OPEN

Original Research

Maternal and Neonatal Outcomes After Respiratory Syncytial Virus Prefusion F Protein Vaccination During Pregnancy

Analysis From the 2024–2025 Immunization Campaign in France

Amélie Gabet, PhD, Marion Bertrand, MSc, Marie-Joëlle Jabagi, PharmD, PhD, Epiphane Kolla, MD, PhD, Valérie Olié, PhD, and Mahmoud Zureik, MD, PhD

OBJECTIVE: To assess the safety of the respiratory syncytial virus prefusion F protein (RSVpreF) vaccine in pregnant women during the 2024–2025 French immunization campaign, with a particular focus on the risk of preterm birth.

METHODS: Using the national health care database, which covers almost 99% of the population in France, we included all women who gave birth after 22 weeks of gestation between September 16 and December 31, 2024. Women vaccinated with RSVpreF were matched 1:1 with unvaccinated women on the basis of gestational age at vaccination, maternal age at pregnancy onset, region of residence, week of conception, history of preterm birth, influenza vaccination during the same pregnancy, and multiple pregnancy. Outcomes included preterm birth, delivery within 1 and 3 weeks after vaccination, stillbirth, small-for-gestational-age (SGA) birth weight, cesarean delivery, hemorrhage, preeclampsia, and major cardiovascular events, including maternal death. Time-to-event analyses were conducted with Poisson regression models with robust variance to estimate weighted incidence rate ratios (IRRs) and their 95% CIs for each outcome.

RESULTS: Among the 29,032 women vaccinated during the study period, 24,891 (85.7%) were successfully matched to 24,891 unvaccinated women in a control group. In the matched cohort, the mean±SD maternal age was 30.9±5.0 years, 3.2% had a history of preterm birth, 0.6% had multiple pregnancies, and 21.8% had received influenza vaccination. No significant increase in the risk of the following outcomes was observed: preterm birth (weighted IRR 0.97, 95% CI, 0.89–1.06), delivery within 1 week (weighted IRR 0.81, 95% CI, 0.72–0.90) or within 3 weeks (weighted IRR 0.97, 95% CI, 0.93–1.00), stillbirth (weighted IRR 0.77, 95% CI, 0.45–1.32), cesarean delivery (weighted IRR 1.00, 95% CI, 0.96–1.03), SGA birth weight (weighted IRR 1.01, 95% CI, 0.96–1.07), postpartum hemorrhage (weighted IRR 1.03, 95% CI, 0.97–1.10), preeclampsia (weighted IRR 1.02, 95% CI, 0.85–1.22), or major adverse cardiovascular event (weighted IRR 0.60, 95% CI, 0.26–1.40) outcomes. Among women vaccinated at or before 32 weeks of gestation, no significant increase in the risk of preterm birth was observed (weighted IRR 1.13, 95% CI, 0.98–1.31).

CONCLUSION: This large observational study found no major safety concerns associated with RSVpreF vaccination during pregnancy. Further research, including international comparisons and evaluations of effectiveness relative to monoclonal antibodies against RSV, will be needed to fully characterize the benefit–risk balance of RSVpreF. Ongoing surveillance remains essential, particularly to monitor rare adverse events.

(Obstet Gynecol 2025;00:1–9)
DOI: 10.1097/AOG.0000000000006121

From the EPI-PHARE, Epidemiology of Health Products (French National Agency for Medicines and Health Products Safety, and French National Health Insurance), Saint-Denis, and University of Paris-Saclay, UVSQ, University Paris-Sud, Inserm, Anti-Infective Evasion and Pharmaco-Epidemiology, CESP (Center for Research in Epidemiology and Population Health), Montigny le Bretonneux, France.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Valérie Olié, PhD, EPI-PHARE, Epidemiology of Health Products, Saint-Denis, France; valerie.olie@assurance-maladie.sante.fr.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/25

A vaccine against severe respiratory syncytial virus (RSV) infection became available in France starting with the 2024–2025 season. Abrysvo, a bivalent recombinant vaccine containing an antigen of the RSV prefusion F protein (RSVpreF), provides passive immunity to the fetus and eventual infant against RSV-associated lower respiratory tract infections and severe related disease up to 5 months of age.[1] In clinical trials, RSVpreF vaccination during pregnancy showed an efficacy of approximately 82% in preventing severe RSV–associated lower respiratory tract infections in infants within the first 3 months of life and approximately 70% over a 6-month period.[1]

In France, vaccination is recommended for pregnant women between 32 and 36 weeks of gestation to ensure transplacental passive immunization of their infants.[2] This late administration window was chosen after a nonsignificant increase in preterm birth observed in women vaccinated before 32 weeks of gestation in the phase III MATISSE (Maternal Immunization Study for Safety and Efficacy) trial.[3] In addition, the development of another RSV vaccine (RSVpreF3) by GlaxoSmithKline was halted because of a confirmed increased risk of preterm birth.[4] It is important to note that this risk has not been observed with other vaccines administered during pregnancy, including pertussis,[5] influenza,[6,7] and coronavirus disease 2019 (COVID-19) vaccines.[8–10]

Data from real-world settings are still limited, and other maternal outcomes have yet to be thoroughly evaluated. Thus, the objective of this study was to evaluate maternal and fetal safety outcomes associated with RSVpreF vaccination among pregnant women in France during the first immunization campaign in 2024–2025, with particular attention to the risk of preterm birth that was noted in earlier studies.

METHODS

Data were retrieved from the French National Health Data System (Système National des Données de Santé), a collection of pseudonymized databases that provide extensive medical information for 99% of the entire French population.[11] The French National Health Data System is based primarily on the National Health Insurance Information System, which includes data on reimbursed health care services and data from hospital stays through the Medicalization Program of Information Systems, covering nearly 67 million people in France. Hospital databases specifically recorded diagnoses coded with the International Classification of Diseases, Tenth Revision (ICD-10), as well as medical procedures performed. The National Health Insurance Information System component included information on all medications dispensed outside hospitals and on long-term disease status, which grants full reimbursement of health care costs related to the specified condition. The exact dates of all these health care encounters are recorded in the databases. Pregnancies were identified with the National Mother-Child Register, derived from the French National Health Data System and covering the period from 2010 to 2024. The development and quality control procedures of the National Mother-Child Register have been described in previous studies.[12–14] EPI-PHARE has direct access to the French National Health Data System through the permanent regulatory access granted to its founding bodies, the National Agency of Drugs and Health Products and the French National Health Insurance. This access is authorized under French Decree No. 2016-1871 of December 26, 2016, which governs the processing of personal data within the French National Health Data System, as well as under Articles R. 1461-13 and 14 of French law.

The RSVpreF vaccination campaign for pregnant women took place from September 15, 2024, to January 31, 2025. However, hospital data related to deliveries were available only up to December 31, 2024. Therefore, the study population included all pregnant women who could have reached at least 36 weeks of gestation (based on the date of the last menstrual period) between September 15 and December 31, 2024, and who gave birth on or before December 31, 2024. Women who were vaccinated at 37 weeks of gestation or later were excluded from the preterm birth analysis. Women who had preeclampsia before the index date were excluded from all analyses.

For each woman in the study population, RSVpreF vaccination status and date were identified from reimbursement data for the vaccine, injection procedure by a pharmacist, or consultation or injection by a midwife or physician. The earliest of these dates was identified as the vaccination date, which will be considered the index date.

A day-by-day 1:1 sequential matching was performed between vaccinated and unvaccinated women from September 15 to December 31, 2024. For women vaccinated on each given day, we identified unvaccinated counterparts (same gestational age on that same calendar day) with the same matching characteristics who had not yet received the vaccine on that date, as previously described elsewhere.[15–17] Matching criteria included age at pregnancy onset (±1 year), region of residence (15 regions in France), week of conception, gestational age at index date (±3 days), multiple pregnancy, influenza vaccination during the pregnancy, and history of preterm birth. Influenza vaccination status was determined from the reimbursement of one of the 2024 influenza vaccines available in France, namely Fluarix Tetra, Vaxigrip Tetra, Influvac Tetra, or Efluelda Tetra (the last available until April 4, 2024). Matching on influenza vaccination aimed to account for systematic differences in characteristics and behaviors, particularly regarding general attitudes toward vaccination, between the vaccinated and unvaccinated populations.[18] The index date for the woman vaccinated by RSVpreF vaccine and her matched control was the date on which the vaccinated woman received the vaccine. To avoid immortal time bias, women who were eventually vaccinated could contribute to the unvaccinated group until the date of their actual vaccination, at which point follow-up was censored and they were rematched as vaccinated individuals.[19] This approach is necessary because, without this consideration, the time between cohort entry and vaccination (during which the outcome could not occur in the vaccinated group) would be incorrectly attributed to the vaccinated period, potentially leading to an artificial reduction in the observed risk among vaccinated individuals. Specifically, for preterm birth, we note that immortal time bias could potentially lead to an underestimation of the risk because women must remain pregnant to be eligible for vaccination. A single set of matched pairs was created that was based on gestational age and other matching characteristics, and this same set was used for all outcome analyses. In subgroup analyses, exclusions were applied within this initial set to ensure that the matching procedure was performed only once and that all outcomes were assessed after the index date.

Maternal and fetal outcomes included *preterm birth* (defined as delivery before 37 completed weeks of gestation); delivery within 1 or 3 weeks after the index date; cesarean delivery, whether elective or emergency (identified by ICD-10 code O82 and corresponding medical procedure codes); stillbirth (identified by ICD-10 codes O36.4, Z37.1, Z37.3, Z37.4, Z37.6, and Z37.7 and considered present if at least one fetus died in the case of multiple pregnancies); *small-for-gestational-age (SGA) birth weight* (defined as birth weight less than the 10th percentile for gestational age)[20]; peripartum or postpartum hemorrhage (identified by ICD-10 codes O46, O67, and O72); preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome (identified by ICD-10 codes O11, O14, and O15); major adverse cardiovascular events (stroke [identified by ICD-10 codes I60–I64], acute coronary syndrome [identified by ICD-10 codes I21–I24], and pulmonary embolism [identified by ICD-10 codes I26, O882]); or death until 1 week postpartum.

For exposed women, the index date was the date of vaccination; the same date was assigned to their matched unexposed counterparts. For preterm birth and delivery timing, follow-up continued until 37 weeks of gestation, ending earlier in cases of death or vaccination (for the unexposed). For delivery outcomes, follow-up ended at delivery, death, or vaccination (in the unexposed group). For maternal outcomes, follow-up continued until the event, death, 1 week after delivery, or December 31, 2024.

All matching variables were described, and additional covariates included sociodemographic factors such as complementary universal health coverage (as a proxy for low income) and the French Deprivation Index of the municipality of residence,[21] pregnancy-related factors before the index date (multiparity, history of cesarean delivery, medically assisted reproduction, placental abnormalities [including retroplacental hematoma], uterine anomalies, severe maternal infections, gestational diabetes, and chronic or gestational hypertension), and medical history and comorbidities before the index date (obesity, tobacco use, alcohol use disorder, opioid use, antihypertensive and lipid-lowering treatments, antidiabetic medications, hypertensive disorders of pregnancy during a previous pregnancy [gestational hypertension, preeclampsia, eclampsia, HELLP syndrome], cardiovascular disease, thromboembolic disease, cancer, chronic respiratory conditions, autoimmune disease, human immunodeficiency virus [HIV] or acquired immunodeficiency syndrome [AIDS], psychiatric illness, use of psychotropic medications, and neurodegenerative disorders). Other vaccinations during pregnancy were also recorded: pertussis vaccines Repevax (Tdap [tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis]-inactivated poliovirus vaccine), Boostrix Tetra (Tdap), and COVID-19 vaccine Comirnaty JN.1 30 micrograms. The algorithm identifying each covariate combined ICD-10 codes from hospital records, long-term disease status, and reimbursement data has been published elsewhere.[12–14,22]

Baseline characteristics of vaccinated women and their matched unvaccinated counterparts were first described. Comparisons were tested with the Mantel–Haenszel χ^2 test. To further reduce residual confounding after matching on seven baseline characteristics, we applied inverse probability of treatment weighting using a propensity score that included the matching covariates as well, an approach that enhances covariate balance and provides doubly robust estimates. Inverse probability of treatment weights were derived from a multivariable logistic regression model estimating the probability of receiving the RSVpreF vaccine from all the covariates mentioned previously. Standardized mean differences before and after weighting were plotted to assess covariate balance between the two groups (Appendix 1, available online at http://links.lww.com/AOG/E415). Time-to-event analyses were conducted with Poisson regression models with robust variance to estimate weighted incidence rate ratios (IRRs) and their 95% CIs for each outcome. Subgroup analyses were performed according to gestational age at index date (32 or less, 33–34, 35–36, 37 or more weeks of amenorrhea), age at pregnancy onset (younger than 30 years vs 30 years or older), history of preterm birth, parity, and influenza and COVID-19 vaccination status. Those variables used for matching were also included in the model for adjustment. Models were adjusted for the time interval between RSVpreF and other vaccinations when applicable.

Sensitivity analyses used Cox proportional hazards models with gestational age as the time scale. A second sensitivity analysis excluded pairs with women who were unvaccinated for pertussis. Because of a violation of the proportional hazards assumption, an interaction term between RSVpreF exposure and gestational age was added to all Cox models. Other sensitivity analyses were performed by computing multivariate models adjusted for the matching covariates and all covariates included in the inverse probability of treatment weighting. Finally, an analysis was performed excluding women who were used as both vaccinated and unvaccinated (data not shown).

The analyses were conducted with SAS Enterprise Guide 8.5. $P<.05$ was considered statistically significant.

RESULTS

Among the 29,032 women vaccinated with the RSVpreF vaccine before December 31, 2024, and who gave birth before that date, 24,891 (85.7%) were successfully matched 1:1 with 24,891 unvaccinated women (Appendix 2, available online at http://links.lww.com/AOG/E415). Among the vaccinated women, 4,452 (17.9%) contributed to the unexposed group before receiving their RSVpreF vaccination (Fig. 1). The median gestational age at the time of vaccination was 34.7 weeks (interquartile range 33.4–35.7). Among vaccinated women, 6.9% received the vaccine before 32 weeks of gestation–most of them near this threshold–and 6.2% received it at 37 weeks or later. The mean±SD maternal age at the beginning of pregnancy was 30.9±5.0 years. Regarding matched characteristics, a history of preterm birth was present in 3.2% of both vaccinated and unvaccinated women, multiple pregnancies were reported in 0.6%, and influenza vaccination was reported in 21.8% (Table 1). Compared with unvaccinated women, those who received RSV RSVpreF were more likely to reside in municipalities belonging to the highest socioeconomic quintile (25.9% vs 20.8%, $P<.0001$), less likely to benefit from complementary health insurance (12.1% vs 20.3%, $P<.0001$), and less frequently multiparous (23.9% vs 30.5%, $P<.0001$) (Table 1 and Appendix 3, available online at http://links.lww.com/AOG/E415). No comorbid condition was significantly associated with RSVpreF vaccination status (Appendix 3).

Preterm birth occurred in 951 vaccinated women (4.1%) and 986 unvaccinated women (4.3%), yielding a weighted IRR of 0.97 (95% CI, 0.89–1.06) (Table 2). No increased risk was observed for delivery within 1 week (weighted IRR 0.81, 95% CI, 0.72–0.90) or

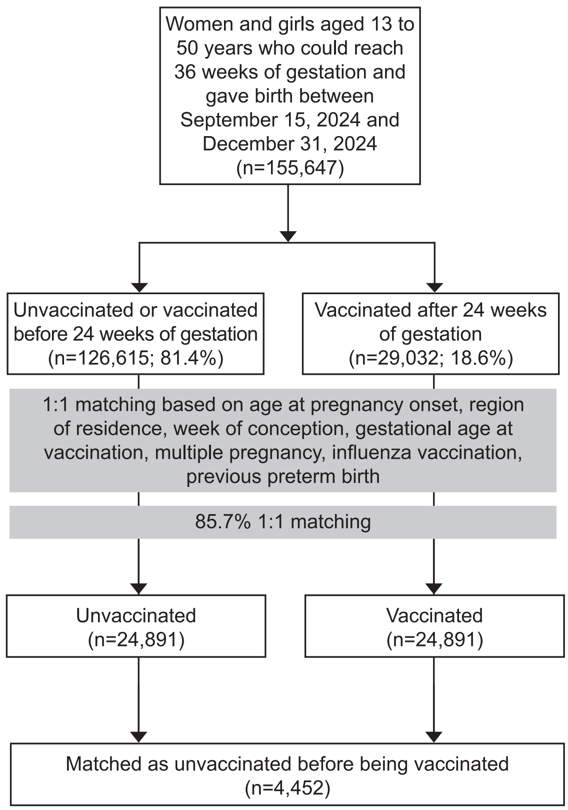

Fig. 1. Flowchart.

Gabet. RSVpreF Vaccine Safety During Pregnancy. Obstet Gynecol 2026.

Table 1. Characteristics of Matched Exposed and Unexposed Women to the Respiratory Syncytial Virus Prefusion F Protein Vaccine

Characteristic	Vaccinated (n=24,891)	Unvaccinated (n=24,891)	*P*
Age at pregnancy onset (y)	30.9±5.0	30.9±5.0	1.00
Complementary solidarity health insurance	3,016 (12.1)	5,051 (20.3)	<.0001
French Deprivation Index quintile			<.0001
1 (less deprived)	6,447 (25.9)	5,176 (20.8)	
2	5,577 (22.4)	5,217 (21.0)	
3	4,744 (19.1)	4,845 (19.5)	
4	4,275 (17.2)	4,859 (19.5)	
5 (more deprived)	3,654 (14.7)	4,591 (18.4)	
Oversea territories	194 (0.8)	203 (0.8)	
Pregnancy-related characteristics			
Gestational age at vaccination (index date) (wk)	34.6±1.8	34.6±1.8	1.00
	34.7 (33.4–35.7)	34.7 (33.4–35.7)	1.00
History of preterm birth	801 (3.2)	801 (3.2)	1.00
History of cesarean delivery	2,514 (10.1)	2,798 (11.2)	<.0001
Multiparous	5,939 (23.9)	7,600 (30.5)	<.0001
Multiple pregnancy	156 (0.6)	156 (0.6)	1.00
HDP during the index pregnancy	1,118 (4.5)	1,100 (4.4)	.47
Chronic hypertension	387 (1.6)	335 (1.3)	.05
Gestational hypertension	721 (2.9)	744 (3.0)	.54
HDP during a previous pregnancy*	795 (3.2)	885 (3.6)	.03
Gestational diabetes	3,664 (14.7)	3,871 (15.6)	.001
Medically assisted reproduction	1,743 (7.0)	1,358 (5.5)	<.0001
Placental abnormalities	525 (2.1)	475 (1.9)	.11
Uterine abnormalities or inflammation	180 (0.7)	139 (0.6)	.02
Severe infection†	2,126 (8.5)	2,232 (9.0)	.09
Non–pregnancy-related comorbidities			
Obesity	2,023 (8.1)	2,126 (8.5)	.10
Alcohol consumption	115 (0.5)	148 (0.6)	.04
Tobacco smoking	2,784 (11.2)	2,871 (11.5)	.22
Opiates intake	36 (0.1)	35 (0.1)	.91
Antihypertensive medications	330 (1.3)	275 (1.1)	.03
Lipid-lowering medications	31 (0.1)	40 (0.2)	.29
Diabetes mellitus	269 (1.1)	283 (1.1)	.55
Cardiovascular diseases	170 (0.7)	167 (0.7)	.87
Venous thromboembolism	76 (0.3)	80 (0.3)	.75
Cancer	207 (0.8)	205 (0.8)	.92
Chronic respiratory diseases	771 (3.1)	734 (2.9)	.33
Autoimmune diseases‡	279 (1.1)	310 (1.2)	.20
HIV or AIDS	30 (0.1)	40 (0.2)	.23
Psychiatric illness	321 (1.3)	297 (1.2)	.33
Psychotropic medications	1,159 (4.7)	1,020 (4.1)	.002
Neurodegenerative diseases	172 (0.7)	167 (0.7)	.79
Epilepsy	152 (0.6)	136 (0.5)	.34
Vaccinations during the index pregnancy			
Pertussis	23,958 (96.3)	19,499 (78.3)	<.0001
Influenza	5,417 (21.8)	5,417 (21.8)	1.00
COVID-19	1,820 (7.3)	1,343 (5.4)	<.0001

HDP, hypertensive disorders of pregnancy; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; COVID-19, coronavirus disease 2019.

Data are mean±SD, n (%), or median (interquartile range) unless otherwise specified.

* Including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome.

† Including pulmonary infections; gastrointestinal infections; skin and subcutaneous tissue infections; urinary tract infections; ear, nose, and throat infections; nervous system infections; musculoskeletal infections; ophthalmologic infections; cardiovascular system infections; and other infections (eg, sepsis, bacterial, viral). A full list can be found in Appendix 1, available online at http://links.lww.com/AOG/E415.

‡ Including inflammatory bowel diseases, rheumatoid arthritis, ankylosing spondylitis, and other chronic inflammatory diseases.

within 3 weeks (weighted IRR 0.97, 95% CI, 0.93–1.00) of vaccination. Similarly, no significant associations were found with stillbirth (weighted IRR 0.77, 95% CI, 0.45–1.32), cesarean delivery (weighted IRR 1.00, 95% CI, 0.96–1.03), whether emergency (weighted IRR 0.99, 95% CI, 0.95–1.04) or scheduled (weighted IRR 1.00, 95% CI, 0.94–1.07), SGA birth weight (weighted IRR 1.01, 95% CI, 0.96–1.07), postpartum hemorrhage (weighted IRR 1.03, 95% CI, 0.97–1.10), preeclampsia (weighted IRR 1.02, 95% CI, 0.85–1.22), or major adverse cardiovascular events (weighted IRR 0.60, 95% CI, 0.26–1.40) (Table 2). No increased risk was found for any outcome at 1, 2, or 3 weeks (Appendix 4, available online at http://links.lww.com/AOG/E415).

Results were consistent across most subgroups, supporting the robustness of the main findings (Appendix 5, available online at http://links.lww.com/AOG/E415, and Table 3). Number of events for each subgroup is shown in Appendix 6, available online at http://links.lww.com/AOG/E415. Among women vaccinated at or before 32 weeks of gestation, outcomes were not significantly different from those of unvaccinated women at the same gestational age. In this group, preterm birth occurred in 8.6% of vaccinated compared with 7.6% of unvaccinated women (weighted IRR 1.13, 95% CI, 0.98–1.31); deliveries within 1 week of vaccination occurred in 0.3% compared with 0.1% (weighted IRR 2.87, 95% CI, 0.89–9.22) and within 3 weeks in 1.8% compared with 1.6% (weighted IRR 1.16, 95% CI, 0.83–1.62). Rates of SGA birth weight (12.7% vs 11.6%, weighted RR 1.11, 95% CI, 0.98–1.25) and preeclampsia (1.4% vs 1.0%, weighted IRR 1.39, 95% CI, 0.91–2.13) were not different between groups. In the subgroup of women vaccinated at or before 32 weeks of gestation, cesarean delivery rates were 24.3% compared with 22.9% (weighted IRR 1.04, 95% CI, 0.96–1.13), and hemorrhage occurred in 8.4% compared with 8.2% (weighted IRR 1.01, 95% CI, 0.86–1.17) (Appendix 5, http://links.lww.com/AOG/E415). In contrast, among women vaccinated later in pregnancy, the relative risks decreased with increasing gestational age at vaccination. This was observed significantly for preterm birth (0.74, 95% CI, 0.60–0.91 at 35–36 weeks of gestation), delivery within 1 week (0.74, 95% CI, 0.60–0.91 at 35–36 weeks) to 3 weeks (0.89, 95% CI, 0.85–0.94), and cesarean delivery (0.84, 95% CI, 0.72–0.99 at 37 weeks or later) (Appendix 5, http://links.lww.com/AOG/E415, and Table 3).

A statistically significant association was observed between RSVpreF vaccination and preterm birth among women who had also received the influenza vaccine (weighted IRR 1.25, 95% CI, 1.02–1.53). No such association with preterm birth was found among women who had not received the influenza vaccine (weighted IRR 0.92, 95% CI, 0.83–1.02) (Table 3).

All findings were consistent across sensitivity analyses using Cox proportional hazards models (Appendix 7), multivariable Poisson regression models (Appendix 8), and analyses restricted to women vaccinated against pertussis (Appendix 9; Appendices 7–9 are available online at http://links.lww.com/AOG/E415).

Table 2. Risk of Maternal and Fetal Outcomes in Women Who Received the Respiratory Syncytial Virus Prefusion F Protein Vaccine (n=24,891) Compared With Unvaccinated Women (n=24,891)

Outcome	RSVpreF Vaccination Events	Unvaccinated Events	Crude IRR (95% CI)	wIRR (95% CI)
Preterm birth*	951 (4.1)	986 (4.3)	0.96 (0.88–1.04)	0.97 (0.89–1.06)
Birth within the week	451 (1.8)	614 (2.5)	0.73 (0.66–0.82)	0.81 (0.72–0.90)
Birth within 2 wk	1,581 (6.4)	1,919 (7.7)	0.82 (0.77–0.87)	0.89 (0.84–0.94)
Birth within 3 wk	3,866 (15.5)	4,262 (17.1)	0.90 (0.87–0.93)	0.97 (0.93–1.00)
Stillbirth	24 (0.1)	33 (0.1)	0.72 (0.42–1.21)	0.77 (0.45–1.32)
Cesarean delivery	5,464 (22.0)	5,354 (21.5)	1.00 (0.97–1.04)	1.00 (0.96–1.03)
Emergency	3,516 (14.1)	3,398 (13.7)	1.02 (0.97–1.06)	0.99 (0.95–1.04)
Scheduled	1,946 (7.8)	1,954 (7.9)	0.98 (0.92–1.04)	1.00 (0.94–1.07)
SGA birth weight	2,774 (11.1)	2,728 (11.0)	1.00 (0.95–1.05)	1.01 (0.96–1.07)
Hemorrhage	1,976 (7.9)	1,894 (7.6)	1.03 (0.97–1.09)	1.03 (0.97–1.10)
Preeclampsia	267 (1.1)	255 (1.0)	1.02 (0.86–1.21)	1.02 (0.85–1.22)
MACE	9 (0.0)	15 (0.1)	0.59 (0.26–1.35)	0.60 (0.26–1.40)

RSVpreF, respiratory syncytial virus prefusion F protein; IRR, incidence rate ratio; wIRR, weighted incidence rate ratio by inverse probability of treatment weighting; SGA, small for gestational age; MACE, major adverse cardiovascular event (acute coronary syndrome, stroke, pulmonary embolism, and death).

Data are n (%) unless otherwise specified.

* For the preterm birth outcome only, analysis restricted to women before 37 weeks of gestation (n=23,041 vaccinated and 23,041 unvaccinated).

Table 3. Subgroup Analyses for the Risk of Maternal and Fetal Outcomes in Women Who Received the Respiratory Syncytial Virus Prefusion F Protein Vaccine Compared With Unvaccinated Women

Characteristic	Preterm Birth	Preeclampsia*
Gestational age (wk)		
32 or less	1.13 (0.98–1.31)	1.39 (0.91–2.13)
33–34	0.98 (0.86–1.13)	0.87 (0.64–1.18)
35–36	0.74 (0.60–0.91)	0.90 (0.67–1.22)
37 or more		0.72 (0.26–2.02)
Maternal age (y)		
Younger than 30	0.93 (0.80–1.07)	0.77 (0.57–1.03)
30 or older	0.96 (0.86–1.07)	1.21 (0.97–1.51)
Previous preterm birth		
Yes	0.88 (0.68–1.15)	1.04 (0.52–2.09)
No	0.97 (0.88–1.06)	1.02 (0.85–1.22)
Multiparous		
Yes	1.05 (0.83–1.32)	1.13 (0.62–2.09)
No	0.95 (0.86–1.06)	1.04 (0.82–1.31)
Influenza vaccination		
Yes†	1.25 (1.02–1.53)	1.23 (0.77–1.96)
No	0.92 (0.83–1.02)	1.00 (0.82–1.21)
COVID-19 vaccination		
Yes†	0.67 (0.19–2.41)	0.88 (0.05–14.10)
No	0.95 (0.87–1.04)	0.99 (0.82–1.18)

COVID-19, coronavirus disease 2019.
Data are weighted incidence rate ratio (95% CI).
* Including eclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome.
† Adjusted for time between vaccine administration when applicable.

DISCUSSION

In this large, population-based cohort study in France, RSVpreF vaccination during pregnancy was not associated with an increased overall risk of adverse maternal or fetal outcomes. In particular, no elevated risk was observed among women who received the vaccine after 32 weeks of gestation. Although slight, nonsignificant increases in the risks of preterm birth, delivery within 1 to 3 weeks, SGA birth weight, and preeclampsia were noted among the small subgroup of women vaccinated at or before 32 weeks of gestation, these findings should be interpreted with caution. This subgroup represented only 6% of vaccinated women, limiting both the statistical power and the generalizability of the observations. Women vaccinated earlier than the recommended window may have been at higher risk of preterm delivery, leading health care professionals to recommend vaccination for the benefit of their potentially premature newborns. The absence of increased risk at later gestational ages, which correspond to the recommended timing of vaccination, is reassuring.

To date, the only other large observational study on maternal and fetal safety outcomes related to the RSVpreF vaccine used data from the TriNetX U.S. Collaborative Network, a real-time federated health research system encompassing about 120 million individuals.[23] The authors found no significant association between RSVpreF vaccination and preterm birth or other fetal outcomes among the 6,387 women and an equal number of unvaccinated women in a control group, aligning with our global results and the findings from the phase III MATISSE trial.[24] Similarly, a cohort study conducted in two hospitals in New York City during the 2023–2024 season, which included 2,973 pregnant individuals (1,026 of whom were vaccinated), found no overall increase in preterm birth risk.[25] However, none of these studies provided subgroup analyses by gestational age, which limits direct comparisons.

A similar signal for preterm birth among women vaccinated at or before 32 weeks of gestation was observed in the MATISSE trial, as well as in a separate phase III maternal trial of the RSVpreF3 vaccine, which was terminated early because of an imbalance in fetal deaths, attributed primarily to prematurity, between the vaccine and placebo groups.[4] The higher risk of preterm birth observed among women vaccinated against both RSV and influenza mirrors findings from RSVpreF3 trials.[4] Nevertheless, the RSVPreF3 study reported this higher risk in low- and middle-income countries only. Although maternal immunization has been broadly shown to be safe in the literature,[5,7,9,10,26] this subgroup effect may reflect differing baseline risk profiles between women who do and those who do not receive influenza vaccination.[18] However, a potential interaction between RSVpreF and influenza vaccines contributing to this signal cannot be ruled out and requires further investigation. Meanwhile, women at high risk of preterm birth may be directed toward a monoclonal antibody strategy for the newborn, along with other high-risk women who wish to receive both influenza vaccination and RSV prevention.

Our findings of a nonsignificant increased risk of hypertensive disorders of pregnancy align with those of the MATISSE trial[1,3] and the New York City study.[25] Preterm birth and preeclampsia were also reported after RSVpreF vaccination in the U.S. Vaccine Adverse Event Reporting System,[27,28] with a median interval of 3 days from vaccination to preterm delivery (range 0–31 days) and approximately two-thirds of cases occurring within the first week. In our study, the median time from vaccination to preterm birth was 14 days; the median interval from vaccination to delivery within 1 week was shorter (data not shown). These differences may reflect underreporting of events occurring beyond the immediate postvaccination period in the Vaccine Adverse Event Reporting System. The potential association between RSVpreF vaccination and complications such as preterm birth and preeclampsia has not been elucidated in previous studies, and the underlying biological mechanisms remain unclear.[3,25] A possible explanation could involve an excessive or dysregulated maternal immune response after vaccination. However, this hypothesis remains unproven, and existing data on maternal immunization—particularly with influenza, pertussis, and COVID-19 vaccines—have not supported an increased risk of such outcomes.[29]

The use of national health care databases allowed us to assess the safety of the RSVpreF vaccine in all eligible pregnant women in France during the study period, providing a comprehensive and population-wide perspective. Despite the large cohort, event rates for rare outcomes such as stillbirth and major adverse cardiovascular events were low, limiting statistical power for these specific end points; however, associations observed in subgroup analyses remained stable across sensitivity analyses, reinforcing the reliability of our results. Some important risk factors for adverse pregnancy outcomes may not have been captured, leaving room for potential residual confounding. To mitigate this, a comprehensive propensity score was restricted to vaccinated women who could be matched to unvaccinated women; the unvaccinated cohort was defined according to characteristics of the vaccinated group, and the estimated associations reflect relative measures within the matched and weighted cohort rather than absolute risks in the overall population. Finally, the date of vaccination was estimated from the closest appropriate medical contact; this may have introduced some misclassification in the timing of exposure, potentially diluting any association between early vaccination and the risk of preterm birth within this subgroup.

In this nationwide study, RSVpreF vaccination during the 2024–2025 season was not associated with overall safety concerns, supporting the favorable safety profile of RSV maternal immunization. A nonsignificant increase in certain risks was noted among women vaccinated at or before 32 weeks of gestation; however, these findings were limited by the small sample size. Further research, including international comparisons and evaluations of effectiveness relative to monoclonal antibodies against RSV, will be needed to fully characterize the benefit–risk balance of RSVpreF. Ongoing surveillance remains essential, particularly to monitor rare adverse events.

REFERENCES

1. Kampmann B, Madhi SA, Munjal I, Simões EAF, Pahud BA, Llapur C, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;388:1451–64. doi: 10.1056/NEJMoa2216480
2. Haute Autorité de Santé. ABRYSVO (vaccin du virus respiratoire syncytial (bivalent, recombinant))—Virus Respiratoire Syncytial (VRS) chez les nourrissons. Accessed February 15, 2025. https://www.has-sante.fr/jcms/p_3535401/fr/abrysvo-vaccin-du-virus-respiratoire-syncytial-bivalent-recombinant-virus-respiratoire-syncytial-vrs-chez-les-nourrissons
3. Madhi SA, Kampmann B, Simões EAF, Zachariah P, Pahud BA, Radley D, et al. Preterm birth frequency and associated outcomes from the MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal trial of the bivalent respiratory syncytial virus prefusion F protein vaccine. Obstet Gynecol 2025;145:147–56. doi: 10.1097/aog.0000000000005817
4. Dieussaert I, Hyung Kim J, Luik S, Seidl C, Pu W, Stegmann JU, et al. RSV prefusion F protein-based maternal vaccine–preterm birth and other outcomes. N Engl J Med 2024;390:1009–21. doi: 10.1056/NEJMoa2305478
5. Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis 2020;20:136. doi: 10.1186/s12879-020-4824-3
6. Zerbo O, Modaressi S, Chan B, Goddard K, Lewis N, Bok K, et al. No association between influenza vaccination during pregnancy and adverse birth outcomes. Vaccine 2017;35:3186–90. doi: 10.1016/j.vaccine.2017.04.074
7. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother 2019;15:687–99. doi: 10.1080/21645515.2018.1540807
8. Prasad S, Kalafat E, Blakeway HA-O, Townsend R, O'Brien P, Morris E, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. Nat Commun 2022;13:2414. doi: 10.1038/s41467-022-30052-w

9. Badell ML, Dude CM, Rasmussen SA, Jamieson DJ. Covid-19 vaccination in pregnancy. BMJ 2022;378:e069741. doi: 10.1136/bmj-2021-069741

10. Rahmati MA-OX, Yon DA-O, Lee SW, Butler L, Koyanagi A, Jacob L, et al. Effects of COVID-19 vaccination during pregnancy on SARS-CoV-2 infection and maternal and neonatal outcomes: a systematic review and meta-analysis. Rev Med Virol 2023;33:e2434. doi: 10.1002/rmv.2434

11. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: from the Système National D'information Interrégimes de l'Assurance Maladie (SNIIRAM) to the Système National des Données de Santé (SNDS) in France. Rev Epidemiol Sante Pub 2017;65(suppl 4):S149–67. doi: 10.1016/j.respe.2017.05.004

12. Tran A, Zureik M, Sibiude J, Miranda S, Drouin J, Marty L, et al. First-trimester exposure to macrolides and risk of major congenital malformations compared with amoxicillin: a French nationwide cohort study. PLoS Med 2025;22:e1004576. doi: 10.1371/journal.pmed.1004576

13. Bernard C, Drouin J, Le Vu S, Botton J, Semenzato L, Bertrand M, et al. COVID-19 vaccination rates among pregnant women in France: a nationwide cohort study. Vaccine 2025;53:127070. doi: 10.1016/j.vaccine.2025.127070

14. Blotière P-O, Weill A, Dalichampt M, Billionnet C, Mezzarobba M, Raguideau F, et al. Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: an application to antiepileptic drug use in 4.9 million pregnant women in France. Pharmacoepidemiol Drug Saf 2018;27:763–70. doi: 10.1002/pds.4556

15. Goldshtein I, Nevo D, Steinberg DM, Rotem RS, Gorfine M, Chodick G, et al. Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection in pregnant women. JAMA 2021;326:728–35. doi: 10.1001/jama.2021.11035

16. Kildegaard H, Jensen A, Andersen PHS, Dalby T, Gram MA, Lidegaard Ø, et al. Safety of pertussis vaccination in pregnancy and effectiveness in infants: a Danish national cohort study 2019-2023. Clin Microbiol Infect 2025;31:995–1002. doi: 10.1016/j.cmi.2025.03.014

17. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412–23. doi: 10.1056/NEJMoa2101765

18. Choi YJ, Jung J, Kang M, Choi MJ, Choi WS, Seo YB, et al. The risk of pregnancy-related adverse outcomes after COVID-19 vaccination: propensity score-matched analysis with influenza vaccination. Vaccine 2025;44:126506. doi: 10.1016/j.vaccine.2024.126506

19. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492–9. doi: 10.1093/aje/kwm324

20. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. Lancet 2014;384:857–68. doi: 10.1016/s0140-6736(14)60932-6

21. Rey G, Jougla E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997–2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health 2009;9:33. doi: 10.1186/1471-2458-9-33

22. Rachas A, Gastaldi-Ménager C, Denis P, Barthélémy P, Constantinou P, Drouin J, et al. The economic burden of disease in France from the National Health Insurance Perspective: the healthcare expenditures and conditions mapping used to prepare the French Social Security Funding Act and the Public Health Act. Med Care 2022;60:655–64. doi: 10.1097/mlr.0000000000001745

23. Jin Hsieh TY, Cheng-Chung Wei J, Collier AR. Investigation of maternal outcomes following respiratory syncytial virus vaccination in the third trimester: insights from a real-world U.S. electronic health records database. Am J Obstet Gynecol. 2025. doi: 10.1016/j.ajog.2025.04.067

24. Simões EAF, Pahud BA, Madhi SA, Kampmann B, Shittu E, Radley D, et al. Efficacy, safety, and immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal respiratory syncytial virus prefusion F protein vaccine trial. Obstet Gynecol 2025;145:157–67. doi: 10.1097/aog.0000000000005816

25. Son M, Riley LE, Staniczenko AP, Cron J, Yen S, Thomas C, et al. Nonadjuvanted bivalent respiratory syncytial virus vaccination and perinatal outcomes. JAMA Netw Open 2024;7:e2419268. doi: 10.1001/jamanetworkopen.2024.19268

26. Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. Eur J Pediatr 2020;179:235–42. doi: 10.1007/s00431-019-03563-w

27. Moro PL, Getahun A, Romanson B, Marquez P, Tepper NK, Olson CK, et al, Safety monitoring of Pfizer's respiratory syncytial virus vaccine in pregnant women in the Vaccine Adverse Event Reporting System, 2023-2024, United States. Vaccine 2025;62:127497. doi: 10.2139/ssrn.5188287

28. Alami AA-O, Pérez-Lloret SA-O, Mattison DA-O. 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:e087850. doi: 10.1136/bmjopen-2024-087850

29. Santé Publique France. Bulletin des infections respiratoires aigues de la semaine 07 (du 10 au 16 Février 2025). Accessed April 15, 2025. https://www.santepubliquefrance.fr/content/download/701062/4587153?version=3

PEER REVIEW HISTORY

Received August 18, 2025. Received in revised form September 30, 2025. Accepted October 2, 2025. Peer reviews and author correspondence are available at http://links.lww.com/AOG/E416.