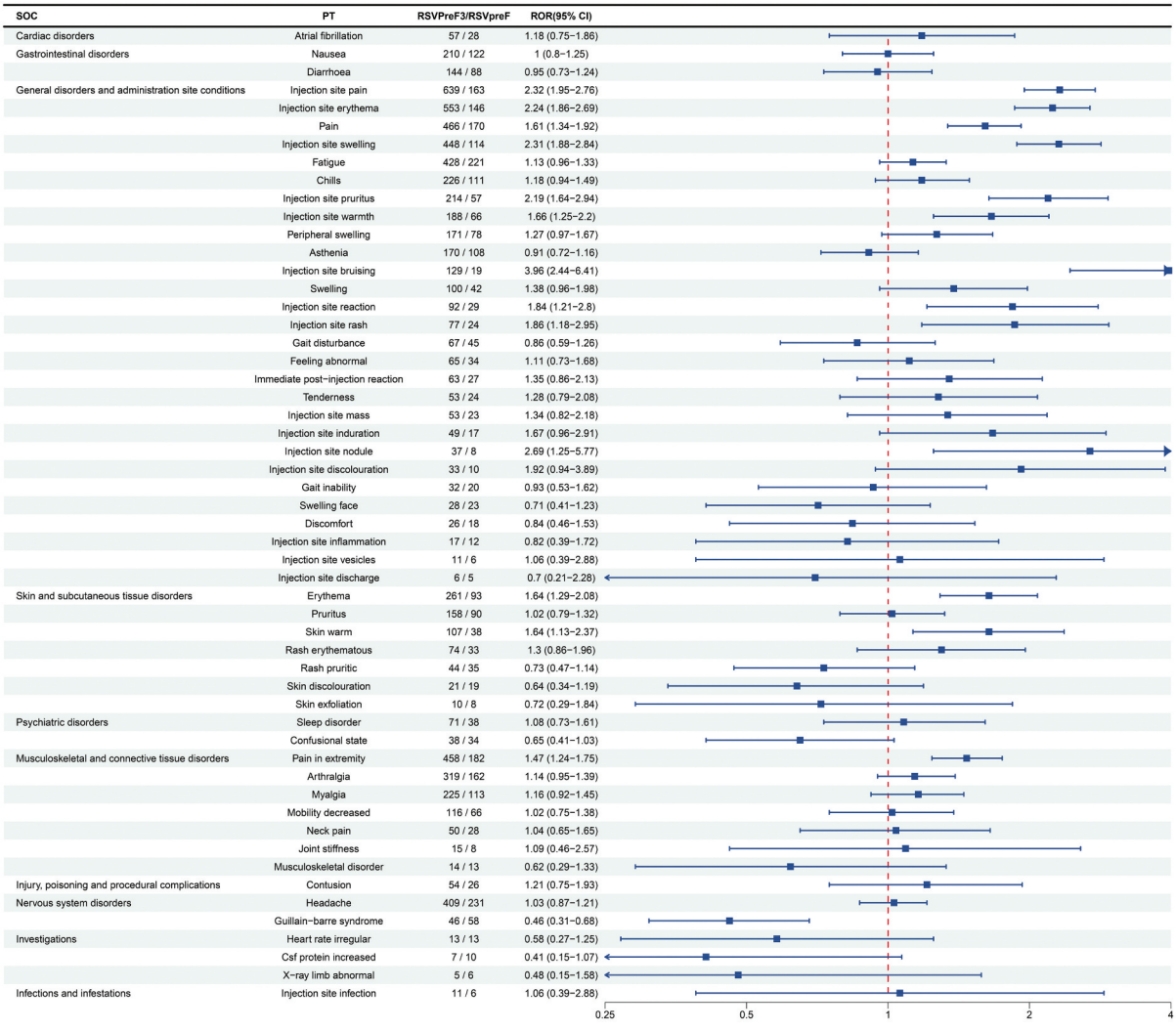

Figure 1. Comparison of RORs and 95% CIs for positive PT signals shared between RSVPreF3 and RSVpreF. RORs were calculated using RSVpreF as the reference group. The x-axis is log-scaled to ensure visual symmetry around the null value (ROR = 1). ROR > 1 indicates a higher reporting frequency with RSVPreF3 relative to RSVpreF. SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval.

serious and non-serious reports. Among the serious report positive PT signals (Table 2), both RSVPreF3 and RSVpreF had 9 PTs classified as Important Medical Events (IMEs), four common to both vaccines: GBS, CSF protein increased, immune thrombocytopenia and thrombocytopenia. Immune thrombocytopenia is also listed as a Designated Medical Event (DME). In the positive PT signals of non-serious reports (Additional file 4: Table S4), RSVPreF3 had 1 PT classified as an IME, while RSVpreF had 4 PTs categorized as IMEs. Atrial fibrillation was the only IME reported for both vaccines.

We further analyzed the positive signals in serious reports for RSVPreF3 and RSVpreF. At the SOC level, RSVPreF3's signals primarily involved General disorders and administration site conditions, Nervous system disorders, and Musculoskeletal and connective tissue disorders. In contrast, RSVpreF's signals were mainly related to Pregnancy, puerperium and perinatal conditions, Nervous system disorders, and Musculoskeletal and connective tissue disorders (Table 2). At the PT level, the shared IMEs include GBS (RSVPreF3, OR: 42.91, 95% CI: 22.61-81.4; RSVpreF, OR: 47.33, 95% CI: 21.31-105.1), immune thrombocytopenia (RSVPreF3, OR: 51.29, 95% CI: 10.3-255.24; RSVpreF, OR: 20.28, 95% CI: 4.2-97.99), and thrombocytopenia (RSVPreF3, OR: 102.59, 95% CI: 12.31-855.06; RSVpreF, all reported as serious), which were more frequently reported as serious. All reports of CSF protein increased were classified as severe (RSVPreF3; RSVpreF). Other IMEs were also more likely to be reported as severe (Table 3).

Time-to-onset analysis and cumulative incidence

Owing to inadequate TTO data for mRNA-1345, this analysis focused on RSVPreF3 and RSVpreF. As shown in Table 4, most AEs occurred within the first week post-vaccination, with a shorter median TTO for RSVPreF3 (0 days, IQR: 0–1) compared to RSVpreF (1 day, IQR: 0–3). This trend persisted across non-serious AEs (RSVPreF3: 0 days, IQR: 0–1; RSVpreF: 1 day, IQR: 0–2), serious AEs (RSVPreF3: 2 days, IQR: 0–7; RSVpreF: 3 days, IQR: 1–10), and serious AEs following sole vaccine administration. For GBS, a serious and clinically relevant AE, the median TTO was 9 days (IQR: 3–12) for RSVPreF3 and 10 days (IQR: 7–16) for RSVpreF, with no significant difference in cumulative reporting incidence ($P = .93$; Figure 2).

Sensitivity analysis

The analysis utilized individual vaccine administration data for serious reports of RSVPreF3 and RSVpreF (Additional file 5: Table S5). For RSVPreF3, of the nine positive IME signals previously identified, all except transient ischemic attack met the criteria of both the ROR and BCPNN algorithms, with the signal for ascending flaccid paralysis showing the highest strength (n = 4, ROR: 341.65; IC: 6.84). Similarly, for RSVpreF, nine positive IME signals satisfied the requirements of both algorithms, with a reported count of five or more. The signal for hemorrhage in Pregnancy demonstrated the highest intensity (n = 7, ROR: 124.46; IC: 5.85). A novel DME signal, autoimmune hepatitis, was detected, showing relatively high signal strength despite a low report count (n = 3, ROR: 5.81, IC: 2.47).

Discussion

Although clinical trials are considered the gold standard for evaluating the safety and efficacy of vaccines, their design, sample size, and observation periods may not fully capture the occurrence of rare or long-term AEs that may arise in real-world settings.[23–25] Especially after a vaccine's initial market approval, ongoing post-market surveillance is critical to identify and assess potential safety risks.[26] This pharmacovigilance study based on real-world data from VAERS contributes to a comprehensive and systematic update of the safety evidence for the RSV vaccine, offering new insights into identifying rare potential side effects.

Our findings indicate an upward trend in AE reports following RSV vaccination over calendar time since the vaccine's approval. This pattern, commonly observed in passive surveillance systems, may reflect increased clinical and public awareness, heightened media attention, and stimulated reporting in the early post-licensure period – a phenomenon known as the Webber effect.[27] While this trend should be interpreted with caution, it underscores the continued need for vigilant post-marketing surveillance to

Table 2. All PT-level positive signals based on serious reports.

Vaccine	SOC	PT	N	ROR (95% Two-Sided CI)	IC (IC025)
RSVPreF3	Blood and lymphatic system disorders	**Immune thrombocytopenia***	6	4.14 (1.84–9.33)	2.01 (0.9)
		Thrombocytopenia*	6	2.84 (1.26–6.38)	1.48 (0.38)
	Cardiac disorders	Cardiac failure congestive*	5	2.79 (1.15–6.76)	1.46 (0.27)
	Gastrointestinal disorders	Nausea	18	1.62 (1.01–2.58)	0.68 (0.01)
		Dysphagia	6	2.49 (1.11–5.6)	1.3 (0.2)
	General disorders and administration site conditions	Asthenia	31	1.84 (1.29–2.63)	0.86 (0.35)
		Injection site pain	20	8.07 (5.13–12.68)	2.93 (2.28)
		Gait inability	12	4.3 (2.42–7.65)	2.07 (1.25)
		Feeling abnormal	10	4.67 (2.48–8.77)	2.18 (1.29)
		Peripheral swelling	9	2.52 (1.3–4.87)	1.31 (0.39)
		Injection site erythema	8	5.5 (2.71–11.15)	2.41 (1.43)
		Injection site swelling	7	5.95 (2.79–12.68)	2.52 (1.47)
		Injected limb mobility decreased	6	6.06 (2.68–13.74)	2.55 (1.43)
	Psychiatric disorders	Confusional state	14	3.93 (2.31–6.7)	1.94 (1.18)
		Mental status changes	6	3.21 (1.43–7.22)	1.66 (0.55)
	Musculoskeletal and connective tissue disorders	Pain in extremity	29	2.65 (1.83–3.84)	1.38 (0.84)
		Arthralgia	26	2.23 (1.51–3.29)	1.13 (0.57)
		Muscular weakness	21	2.91 (1.89–4.5)	1.51 (0.89)
		Mobility decreased	10	2.16 (1.15–4.04)	1.09 (0.21)
		Musculoskeletal disorder	6	5.09 (2.25–11.51)	2.3 (1.19)
		Immunization reaction	7	4.24 (2–9)	2.05 (1.01)
		Contusion	6	4.98 (2.2–11.24)	2.27 (1.16)
	Nervous system disorders	Guillain-barre syndrome*	32	6.85 (4.79–9.79)	2.7 (2.18)
		Hypoaesthesia	13	1.76 (1.02–3.05)	0.81 (0.03)
		Loss of consciousness*	12	2.65 (1.5–4.7)	1.39 (0.57)
		Transient ischemic attack*	8	2.89 (1.43–5.83)	1.51 (0.53)
		Lethargy	8	3.59 (1.78–7.25)	1.81 (0.84)
		Unresponsive to stimuli*	7	3.43 (1.62–7.26)	1.75 (0.71)
		Dysarthria	6	3.97 (1.76–8.94)	1.96 (0.85)
		Areflexia	6	20.03 (8.51–47.11)	4.14 (2.98)
		Ascending flaccid paralysis*	5	119.56 (36.46–392.09)	6.03 (4.59)
	Investigations	Platelet count decreased	13	5.42 (3.11–9.45)	2.39 (1.6)
		CSF protein increased*	7	11.42 (5.28–24.69)	3.41 (2.34)
		Magnetic resonance imaging head abnormal	6	3.51 (1.56–7.9)	1.78 (0.68)
		Electrocardiogram abnormal	5	2.76 (1.14–6.69)	1.44 (0.25)
		Blood sodium decreased	5	4.05 (1.66–9.86)	1.99 (0.79)
RSVpreF	Blood and lymphatic system disorders	**Immune thrombocytopenia***	7	3.55 (1.67–7.55)	1.79 (0.75)
		Thrombocytopenia*	7	2.45 (1.16–5.19)	1.27 (0.23)

(*Continued*)

Table 2. (Continued).

Vaccine	SOC	PT	N	ROR (95% Two-Sided CI)	IC (IC025)
	Gastrointestinal disorders	Dysphagia	7	2.24 (1.06–4.74)	1.14 (0.11)
		Constipation	6	3.22 (1.43–7.26)	1.65 (0.54)
	Pregnancy, puerperium and perinatal conditions	Premature delivery	44	266.61 (152.12–467.26)	6.2 (5.64)
		Delivery	13	47.24 (24.44–91.3)	5.02 (4.13)
		Premature baby	13	77.81 (37.75–160.36)	5.47 (4.54)
		Preterm premature rupture of membranes	10	203.27 (69.43–595.13)	6.09 (4.96)
		Premature rupture of membranes	9	152.39 (54.2–428.46)	5.94 (4.77)
		Uterine contractions during pregnancy	8	135.4 (46.95–390.53)	5.87 (4.65)
		Hemorrhage in pregnancy*	7	118.43 (39.77–352.65)	5.78 (4.5)
		Fetal death*	6	33.82 (13.41–85.28)	4.68 (3.44)
		Pre-eclampsia	6	38.05 (14.88–97.32)	4.8 (3.55)
		Fetal hypokinesia*	5	42.26 (14.88–120.05)	4.91 (3.55)
		Induced labor	5	101.43 (29.35–350.6)	5.68 (4.21)
	General disorders and administration site conditions	Feeling abnormal	12	4.32 (2.42–7.71)	2.06 (1.24)
		Gait inability	11	2.97 (1.63–5.42)	1.54 (0.69)
	Skin and subcutaneous tissue disorders	Petechiae	6	4.06 (1.79–9.18)	1.98 (0.86)
	Surgical and medical procedures	Cesarean section	26	120.87 (68.41–213.54)	5.79 (5.1)
	Musculoskeletal and connective tissue disorders	Muscular weakness	28	2.95 (2.02–4.3)	1.52 (0.98)
		Mobility decreased	17	2.82 (1.74–4.57)	1.46 (0.77)
		Back pain	13	2.35 (1.36–4.08)	1.21 (0.43)
		Neck pain	9	2.96 (1.52–5.74)	1.53 (0.6)
		Musculoskeletal disorder	7	4.47 (2.09–9.53)	2.11 (1.06)
	Injury, poisoning and procedural complications	Contusion	5	3.05 (1.25–7.44)	1.58 (0.38)
	Nervous system disorders	Guillain-barre syndrome*	51	8.49 (6.36–11.33)	2.96 (2.54)
		Paresthesia	18	1.8 (1.13–2.88)	0.84 (0.17)
		Hypoaesthesia	17	1.76 (1.09–2.85)	0.8 (0.11)
		Facial paralysis*	9	3.41 (1.75–6.63)	1.73 (0.8)
		Dysstasia	8	3.81 (1.88–7.73)	1.89 (0.91)
		Neurological symptom	5	2.86 (1.18–6.97)	1.49 (0.29)
		Paralysis*	5	2.77 (1.14–6.74)	1.44 (0.25)
	Investigations	Platelet count decreased	16	4.98 (3.01–8.24)	2.25 (1.53)
		CSF protein increased*	10	12.24 (6.34–23.62)	3.46 (2.54)
		Scan with contrast abnormal	6	5.91 (2.59–13.47)	2.49 (1.37)
		Magnetic resonance imaging head abnormal	6	2.68 (1.19–6.03)	1.4 (0.29)
		Magnetic resonance imaging abnormal	5	4.97 (2.02–12.21)	2.26 (1.04)

ROR, reporting odds ratio; SOC, system organ classes; PT: preferred term; CI, confidence interval; IC, information component; IC025, lower one-sided for IC; N, number of target adverse events.

*Classified as an Important Medical Events (IME), with those in bold also being listed as Designated Medical Event (DME), as defined and updated by the European Medicines Agency (EMA).

Table 3. Differences in clinical characteristics of severe and non-severe reports.

Vaccine	PT	a	b	c	d	OR (95%CI)
RSVPreF3	**Immune thrombocytopenia***	6	284	2	4855	51.29 (10.3–255.24)
	Thrombocytopenia*	6	284	1	4856	102.59 (12.31–855.06)
	Cardiac failure congestive*	5	285	0	4857	>170.42
	Nausea	18	272	192	4665	1.61 (0.98–2.65)
	Dysphagia	6	284	12	4845	8.53 (3.18–22.89)
	Asthenia	31	259	139	4718	4.06 (2.7–6.11)
	Injection site pain	20	270	619	4238	0.51 (0.32–0.8)
	Gait inability	12	278	20	4837	10.44 (5.05–21.57)
	Feeling abnormal	10	280	55	4802	3.12 (1.57–6.18)
	Peripheral swelling	9	281	162	4695	0.93 (0.47–1.84)
	Injection site erythema	8	282	545	4312	0.22 (0.11–0.46)
	Injection site swelling	7	283	441	4416	0.25 (0.12–0.53)
	Injected limb mobility decreased	6	284	73	4784	1.38 (0.6–3.21)
	Confusional state	14	276	24	4833	10.21 (5.23–19.97)
	Mental status changes	6	284	0	4857	>205.23
	Pain in extremity	29	261	429	4428	1.15 (0.77–1.7)
	Arthralgia	26	264	293	4564	1.53 (1.01–2.33)
	Muscular weakness	21	269	46	4811	8.16 (4.8–13.88)
	Mobility decreased	10	280	106	4751	1.6 (0.83–3.1)
	Musculoskeletal disorder	6	284	8	4849	12.81 (4.41–37.16)
	Immunization reaction	7	283	12	4845	9.99 (3.9–25.56)
	Contusion	6	284	48	4809	2.12 (0.9–4.99)
	Guillain-barre syndrome*	32	258	14	4843	42.91 (22.61–81.4)
	Hypoaesthesia	13	277	60	4797	3.75 (2.04–6.92)
	Loss of consciousness*	12	278	22	4835	9.49 (4.65–19.37)
	Transient ischemic attack*	8	282	2	4855	68.87 (14.56–325.81)
	Lethargy	8	282	64	4793	2.12 (1.01–4.47)
	Unresponsive to stimuli*	7	283	18	4839	6.65 (2.75–16.05)
	Dysarthria	6	284	3	4854	34.18 (8.5–137.39)
	Areflexia	6	284	0	4857	>205.23
	Ascending flaccid paralysis*	5	285	0	4857	>170.42
	Platelet count decreased	13	277	4	4853	56.94 (18.45–175.77)
	CSF protein increased*	7	283	0	4857	>240.28
	Magnetic resonance imaging head abnormal	6	284	0	4857	>205.23
	Electrocardiogram abnormal	5	285	6	4851	14.18 (4.3–46.76)
	Blood sodium decreased	5	285	0	4857	>170.42
RSVpreF	**Immune thrombocytopenia***	7	401	2	2324	20.28 (4.2–97.99)
	Thrombocytopenia*	7	401	0	2326	>81.21
	Dysphagia	7	401	10	2316	4.04 (1.53–10.68)
	Constipation	6	402	3	2323	11.56 (2.88–46.4)
	Premature delivery	44	364	36	2290	7.69 (4.88–12.11)
	Delivery	13	395	10	2316	7.62 (3.32–17.5)
	Premature baby	13	395	31	2295	2.44 (1.26–4.7)
	Preterm premature rupture of membranes	10	398	4	2322	14.59 (4.55–46.73)
	Premature rupture of membranes	9	399	6	2320	8.72 (3.09–24.64)
	Uterine contractions during pregnancy	8	400	4	2322	11.61 (3.48–38.74)
	Hemorrhage in pregnancy*	7	401	2	2324	20.28 (4.2–97.99)
	Fetal death*	6	402	8	2318	4.32 (1.49–12.53)
	Pre-eclampsia	6	402	4	2322	8.66 (2.43–30.84)
	Fetal hypokinesia*	5	403	11	2315	2.61 (0.9–7.55)
	Induced labor	5	403	2	2324	14.42 (2.79–74.56)
	Feeling abnormal	12	396	22	2304	3.17 (1.56–6.46)
	Gait inability	11	397	9	2317	7.13 (2.94–17.32)
	Petechiae	6	402	1	2325	34.7 (4.17–289.01)
	Cesarean section	26	382	10	2316	15.76 (7.54–32.95)
	Muscular weakness	28	380	41	2285	4.11 (2.51–6.72)
	Mobility decreased	17	391	49	2277	2.02 (1.15–3.54)
	Back pain	13	395	31	2295	2.44 (1.26–4.7)
	Neck pain	9	399	19	2307	2.74 (1.23–6.1)
	Musculoskeletal disorder	7	401	6	2320	6.75 (2.26–20.19)
	Contusion	5	403	21	2305	1.36 (0.51–3.63)
	Guillain-barre syndrome*	51	357	7	2319	47.33 (21.31–105.1)
	Paresthesia	18	390	38	2288	2.78 (1.57–4.92)
	Hypoaesthesia	17	391	23	2303	4.35 (2.3–8.22)

(*Continued*)

Table 3. (Continued).

Vaccine	PT	a	b	c	d	OR (95%CI)
	Facial paralysis*	9	399	1	2325	52.44 (6.63–415.09)
	Dysstasia	8	400	14	2312	3.3 (1.38–7.92)
	Neurological symptom	5	403	0	2326	>57.72
	Paralysis*	5	403	1	2325	28.85 (3.36–247.56)
	Platelet count decreased	16	392	5	2321	18.95 (6.9–52.01)
	CSF protein increased*	10	398	0	2326	>116.88
	Scan with contrast abnormal	6	402	0	2326	>69.43
	Magnetic resonance imaging head abnormal	6	402	0	2326	>69.43
	Magnetic resonance imaging abnormal	5	403	4	2322	7.2 (1.93–26.94)

The above-mentioned are positive adverse event signals based on serious reports. A single VAERS report may contain multiple adverse events.
OR, odds ratio; PT: preferred term; CI, confidence interval.
a, The number of serious reports containing target adverse vaccine event; b, The number of serious reports excluding target adverse vaccine event; c, The number of non-serious reports containing target adverse vaccine event; d, The number of non-serious reports excluding target adverse vaccine event.
*Classified as an Important Medical Events (IME), with those in bold also being listed as Designated Medical Event (DME), as defined and updated by the European Medicines Agency (EMA).
For rows where c = 0, a continuity correction of 0.5 was applied to compute the odds ratio, which is presented as a lower bound (e.g., " >x"). Confidence intervals were not calculated in these cases.

Table 4. Analysis of time-to-onset following post-RSV vaccine administration.

Categories	Vaccine	Cases (n)	Median (days)	IQR (days)	Min–Max (days)
All reports	RSVPreF3	3949	0	0–1	0–732
	RSVpreF	2081	1	0–3	0–418
	mRNA-1345	27	1	0–2	0–25
Guillain – Barre syndrome	RSVPreF3	27	9	3–12	0–50
	RSVpreF	43	10	7–16	0–37
Serious AEs	RSVPreF3	231	2	0–7	0–365
	RSVpreF	328	3	1–10	0–251
Non-serious AEs	RSVPreF3	3718	0	0–1	0–732
	RSVpreF	1753	1	0–2	0–418
Sole administration	RSVPreF3	3174	0	0–1	0–474
	RSVpreF	1640	1	0–3	0–418
	mRNA-1345	20	1	0–2	0–12
Sole administration (serious reports)	RSVPreF3	164	2	0–7	0–365
	RSVpreF	269	3	1–10	0–251

n, number of reports that include available time-to-onset data; TTO,Time-to-onset; IQR, interquartile range; CI, confidence interval.

detect potential safety signals. Such surveillance can also inform vaccination strategies by supporting early safety communication, identifying at-risk subgroups, and guiding post-vaccination monitoring efforts. AE reports were predominantly from older adults aged ≥60 years and women, mostly following single-dose administration, reflecting ACIP's 2023 recommendation for shared clinical decision-making in this population and the greater tendency among women to seek health information and recognize vaccine side effects, which may lead to more informed vaccination decisions.[14,28] Among the three RSV vaccines, RSVpreF showed a higher proportion of severe AE reports, potentially due to enhanced monitoring in pregnancy and a conservative reporting approach.[29] Most of these reports concern single-use, which may be attributed to insufficient clinical data regarding the co-administration of RSV vaccines with other vaccines and the uncertainty around their combined safety. However, recent studies have shown that co-administration of the protein subunit RSV vaccine, mRNA COVID-19 vaccines, and high-dose influenza vaccines is safe and generates non-inferior humoral immune responses.[30] Further studies have indicated that co-administration of the RSV mRNA-1345 vaccine with SIIV4 or mRNA-1273.214 vaccines produced antibody responses that were non-inferior to those of the vaccines administered independently, at least according to geometric mean titers (GMTs).[31] Given the increasing complexity of vaccination schedules for adult populations, particularly elderly individuals with comorbidities, the co-administration of vaccines is expected to be a key strategy in increasing vaccination rates, improving compliance, and optimizing existing vaccination plans.[32]

The VAERS analysis reveals a high consistency in the standard favorable PTs signals for the protein subunit RSV vaccines (RSVPreF3 and RSVpreF), primarily involving general disorders and administration site conditions, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders at the SOC level.[33] RSVPreF3 and RSVpreF differ in formulation, target populations, and safety profiles. RSVPreF3 is an AS01E-adjuvanted vaccine approved for adults ≥60 years and at-risk adults aged 50–59

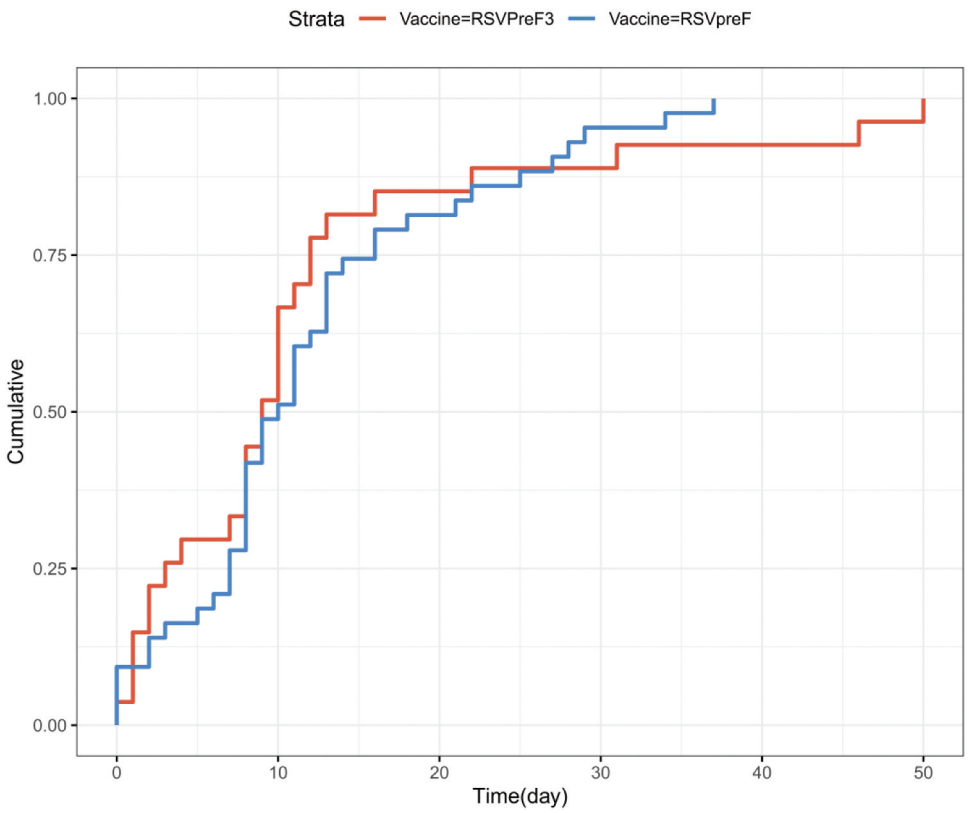

Figure 2. Cumulative reporting incidence of GBS after RSVPreF3 and RSVpreF vaccination. No significant difference was observed (log-rank $P = .93$). AE, adverse event; GBS, Guillain–barre syndrome.

years, associated with a higher frequency of mild, self-limiting local and systemic reactions, which may be related to the adjuvant.[10,34] RSVpreF is a non-adjuvanted vaccine approved for pregnant individuals (to confer passive immunity to infants), adults ≥60 years, and high-risk adults aged 18–59 years. While RSVpreF generally shows lower reactogenicity, it has a higher reporting frequency of GBS in VAERS; however, both vaccines exhibit disproportionality signals for GBS, which likely reflect reporting differences rather than confirmed clinical risk.[14] Chills are the most commonly reported unexpected AE not mentioned on the FDA labels for both vaccines. The report count for RSV mRNA-1345 vaccine is low, with only one unexpected AE signal – diarrhea – being detected. These findings highlight the differing AE profiles of RSVPreF3 and RSVpreF in passive surveillance and support continued monitoring to contextualize observed disproportionality patterns. Among these, the results for mRNA-1345 should be interpreted with greater caution, as the small sample size may affect the reliability of signal detection.

In clinical decision-making and public health practice, vaccine safety assessments should rely on detecting safety signals and consider the clinical severity, tolerability, and potential impact of AEs on patient management.[35,36] For example, mild and self-limiting AEs, such as local injection site reactions, although common, generally do not impact clinical decision-making; however, rare but severe AEs, such as GBS, particularly in high-risk populations, warrant close monitoring and a more detailed risk assessment and stratified management approach. In this study, we conducted an in-depth analysis of rare potential side effects of the RSV vaccine based on serious and non-serious AE reports from VAERS. The results indicate that for protein subunit RSV vaccines (RSVPreF3 and RSVpreF), key positive IME signals that require close monitoring are primarily related to inflammatory neurologic events, such as GBS, loss of consciousness, unresponsive to stimuli, ascending flaccid paralysis, and facial paralysis. Additionally, immune thrombocytopenia is a notable positive DME signal in the blood system. In the cardiovascular system, atrial fibrillation should be particularly monitored, as phase 3 clinical trials suggest a potential risk.[37] Furthermore, a positive disproportionality signal for cardiac failure congestive was detected for RSVPreF3, with

all associated reports categorized as serious. As the only RSV vaccine approved for pregnant women, RSVPreF has reported three positive IME signals related to pregnancy: hemorrhage in pregnancy, fetal death, and fetal hypokinesia. Although this study cannot confirm whether RSV vaccination increases the risk of these severe AEs, it remains essential to maintain clinical vigilance, especially in high-risk populations.

The timing of AEs is a crucial factor influencing clinical decision-making, as it helps clinicians identify critical periods that require close monitoring, thus providing early insights for precision prevention and treatment strategies tailored to different populations.[38] In our study, we conducted a descriptive analysis of TTO across different categories of adverse events, along with a comparison of cumulative reporting incidence for GBS, a serious and clinically relevant outcome. The majority of reported events occurred within the first week following vaccination, with serious events tending to have longer onset intervals than non-serious ones. Notably, RSVPreF3 was generally associated with shorter TTO values compared to RSVpreF across multiple subgroups, while cumulative GBS incidence was similar between the two. Approximately 23% of TTO data were excluded due to missing or implausible dates (e.g., onset preceding vaccination). Given VAERS' passive reporting nature and the probable nonrandom pattern of missingness linked to reporting behavior and AE characteristics, we did not perform imputation or sensitivity analyses to avoid introducing potential bias or false precision. Nonetheless, we recognize that carefully designed sensitivity analyses could yield valuable insights and plan to address this in future research.

To further enhance the precision of signal detection and mitigate confounding from co-administration, we conducted a sensitivity analysis restricted to serious reports involving individual RSV vaccine administration. This approach reaffirmed the robustness of the initial IME signals, as all previously identified signals met the predefined thresholds of both the ROR and BCPNN algorithms, with the exception of transient ischemic attack. Notably, several new signals emerged for RSVpreF in this subset, including one designated medical event (autoimmune hepatitis) and three important medical events (fetal distress syndrome, fetal growth restriction, and premature separation of placenta). Although these signals met statistical criteria in both algorithms, they were based on fewer than five individual reports and thus did not meet the minimum case count threshold for a positive signal. In light of the small sample size and known statistical instability of rare events in spontaneous reporting systems, these novel findings should be interpreted with caution.

Like other spontaneous public health reporting systems, VAERS has serious limitations. First, due to the voluntary nature of reporting issues such as reporting bias, underreporting, inconsistent data quality, diagnostic uncertainty, and incomplete data inevitably lead to unquantifiable biases in this study. Second, while some AEs may be directly attributable to the vaccine, others could be caused by underlying diseases, concomitant medications, or other vaccines or occur coincidentally shortly after vaccination. Therefore, the AEs reported in VAERS do not imply a causal relationship. Rather, the signals identified through disproportionality analysis reflect statistical associations that require further validation in structured studies. Third, the absence of structured denominator data – including total vaccine exposure counts and unvaccinated controls – VAERS cannot support quantitative risk assessment, estimation of true AE incidence rates, or direct comparisons between vaccinated and unvaccinated populations. Fourth, disproportionality analysis involves multiple testing across many PTs, and without adjustment for multiplicity, this may lead to false-positive signal inflation. Fifth, the lack of data on background incidence rates and potential confounding by indication – such as underlying comorbidities that may influence both the likelihood of vaccination and the occurrence of certain AEs – can further bias signal interpretation. Additionally, use of a broad and demographically heterogeneous comparator pool may bias the estimation of expected AE frequencies for products indicated for specific subgroups. This concern is particularly relevant for RSVPreF3 and RSVpreF, which share an indication for older adults (≥60 years), and for RSVpreF, which is also approved for pregnant individuals. However, pregnancy status cannot be reliably captured through structured fields in the VAERS database. Although a recent study demonstrated that integration of free-text narratives and coded terms may allow partial inference of pregnancy status, the lack of standardized coding limits the consistency and reproducibility of such stratification.[39] Furthermore, given the exploratory and descriptive nature of this study, we did not perform systematic stratification or multivariable adjustment for other key covariates, including age, sex, seasonal variation, comorbidities, and concomitant vaccine administration. We acknowledge that future research incorporating stratified and adjusted comparator groups based on

clinical indication and demographic characteristics will be essential to enhance the specificity, reliability, and interpretability of disproportionality signals – particularly in high-risk populations such as older adults and pregnant individuals.

Conclusions

We have described notable reporting patterns related to RSV vaccines using real-world data from VAERS. For protein subunit vaccines (RSVPreF3 and RSVpreF), disproportionately elevated reporting was observed for inflammatory neurological events (e.g., GBS, facial paralysis), immune thrombocytopenia, and atrial fibrillation – AEs that are clinically significant and merit further investigation, especially in older adults. Additionally, for RSVpreF, higher-than-expected reporting frequencies were noted for pregnancy-related events, including hemorrhage in pregnancy, fetal death, and fetal hypokinesia. These findings are hypothesis-generating and do not imply causality, but they may serve as a basis for further structured research in high-risk populations. In contrast, commonly reported mild adverse events such as injection site pain or fatigue, which are expected and generally well-tolerated, are not considered priorities for future investigation. Continued pharmacovigilance and focused, hypothesis-driven studies may help clarify these safety signals and support risk – benefit evaluations in clinical practice.

Abbreviations

RSV	Respiratory syncytial virus
LRTIs	Lower respiratory tract infections
ERD	Enhanced respiratory/RSV disease
preF	pre-fusion
ACIP	Advisory Committee on Immunization Practices
FDA	U.S. Food and Drug Administration
GBS	Guillain-Barre syndrome
CDC	Centers for Disease Control and Prevention
AEs	Adverse events
VAERS	Vaccine Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Classes
PT	Preferred Terms
IRB	Institutional Review Board
ROR	Reporting Odds Ratio
BCPNN	Bayesian Confidence Propagation Neural Network
CI	Confidence interval
TTO	Time-to-onset
IQR	Interquartile range
FDR	False discovery rate
IME	Important Medical Event
DME	Designated Medical Event
OR	Odds Ratio
GMTs	Geometric mean titers

Acknowledgments

We express our gratitude to the workers of the CDC's Immunization Safety Office, whose efforts facilitated the execution of this activity. Z.C.B. designed the study and wrote the initial draft. X.Y. handled data organization and formal analysis. L.Q.C. contributed to the methodology and validation. Y.X.L. oversaw the project, secured funding, and reviewed and edited the manuscript. All authors read and approved the final manuscript.

Author contributions

CRediT: **Zhuocheng Bao:** Conceptualization, Writing – original draft; **Weixi Gao:** Methodology, Writing – review & editing; **Xiao Yu:** Formal analysis; **Liqing Chai:** Data curation; **Yuxiang Liu:** Funding acquisition, Supervision.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was supported by the Natural Science Research Project of Basic Research Programme in Shanxi Province [202203021221268] & Young Scientists Fund of National Natural Science foundation of China [82305030] & College Students Innovation Training Program Projects of Institutions of Higher Learning in Shanxi Province [20250349] & Shanxi Provincial Postdoctoral Science Foundation [KY0139] & Shanxi Provincial Administration of Traditional Chinese Medicine Scientific Research Program [2023ZYYC041].

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Data availability statement

The datasets generated and/or analyzed during the current study are available in the VAERS database (https://vaers.hhs.gov/data/datasets.html). Additional relevant data is either uploaded as supplemental information or included in the article.

Ethics approval and consent to participate

Ethical approval was not needed since the study utilized deidentified publically accessible data.

References

1. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus–a comprehensive review. Clin Rev Allergy Immunol. 2013;45(3):331–379. doi: 10.1007/s12016-013-8368-9.
2. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, Prieto-Merino D, Cousens S, Black RE, Liu L. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the sustainable development goals. Lancet Child Adolesc Health. 2022;6(2):106–115. doi: 10.1016/S2352-4642(21)00311-4.
3. Savic M, Penders Y, Shi T, Branche A, Pircon JY. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: a systematic literature review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13031. doi: 10.1111/irv.13031.
4. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, Madhi SA, Omer SB, Simoes EAF, Campbell H, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047–2064. doi: 10.1016/S0140-6736(22)00478-0.
5. Polack FP, Alvarez-Paggi D, Libster R, Caballero MT, Blair RV, Hijano DR, de la Iglesia Niveyro PX, Menendez DR, Gladwell W, Avendano LM, et al. Fatal enhanced respiratory syncytial virus disease in toddlers. Sci Transl Med. 2021;13(616):eabj7843. doi: 10.1126/scitranslmed.abj7843.
6. Ruckwardt TJ. The road to approved vaccines for respiratory syncytial virus. NPJ Vaccin. 2023;8(1):138. doi: 10.1038/s41541-023-00734-7.
7. Crank MC, Ruckwardt TJ, Chen M, Morabito KM, Phung E, Costner PJ, Holman LA, Hickman SP, Berkowitz NM, Gordon IJ, et al. A proof of concept for structure-based vaccine design targeting RSV in humans. Science. 2019;365(6452):505–509. doi: 10.1126/science.aav9033.

8. Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, Havers FP. Use of respiratory syncytial virus vaccines in older adults: recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(29):793–801. doi: 10.15585/mmwr.mm7229a4.
9. Fleming-Dutra KE, Jones JM, Roper LE, Prill MM, Ortega-Sanchez IR, Moulia DL, Wallace M, Godfrey M, Broder KR, Tepper NK, et al. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the Prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants: recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(41):1115–1122. doi: 10.15585/mmwr.mm7241e1.
10. Walsh EE, Perez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, Polack FP, Llapur C, Doreski PA, Ilangovan K, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. N Engl J Med. 2023;388(16):1465–1477. doi: 10.1056/NEJMoa2213836.
11. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, Schwarz TF, van zyl-Smit RN, Campora L, Dezutter N, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. N Engl J Med. 2023;388(7):595–608. doi: 10.1056/NEJMoa2209604.
12. Wilson E, Goswami J, Baqui AH, Doreski PA, Perez-Marc G, Zaman K, Monroy J, Duncan CJA, Ujiie M, Ramet M, et al. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults. N Engl J Med. 2023;389(24):2233–2244. doi: 10.1056/NEJMoa2307079.
13. Shaaban FL, Bont LJ. The big five vexing questions of respiratory syncytial virus immunisation. Lancet Respir Med. 2025;13(6):477–478. doi: 10.1016/S2213-2600(25)00093-1.
14. Britton A, Roper LE, Kotton CN, Hutton DW, Fleming-Dutra KE, Godfrey M, Ortega-Sanchez IR, Broder KR, Talbot HK, Long SS, et al. Use of respiratory syncytial virus vaccines in adults aged ≥60 years: updated recommendations of the Advisory Committee on Immunization Practices — United States, 2024. MMWR Morb Mortal Wkly Rep. 2024;73(32):696–702. doi: 10.15585/mmwr.mm7332e1.
15. Anderer S. FDA issues warning of Guillain-barre syndrome risk for 2 RSV vaccines. JAMA. 2025;333(12):1023–1024. doi: 10.1001/jama.2025.0545.
16. Branche AR. Real-world effectiveness studies of the benefit of RSV vaccines. Lancet. 2024;404(10462):1498–1500. doi: 10.1016/S0140-6736(24)02150-0.
17. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398–4405. doi: 10.1016/j.vaccine.2015.07.035.
18. Shimabukuro TT, Su JR, Marquez PL, Mba-Jonas A, Arana JE, Cano MV. Safety of the 9-valent human papillomavirus vaccine. Pediatrics. 2019;144(6). doi: 10.1542/peds.2019-1791.
19. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427–436. doi: 10.1002/pds.1742.
20. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519–523. doi: 10.1002/pds.1001.
21. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315–321. doi: 10.1007/s002280050466.
22. US Food and Drug Administration. Code of Federal Regulations title 21, volume (21CFR600.80). 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-600/subpart-D.
23. Bothwell LE, Greene JA, Podolsky SH, Jones DS, Malina D. Assessing the gold standard–lessons from the history of RCTs. N Engl J Med. 2016;374(22):2175–2181. doi: 10.1056/NEJMms1604593.
24. Dodd C, Andrews N, Petousis-Harris H, Sturkenboom M, Omer SB, Black S. Methodological frontiers in vaccine safety: qualifying available evidence for rare events, use of distributed data networks to monitor vaccine safety issues, and monitoring the safety of pregnancy interventions. BMJ Glob Health. 2021;6(Suppl 2):e003540. doi: 10.1136/bmjgh-2020-003540.
25. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill. 2013;18(37). doi: 10.2807/1560-7917.ES2013.18.37.20585.
26. Sharrar RG, Dieck GS. Monitoring product safety in the postmarketing environment. Ther Adv Drug Saf. 2013;4(5):211–219. doi: 10.1177/2042098613490780.
27. Hartnell NR, Wilson JP. Replication of the weber effect using postmarketing adverse event reports voluntarily submitted to the United States food and drug administration. Pharmacotherapy. 2004;24(6):743–749. doi: 10.1592/phco.24.8.743.36068.
28. Baldwin AS, Bruce CM, Tiro JA. Understanding how mothers of adolescent girls obtain information about the human papillomavirus vaccine: associations between mothers' health beliefs, information seeking, and vaccination intentions in an ethnically diverse sample. J Health Psychol. 2013;18(7):926–938. doi: 10.1177/1359105312445078.
29. Haws RA, Yakoob MY, Soomro T, Menezes EV, Darmstadt GL, Bhutta ZA. Reducing stillbirths: screening and monitoring during pregnancy and labour. BMC Pregnancy Childbirth. 2009;9(Suppl S1):S5. doi: 10.1186/1471-2393-9-S1-S5.

30. Melgar M, Britton A. RSV vaccination in adults: work group interpretations. Meeting of the Advisory Committee on Immunization Practices (ACIP) Respiratory Syncytial Virus (RSV) Vaccines, Adults October: 2024; Atlanta, Georgia, USA; 2024.
31. Goswami J, Cardona JF, Hsu DC, Simorellis AK, Wilson L, Dhar R, Tomassini JE, Wang X, Kapoor A, Collins A, et al. Safety and immunogenicity of mRNA-1345 RSV vaccine coadministered with an influenza or COVID-19 vaccine in adults aged 50 years or older: an observer-blinded, placebo-controlled, randomised, phase 3 trial. Lancet Infect Dis. 2025;25(4):411–423. doi: 10.1016/S1473-3099(24)00589-9.
32. Bonanni P, Steffen R, Schelling J, Balaisyte-Jazone L, Posiuniene I, Zatonski M, Van Damme P. Vaccine co-administration in adults: an effective way to improve vaccination coverage. Hum Vaccin Immunother. 2023;19(1):2195786. doi: 10.1080/21645515.2023.2195786.
33. Hause AM, Moro PL, Baggs J, Zhang B, Marquez P, Melgar M, Britton A, Stroud E, Myers TR, Rakickas J, et al. Early safety findings among persons aged >/=60 years who received a respiratory syncytial virus vaccine - United States, May 3, 2023-April 14, 2024. MMWR Morb Mortal Wkly Rep. 2024;73(21):489–494. doi: 10.15585/mmwr.mm7321a3.
34. Domnich A, Orsi A, Lai PL, Massaro E, Trombetta C-S, Pastorino J, Roihl C, Tardito S, Pianta M, Icardi G, et al. Enhanced safety surveillance of the adjuvanted respiratory syncytial virus vaccine among Italian older adults. Vaccine. 2025;24:100647. doi: 10.1016/j.jvacx.2025.100647.
35. Di Pasquale A, Bonanni P, Garcon N, Stanberry LR, El-Hodhod M, Tavares Da Silva F. Vaccine safety evaluation: practical aspects in assessing benefits and risks. Vaccine. 2016;34(52):6672–6680. doi: 10.1016/j.vaccine.2016.10.039.
36. Banerjee AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, Flamion B, Cleeland C, Basch E. Patient-reported outcomes safety event reporting C: patient-reported outcome measures in safety event reporting: PROSPER consortium guidance. Drug Saf. 2013;36(12):1129–1149. doi: 10.1007/s40264-013-0113-z.
37. Birabaharan M, Johns ST, Kaelber DC, Martin TCS, Mehta SR. Atrial fibrillation after RSV vaccination among older adults. Clin Infect Dis. 2024; doi: 10.1093/cid/ciae649.
38. Sox HC, Higgins MC, Owens DK, Schmidler GS. Medical decision making. Hoboken (NJ): John Wiley & Sons; 2024.
39. Alami A, Perez-Lloret S, Mattison DR. Safety surveillance of respiratory syncytial virus (RSV) vaccine among pregnant individuals: a real-world pharmacovigilance study using the Vaccine Adverse Event Reporting System. BMJ Open. 2025;15(4):e087850. doi: 10.1136/bmjopen-2024-087850.