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Safety surveillance of respiratory syncytial virus (RSV) vaccine among pregnant individuals: a real-world pharmacovigilance study using the Vaccine Adverse Event Reporting System

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ABSTRACT

Objectives To describe the post-marketing safety profile of respiratory syncytial virus prefusion F (RSVpreF) vaccine among pregnant individuals.

Design This study analysed adverse event (AE) reports submitted to the U.S. Food and Drug Administration's Vaccine Adverse Event Reporting System (VAERS) database following RSVpreF immunisation from 1 September 2023 to 23 February 2024.

Setting VAERS, as a national spontaneous vaccine safety surveillance system, provides insights into the safety profile of the RSVpreF vaccine in a real-world setting.

Participants Surveillance data included all AE reports submitted to VAERS in pregnant individuals following vaccination.

Exposure Receipt of RSVpreF vaccine among pregnant individuals in the USA.

Primary and secondary outcome measures Descriptive statistics were used to assess all AE reports with RSVpreF, including frequency, gestational age at vaccination, time to AE onset, reported outcomes and proportion of serious reports. Data mining techniques were employed to identify disproportionate reporting of RSVpreF-event pairs. Reports of preterm births were clinically reviewed.

Results VAERS received 77 reports pertaining to RSVpreF vaccination in pregnant individuals, with 42 (54.55%) classified as serious. The most frequently reported non-pregnancy-specific AEs were headache, injection site erythema and injection site pain. For pregnancy-specific AEs, preterm birth was the most frequently reported (12.8%), followed by AE terms such as preterm premature rupture of membranes and caesarean section (each at 3.3%), and cervical dilatation, haemorrhage during pregnancy and uterine contractions during pregnancy (each at 1.4%). Our disproportionality analysis indicated signals for various AEs, particularly preterm birth, indicating that reports of preterm birth in conjunction with RSVpreF vaccination were observed more frequently than statistically expected. Most of the reported preterm births were moderate to late, occurring between 32 and less than 37 weeks of gestation. The median time from immunisation to the onset of preterm birth was 3 days, with two-thirds of cases reported within a week of vaccination.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uses the Vaccine Adverse Event Reporting System (VAERS) database, a U.S. national pharmacovigilance system, that provides a near real-time surveillance capacity for identifying rare adverse events not previously detected during prelicensure trials.

⇒ The use of specific diagnostic codes from the Brighton collaboration guide ensured accurate identification of preterm birth cases, while clinical review helped to minimise misclassification risks inherent in relying solely on reported adverse events.

⇒ The Bayesian Confidence Propagation Neural Network (BCPNN) method was used to calculate the information component (IC) statistic, chosen for its ability to handle low expected counts and minimize the risk of flagging false signals. This approach enabled comparison of observed-to-expected reporting rates of adverse events following immunization (AEFIs) with the RSVPreF vaccine against those with all other U.S. Food and Drug Administration-approved vaccines routinely administered during pregnancy, such as inactivated influenza, COVID-19 and pertussis vaccines.

⇒ As a passive surveillance system, VAERS is subject to various reporting biases, such as over-reporting, stimulated reporting and under-reporting, which are particularly significant for pregnancy-specific and neonatal-specific adverse events.

⇒ Events temporally close to vaccination are more likely to be reported; however, reporting often depends on medical suspicion, potentially introducing bias in how adverse events are captured.

Conclusions The AEs reported to VAERS among pregnant individuals vaccinated with RSVpreF largely aligned with the safety profile observed in prelicensure studies; however, this analysis also highlights the previously observed safety signal for preterm birth. Active surveillance studies focusing on maternal and perinatal outcomes are needed to further evaluate this signal and guide future clinical recommendations.

INTRODUCTION

Pregnant individuals and their newborns face an increased risk from vaccine-preventable diseases and adverse outcomes.[1 2] Vaccines such as those against influenza, pertussis, and COVID-19 are therefore recommended, not only to protect mothers but also to confer immunity to their infants, reducing the risk of severe illnesses. Among the various pathogens of concern, respiratory syncytial virus (RSV) represents a substantial burden for infants under 6 months of age,[3] accounting for around 1.4 million hospitalisations and 45 700 deaths globally each year.[4] In the U.S., RSV infections stand as the leading cause of infant hospitalisations among those younger than 6 months,[5] highlighting the need for an effective intervention to reduce the burden of the disease,[6] all while weighing potential benefits and risks.[3 5] In response, the U.S. Food and Drug Administration (FDA) has recently approved two agents for protecting infants against severe RSV illness: nirsevimab, a long-acting monoclonal antibody developed for newborns[7] and RSV prefusion F (RSVpreF) vaccine (Abrysvo, Pfizer), a novel vaccine formulated with the prefusion F protein, approved for pregnant individuals.[8]

In efforts to protect newborns against severe RSV illnesses, GlaxoSmithKline (GSK) and Pfizer have both conducted clinical trials of RSV vaccines administered during pregnancy, with the goal of conferring immunity to infants.[9] GSK prematurely halted its trial due to concerns of an elevated risk of preterm birth[10]— a condition defined as birth occurring before 37 completed weeks of gestation.[11] Data from GSK's clinical trial indicated a relative risk of 1.37 (95% CI 1.08 to 1.74; p = 0.01) for preterm births among vaccinated pregnant individuals compared with the placebo group, with 238 preterm births out of 3496 (6.8%) in the vaccine arm and 86 out of 1739 (4.9%) in the placebo group.[10] This translates to approximately one additional preterm birth for every 54 vaccinated mothers. The trial, which spanned 24 countries and included a substantial proportion of participants from middle- and low-income countries, underscored a potential safety signal in populations where RSV-attributable deaths are most prevalent,[4] further amplifying the importance of these findings. However, GSK could not identify a definitive mechanism to explain the observed increase in preterm births, raising questions about the underlying factors.

Similarly, Pfizer's two maternal RSV vaccine trials, which excluded pregnant individuals at increased risk of preterm delivery, also reported a numerical increase in preterm births, although the findings did not reach statistical significance.[8] Pfizer's phase 2b trial reported six preterm births out of 114 pregnancies (5.3%) in the vaccine group and 3 out of 116 (2.6%) in the placebo group.[12] In the subsequent phase 3 trial, preterm births were reported in 5.7% (202/3568) of infants born to vaccinated mothers compared with 4.7% (169/3558) in the placebo group.[13] Notably, over half of the preterm births occurred more than 30 days after vaccination, with most preterm births occurring at or after 33 weeks of gestation.[13]

While the statistical significance observed in GSK's trial was not replicated in Pfizer's studies, the consistent pattern of imbalance in preterm births across both maternal studies raises concerns that merit vigilant consideration, particularly given that the Pfizer trial showed differences between the vaccine and placebo groups across all three pathways to preterm birth—premature preterm rupture of membranes, preterm labour and provider-induced preterm birth—highlighting the complexity of these findings.[5]

Amidst persistent concerns about the potential association between RSV vaccines and an increased risk of preterm birth, the FDA approved RSVpreF, recognising the potential risks and including a label warning, while mandating postmarket follow-up studies.[8] The agency determined that administering RSVpreF between 32 and 36 weeks of gestation offers a favourable benefit-risk balance, reducing the risk of preterm birth before 32 weeks, a period associated with higher morbidity and mortality.[8 14]

The uncertainty surrounding the observed safety signal of preterm birth after RSV vaccination persists, as available clinical data do not allow for a determination of whether this association is coincidental or indicative of a potential risk.[5 8] Given the clinical trial findings and the need to weigh the benefits against the risks, vigilant post-marketing surveillance and close monitoring of reported adverse events following immunization (AEFI) have become indispensable.[5 15] Driven by public interest and concerns, this study aims to describe the post-marketing safety profile of the RSVpreF vaccine among pregnant individuals in the U.S.

METHODS

Data source

We used the Vaccine Adverse Event Reporting System (VAERS) database, a U.S. national spontaneous-reporting system coadministered by the Centers for Disease Control and Prevention and the FDA. VAERS collects reports on post-vaccination AEs from a wide range of reporters, including patients, parents, healthcare providers, vaccine manufacturers and other stakeholders, irrespective of whether the events are plausibly associated with the vaccine.[16]

This system captures comprehensive data, including demographic details, medical history, specifics related to the AE and vaccine-related data. AEs are systematically

coded using the Medical Dictionary for Regulatory Activities (MedDRA), with each report assigned various MedDRA Preferred Terms that represent signs, symptoms and diagnostic results, without necessarily confirming a medical diagnosis.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[17]

Eligibility criteria

To examine the safety profile of the RSVpreF vaccine during pregnancy following its U.S. approval, we extracted all reports of AEFI from the VAERS database spanning from 1 September 2023 to 23 February 2024. The raw data were downloaded from the publicly accessible VAERS website (https://vaers.hhs.gov/data/datasets.html). To identify AE reports among pregnant individuals within our dataset, we narrowed the scope of extracted reports to those of women aged 18–49 years and leveraged MedDRA coding alongside text-string searches, following Moro *et al*'s methodology.[18] Our approach included automated searches for reports with MedDRA terms related to pregnancy and perinatal conditions, specific terms indicating exposure during pregnancy, as well as a text search for 'preg' in symptom descriptions, medical histories, and current illness fields, while filtering out any negations of pregnancy (online supplemental table S1). Reports fitting any of these criteria were included in our analysis dataset for further evaluation.

Statistical analysis

Descriptive analyses

Descriptive analyses included frequencies of reported AEs, maternal age, gestational age at time of vaccination, time to AE onset, reported outcomes, and the proportion of serious reports.

Given clinical trial findings, in which the majority of serious AEs reported by maternal participants vaccinated with the RSVpreF vaccine—irrespective of causality—were related to pregnancy complications such as preterm births and hypertensive disorders (eg, pre-eclampsia, gestational hypertension),[8 9 19] these AEs were considered to be of special interest, warranting close vigilance. Accordingly, for surveillance purposes, we defined 'preterm birth' using the diagnostic codes from the Brighton collaboration—Preterm Birth and Assessment of Gestational Age Companion guide,[20] which employs specific MedDRA codes to precisely define and identify medical concepts of preterm birth. These terms were considered relevant to study hypotheses related to preterm birth as a vaccine-product related reaction.[20] For additional details, refer to the supplementary material (online supplemental table S2).

Data mining (disproportionality analyses)

For disproportionality analyses, we employed the Bayesian confidence propagation neural network (BCPNN),[21] chosen for its ability to handle low expected counts and stabilise the observed-to-expected ratios even in data-sparse scenarios.[22] The BCPNN method uses Bayesian statistics within a neural network framework to calculate the information component (IC), a logarithmic measure comparing the observed to expected reporting rates of specific vaccine-AE pairs under the assumption of no vaccine-AE association.[23] This method was particularly appropriate for our study, as it mitigates the potential risk of false positives for infrequent events and small datasets compared with frequentist disproportionality measures.[23] Using the BCPNN method, we calculated signal scores for AEs associated with RSVpreF, assessing how specific RSVpreF-AEFI combinations are different from the entire database. This includes comparisons with all spontaneously reported AEFI for other FDA-approved vaccines in pregnant individuals, such as inactivated influenza, COVID-19 and pertussis vaccines. We estimated the IC using the method by Noren *et al*,[21] where a signal is flagged if the 2.5% quantile of the posterior distribution of the IC (IC_{025}) exceeds zero, indicating potential disproportionality that warrants further examination.[23] As a sensitivity analysis, we also calculated the proportional reporting ratio (PRR) scores. The PRR disproportionality method is widely used for signal generation due to its high sensitivity. However, its susceptibility to small random fluctuations can lead to higher false-positive rates, particularly in data-sparse situations.[21] Details of the formulas and signal detection criteria used for both the IC and PRR methods are described in the supplementary material (online supplemental S3).

Adhering to methodologies from previous studies,[18 24] we excluded reports from our disproportionality analysis where the vaccine type was unspecified or pertained to vaccines contraindicated in pregnancy by the FDA, including live attenuated influenza, measles, mumps and rubella combination and varicella vaccines.[25] We also excluded terms not evaluable as suspected adverse reactions, such as MedDRA terms related to pregnancy exposure and diagnostic testing, ensuring consistency with the approaches of comparable studies.[26] All analyses were conducted using R statistical software (R V.4.1.3), with pharmacovigilance signal detection computed using the PhViD package.[27] All code for data cleaning and analysis is available from the corresponding author on reasonable request.

Clinical reviews

Guided by the disproportionality analysis, our clinical review led by D.R.M., an obstetrics and gynaecology physician, focused on pregnancy-specific AEFI with disproportionality scores exceeding the signal detection threshold, with particular focus on preterm birth cases. Once identified through data mining, full reports for these AEFI were retrieved for detailed evaluation. The review aimed to validate the identified cases, distinguishing between new-onset events from those with pre-existing conditions or complications, with ineligible cases flagged for exclusion.

Table 1 Characteristics of VAERS reports received following RSVpreF vaccine in pregnant individuals, USA, 1 September 2023–23 February 2024

Characteristic	
Total reports	77
Serious reports, n (%)*	42 (54.55)
Maternal age in years, median (range)	32 (21–41)
Gestational age in weeks at the time of vaccination, median (range)	35 (9–38)
Interval from vaccination to adverse event in days, median (range)	1 (0–37)
Number of reports given with other vaccines, n (%)	6 (7.79)
Type of facility administering the vaccine, n (%)	
Pharmacy or store	36 (46.75)
Private	27 (35.06)
Unknown	7 (9.09)
Other	2 (2.60)
Public	2 (2.60)
Workplace clinic	2 (2.60)
Military	1 (0.01)
Reported outcome, n (%)†	
Hospitalised	28 (47.46)
Doctor or other healthcare professional office/ clinic visit	15 (25.42)
Emergency room/department or urgent care visit	14 (23.73)
Disability	1 (1.69)
Congenital anomaly or birth defect	1 (1.69)

*Reports are classified as serious in accordance with the Code of Federal Regulations criteria, which classify an AEFI report as serious if it involves death, necessitates hospitalisation or extends a current hospital stay, is life-threatening or leads to a substantial and lasting disability.
†A single VAERS report may have multiple outcomes.
AEFI, Adverse Events Following Vaccination; RSVpreF, Respiratory Syncytial Virus prefusion F; VAERS, Vaccine Adverse Event Reporting System.

Patient and public involvement

Patients and/or the public were not involved in this study.

RESULTS

Between September 2023 and February 2024, the VAERS database received a total of 547 reports that met the study's criteria for pregnancy-related AEFI reports. Of these, 77 reports pertained to RSVpreF vaccination, with maternal ages ranging from 21 to 41 years. Most of the immunizations, 76.7%, occurred during the third trimester, with a median onset time of 1 day for AEs post-vaccination. Over half of the RSVpreF-linked reports, 54.6%, were deemed serious; among these, 47.5% led to hospitalisations, 25.4% to doctor or clinic visits and 23.7% to emergency room or urgent care visits. Table 1 provides further details on the characteristics of VAERS reports following RSVpreF vaccination.

Reports submitted to VAERS often included multiple terms to describe the AEs, which can be grouped into three main categories[28]: non-pregnancy-specific (such as local and systemic reactions), pregnancy-specific and fetus-related AEs (Table 2). In total, 211 suspected adverse reaction terms associated with the RSVpreF vaccine were documented, comprising 143 non-pregnancy-specific terms (67.8%), 61 pregnancy-specific AE terms (28.9%) and seven fetus-related AE terms (3.3%). For non-pregnancy-specific AEs, the most common terms included headache, injection site erythema and injection site pain, reported at rates of 3.8%, 3.8% and 2.8%, respectively. Preterm birth emerged as the leading pregnancy-specific AE at 12.8%, with premature separation of placenta, caesarean section, cervical dilatation, pregnancy haemorrhage and uterine contractions each reported less frequently.

Disproportionality analysis

In the disproportionality analysis of RSVpreF vaccine-AEFI with three or more reports, a signal was detected for preterm birth, marked by an IC value of 2.18 (95% CI 1.54 to 2.63), exceeding the threshold indicative of disproportionality. In addition, this analysis revealed signals for other MedDRA terms such as caesarean section, preterm premature rupture of membranes, cervical dilatation, injection site pain, warmth, erythema and inappropriate product administration scheduling, as outlined in online supplemental table S5. Notably, no signals were identified for haemorrhage in pregnancy, and conditions such as gestational hypertension, stillbirth and pre-eclampsia were not assessed as they each had fewer than three reports, falling below the evaluation threshold. Results from the PRR data mining method, which was conducted as a sensitivity analysis, are also provided in the supplementary material (online supplemental table S6), with consistent findings supporting the BCPNN results.

RSVpreF vaccine and preterm birth

In appraising AEs of special interest associated with RSVpreF vaccination, preterm birth emerged with a signal of disproportionate reporting, indicating that the RSVpreF-preterm birth combination was reported more frequently than expected relative to other vaccine-event pairs in the VAERS database, highlighting a signal that warrants further investigation.[23] The median maternal age of these cases was 33 years, ranging from 25 to 40. According to the WHO classification,[11] the identified cases were further categorised as follows:

- No cases in the extremely preterm category (<28 weeks).
- A single case in the very preterm category (28–<32 weeks).
- 21 cases fell into the moderate or late preterm category (32–<37 completed weeks of gestation).
- Information on gestational age was not available for five cases.

Table 2 Most reported adverse event terms following RSVpreF vaccination in VAERS

Adverse event	N	%*
Pregnancy-specific AEFI		
Preterm birth	27	12.8
Caesarean section	7	3.3
Preterm premature rupture of membranes	7	3.3
Cervical dilatation	3	1.4
Haemorrhage in pregnancy	3	1.4
Uterine contractions during pregnancy	3	1.4
Gestational hypertension	2	0.9
Induced labour	2	0.9
Pre-eclampsia	2	0.9
Premature separation of the placenta	2	0.9
Stillbirth	1	0.5
Cervical incompetence	1	0.5
Amniotic fluid index decreased	1	0.5
Non-pregnancy-specific AEFI		
Headache	8	3.8
Injection site erythema	8	3.8
Pain	7	3.3
Injection site pain	6	2.8
Nausea	6	2.8
Fatigue	5	2.4
Inappropriate schedule of product administration	4	1.9
Vomiting	4	1.9
Arthralgia	3	1.4
Chills	3	1.4
Diarrhoea	3	1.4
Dizziness	3	1.4
Injection site pruritus	3	1.4
Injection site swelling	3	1.4
Injection site warmth	3	1.4
Myalgia	3	1.4
Other less frequently reporter terms†	71	NA
Fetus related outcomes		
Fetal hypokinesia	2	0.9
Fetal death	1	0.5
Fetal growth restriction	1	0.5
Fetal heart rate abnormal	1	0.5
Fetal heart rate deceleration abnormality	1	0.5
Fetal heart rate decreased	1	0.5

Continued

Table 2 Continued

Adverse event	N	%*

*The percentages refer to the total number of adverse event terms reported with RSVpreF vaccine, n=211.
†Other less frequently reported non-pregnancy-specific PTs, including those reported only once, are detailed in the supplementary material (online supplemental table S4).
AEFI, Adverse Events Following Vaccination; PT, Preferred Term; RSVpreF, Respiratory Syncytial Virus prefusion F; VAERS, Vaccine Adverse Event Reporting System .

The median time from RSVpreF vaccination to the onset of preterm delivery was 3 days, spanning from 0 to 31 days, and notably, two-thirds of the cases occurred within a week of immunisation (online supplemental table S7). On further examination of these preterm birth AEFI reports, instances of co-vaccination were uncommon, only involving two cases—one with the tetanus, diphtheria, acellular pertussis vaccine and another with the COVID-19 vaccine administered alongside RSVpreF. Of the 27 reports of preterm birth, 25 were classified as serious. Some cases were associated with more than one outcome. Among the 37 outcomes recorded, hospitalization was the most frequently reported (25 instances), followed by emergency or urgent care visits (9 instances), doctor or clinic visits (2 instances), and a single instance of disability reported. Notably, there were no reports of death or life-threatening events.

In the comprehensive clinical review of these identified preterm birth reports, no cases were excluded; however, assessing the certainty level of cases (definite, probable or possible) presented challenges due to the varying completeness of the reports. Essential information required for this assessment,[20] such as details of maternal history, date of the last menstrual period or the date of assisted reproductive technology interventions, ultrasound scan results, maternal physical exams, fundal height measurements, newborn birth weight and physical exams were often missing. This lack of key data hindered our ability to assess causality and accurately classify the cases with a high degree of certainty.

DISCUSSION

This study provides an early post-authorisation safety analysis of the RSVpreF vaccine among pregnant individuals, drawing on voluntarily submitted reports to VAERS. As a passive surveillance system, VAERS offers valuable real-world insights into a vaccine's safety profile in clinical practice. However, it is not designed to determine causality; rather, its primary purpose is to signal potential concerns that warrant further investigation.[16] Because reporting is voluntary, these data do not capture the entire population of pregnant individuals who received the vaccine or all those who experienced an AE. Within this context, our target population comprised pregnant individuals in the USA who were vaccinated with RSVpreF, developed AEs

following immunisation and had these events reported to VAERS.

Considering the study's preliminary findings, it is important to evaluate how they align with results from prelicensure clinical studies. The safety profile of RSVpreF in pregnant individuals, previously assessed in clinical studies,[12 13] highlighted self-limiting AEs such as injection site pain and headaches, with a slight increase in pre-eclampsia rates among the vaccine group.[29] However, concerns about preterm births were raised,[8 15] underscoring the need for ongoing surveillance, particularly given the trial's exclusion of individuals at higher risk for preterm delivery. According to the trial protocol, the manufacturer was examining preterm birth as an AE of special interest.[13 15] However, pregnant individuals at higher risk for preterm delivery, due to factors such as high body mass index, in vitro fertilisation pregnancies, alongside other risk factors, were excluded from both phase 2b and phase 3 trials of RSVpreF vaccine.[8 19] Similarly, those with a history of pregnancy complications were generally not enrolled.[19]

In light of these exclusions and the remaining questions regarding preterm birth risk, our analysis revealed that the pattern of reported non-pregnancy-specific AEs mirrored those identified during the RSVpreF vaccine's prelicensure phase. However, among pregnancy-specific AEs, preterm birth emerged as the most reported AEFI, alongside reports of caesarean section, preterm premature rupture of membranes, cervical dilatation, pregnancy haemorrhage and uterine contractions. A closer look at the reported preterm birth cases showed a median interval time of 3 days between vaccination and AE onset, with two-thirds of the reports occurring within the first week after immunisation. In contrast, clinical trial data indicated that most reported preterm births occurred more than 30 days post-vaccination.[8] Additionally, our disproportionality analysis, which compared the reporting frequency of specific vaccine-event pairs relative to the overall reporting frequencies in the VAERS database, highlighted a potential safety signal for preterm birth, with reports of this event occurring more frequently than expected for the RSVpreF vaccine. Nevertheless, the inherent limitations of VAERS data preclude drawing conclusions regarding any direct association between RSVpreF vaccination and preterm birth.

Understanding the complex and largely unknown pathophysiology behind preterm births is essential, particularly given the various maternal, fetal and placental factors at play.[30] This complexity in causation underscores the importance of approaching these vaccine-related AEs through a wider comprehensive lens. When we compare the pregnancy-specific symptomatology associated with the RSVpreF vaccine with those associated with other vaccines recommended during pregnancy, distinct differences in the pregnancy-specific AE profiles can be noticed. For seasonal influenza vaccines, spontaneous abortion (fetal death occurring <20 weeks gestation) was the most commonly reported pregnancy-specific AE, followed by stillbirth (fetal death occurring ≥20 weeks gestation), with six reported preterm birth cases, accounting for only 1.1% of reported AEs.[24] The 2009 H1N1 influenza vaccine similarly had miscarriage as the leading reported AE, with reports also noting stillbirths and 7 cases of preterm births constituting just 2.4% of reported AEFI.[31] For hepatitis A and hepatitis AB vaccines, spontaneous abortions were the most frequently reported AEs, with preterm deliveries being less common (5.0% or 7 cases) alongside elective terminations.[18] With the COVID-19 vaccine, spontaneous abortion was the most commonly pregnancy-related AEs reported to VAERS, with preterm delivery being comparatively rare (0.9% or 2 cases).[28 32] These patterns drawn from the VAERS database for various vaccines and across different time intervals diverge with the reported AE profile following RSVpreF vaccination, where preterm birth was the most frequently pregnancy-specific AE reported, underscoring a unique AE profile for the RSVpreF vaccine in pregnant individuals.

The strengths of our study stem from leveraging VAERS, a comprehensive pharmacovigilance system, with a broad national scope, capacity for near-real-time surveillance and adeptness at detecting rare AEFI.[33] However, it is essential to interpret our findings within the context of VAERS' intrinsic limitations. Our analysis, reliant on participant-reported data, is limited by the lack of comprehensive information on several risk factors for adverse pregnancy outcomes, such as complete maternal history, lifestyle behaviours (including smoking and drug use), comorbidities and infections.[34] In addition, VAERS is prone to various reporting biases,[35] including over-reporting, stimulated reporting and under-reporting, which, despite mandatory reporting requirements, are probably substantial for pregnancy-specific and neonatal-specific AEs.[28] Also, events temporally close to vaccination are more likely to be reported[24]; however, reporting is still dependent on and influenced by medical suspicion, which can be influenced by the perception of a causal relationship with the vaccine, even among healthcare providers who under-report events that are not clearly related to vaccination.[36] Notable limitations also include our inability to ascertain the total number of RSVpreF vaccine doses administered and the absence of an unvaccinated comparator group, which restricts our ability to estimate incidence rates and relative risks from VAERS data alone. Although a signal was detected for preterm birth with the RSVpreF vaccine, these findings remain hypothesis-generating, underscoring the need for further research.

CONCLUSION

In this passive pharmacovigilance study of the RSVpreF vaccine among pregnant individuals, the overall pattern of reported AEs aligned closely with the safety profile observed in prelicensure studies, particularly for non-pregnancy-specific AEFIs. However, our analysis

highlighted a signal of disproportionate reporting for preterm birth that warrants further investigation. Hypertensive disorders of pregnancy, including pre-eclampsia, which were observed more frequently in the vaccine group during prelicensure studies, did not emerge as a safety signal in our post-licensure analysis. Despite the inherent limitations of passive surveillance systems, our analysis contributes to the current understanding of the safety of this vaccine in pregnancy. Further research, potentially via pregnancy registries or by leveraging existing healthcare databases for prospective cohort studies is imperative to further explore this signal.

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Contributors AA and DRM designed the study. AA handled the acquisition, analysis and interpretation of data. AA drafted the manuscript and conducted the statistical analysis. DRM provided the clinical assessment. SP-L and DRM critically reviewed and revised the manuscript. All authors have approved the final version for publication. AA is responsible for the overall content as guarantor. DRM supervised the study.

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REFERENCES

1 Mitchell SL, Schulkin J, Power ML. Vaccine hesitancy in pregnant Women: A narrative review. *Vaccine (Auckl)* 2023;41:4220–7.
2 Fischer GW, Ottolini L, Mond CJJ. Prospects for vaccines during pregnancy and in the newborn period. *Clin Perinatol* 1997;24:231–49.
3 Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, *et al*. Respiratory Syncytial Virus Seasonality: A Global Overview. *J Infect Dis* 2018;217:1356–64.
4 Li Y, Wang X, Blau DM, *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. *The Lancet* 2022;399:2047–64.
5 Rasmussen SA, Jamieson DJ. Maternal RSV Vaccine - Weighing Benefits and Risks. *N Engl J Med* 2024;390:1050–1.
6 Halasa N, Zambrano LD, Amarin JZ, *et al*. Infants Admitted to US Intensive Care Units for RSV Infection During the 2022 Seasonal Peak. *JAMA Netw Open* 2023;6:e2328950.
7 Drysdale SB, Cathie K, Flamein F, *et al*. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *N Engl J Med* 2023;389:2425–35.
8 Fleming-Dutra KE, Jones JM, Roper LE, *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;72:1115–22.
9 Boytchev H. Concerns over informed consent for pregnant women in Pfizer's RSV vaccine trial. *BMJ* 2023;383:p2620.
10 Dieussaert I, Hyung Kim J, Luik S, *et al*. RSV Prefusion F Protein-Based Maternal Vaccine - Preterm Birth and Other Outcomes. *N Engl J Med* 2024;390:1009–21.
11 Lawn J. *Born too soon: the global action report on preterm birth*. 2012.
12 Simões EAF, Center KJ, Tita ATN, *et al*. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *N Engl J Med* 2022;386:1615–26.
13 Kampmann B, Madhi SA, Munjal I, *et al*. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023;388:1451–64.
14 LABEL: abrysvo- respiratory syncytial virus vaccine kit. 2023. Available: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=be18292e-b1a2-4815-a0ed-003efaa6bea3
15 Boytchev H. Maternal RSV vaccine: Further analysis is urged on preterm births. *BMJ* 2023;381:p1021.
16 Chen R, Rastogi S, Mullen J, *et al*. The vaccine adverse event reporting system (VAERS). *Vaccine (Auckl)* 1994;12:542–50.
17 Elm E von, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
18 Moro PL, Museru OI, Niu M, *et al*. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. *Am J Obstet Gynecol* 2014;210:561.
19 Pfizer Medical Information. ABRYSVO Adverse Reactions. 2025 Available: https://www.pfizermedicalinformation.com/abrysvo/adverse-reactions
20 Kochhar S. AESI case definition companion guide: preterm birth and assessment of gestational age. 2022.
21 Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. *Stat Methods Med Res* 2013;22:57–69.
22 Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf* 2009;18:427–36.
23 Bate A. The use of bayesian confidence propagation neural network in pharmacovigilance: umeå university. 2003.
24 Moro P, Baumblatt J, Lewis P, *et al*. Surveillance of Adverse Events After Seasonal Influenza Vaccination in Pregnant Women and Their Infants in the Vaccine Adverse Event Reporting System, July 2010–May 2016. *Drug Saf* 2017;40:145–52.
25 Centers for Disease Control and Prevention. *Guidelines for Vaccinating Pregnant Women*,
26 Santi Laurini G, Montanaro N, Motola D. Safety of COVID-19 vaccines in pregnancy: a VAERS based analysis. *Eur J Clin Pharmacol* 2023;79:657–61.
27 Ahmed I, Poncet A. PhViD: an R package for pharmacovigilance signal detection. 2016.
28 Shimabukuro TT, Kim SY, Myers TR, *et al*. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med* 2021;384:2273–82.
29 U.S. Food and Drug Administration (FDA). FDA approves first vaccine for pregnant individuals to prevent rsv in infants. 2023.

30 Quinn J-A, Munoz FM, Gonik B, *et al*. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine (Auckl)* 2016;34:6047–56.
31 Moro PL, Broder K, Zheteyeva Y, *et al*. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System. *Am J Obstet Gynecol* 2011;205:473.
32 Moro PL, Olson CK, Zhang B, *et al*. Safety of Booster Doses of Coronavirus Disease 2019 (COVID-19) Vaccine in Pregnancy in the Vaccine Adverse Event Reporting System. *Obstetrics & Gynecology* 2022;140:421–7.
33 Ellenberg SS, Foulkes MA, Midthun K, *et al*. Evaluating the safety of new vaccines: summary of a workshop. *Am J Public Health* 2005;95:800–7.
34 Källén B. The problem of confounding in studies of the effect of maternal drug use on pregnancy outcome. *Obstet Gynecol Int* 2012;2012:148616.
35 Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. *Public Health Rep* 1997;112:10–20.
36 Patrignani A, Palmieri G, Ciampani N, *et al*. Under-Reporting of Adverse Events Following Immunization Observed in a Single Hospital Setting in Italy. *Italian Journal of Pharmacoeconomics and Pharmacoutilization* 2019;11:19–28.