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Sequential Safety Surveillance of RSVpreF Vaccination During Pregnancy Early in the Postapproval Period

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Abstract

IMPORTANCE Respiratory syncytial virus (RSV) is a leading cause of infant hospitalizations. In August 2023, the US Food and Drug Administration approved a bivalent RSV prefusion F subunit–based vaccine (RSVpreF) for maternal immunization to protect newborns. Sequential surveillance analysis provides information on the safety of a vaccine during its initial uptake.

OBJECTIVE To report the sequential surveillance findings for 10 prespecified safety outcomes of exposure to RSVpreF during pregnancy over the course of its first vaccination season in the US.

DESIGN, SETTING, AND PARTICIPANTS This cohort study with a sequential surveillance design used health plan data from 5 research partners. Health insurance data were analyzed across 5 sequential surveillance periods from April 25, 2024, through April 10, 2025. Pregnancies of individuals aged 15 to 54 years that culminated in a live birth or stillbirth and reached 32 gestational weeks were included. Cohorts included pregnancies exposed to RSVpreF (between September 22, 2023, and August 9, 2024); comparator pregnancies receiving influenza, COVID-19, and/or Tdap (tetanus, diphtheria, and acellular pertussis) vaccines but not the RSVpreF concurrently; and historical comparator pregnancies (vaccinated between September 1, 2018, and January 31, 2023).

EXPOSURE RSVpreF or comparator vaccines (influenza, COVID-19, and/or Tdap but not RSVpreF) between 32 through 36 weeks' gestation.

MAIN OUTCOMES AND MEASURES Primary outcomes were preterm birth and pregnancy-associated hypertensive disorders (composite of gestational hypertension; preeclampsia; eclampsia; hemolysis, elevated liver enzymes, and low platelet syndrome; or preexisting hypertension superimposed with preeclampsia or eclampsia). Secondary outcomes included premature rupture of membranes (PROM), preterm labor without preterm delivery, preterm PROM, maternal Guillan-Barré syndrome, and stillbirth. Infant outcomes were large for gestational age, small for gestational age, and low birth weight. Crude incidence proportions (IPs) and adjusted relative risks (ARR) were identified for these outcomes.

RESULTS Among the 13 619 RSVpreF-exposed pregnancies included in the analysis, the mean (SD) maternal age was 33.3 [4.6] years. The most common safety outcomes were pregnancy-associated hypertensive disorders (IP, 17.3%; 95% CI, 16.6%-17.9%) and PROM (IP, 14.1%; 95% CI, 13.5%-14.7%). Risk of preterm birth was not elevated compared with the concurrent comparator (ARR, 0.79; 95% CI, 0.65-0.98) or historical comparator (ARR, 0.87; 95% CI, 0.78-0.96). Beginning with the second surveillance period, statistically significantly elevated risks were detected for pregnancy-associated

(continued)

Key Points

Question What is the safety profile of a bivalent respiratory syncytial virus prefusion F subunit–based vaccine (RSVpreF) for maternal immunization to protect newborns?

Findings In this cohort study of 13 619 RSVpreF-exposed pregnancies, a sequential surveillance analysis found potential elevated risks for pregnancy-associated hypertensive disorders, premature rupture of membranes (PROM), and preterm PROM. No statistically significant associations were observed between RSVpreF vaccination during pregnancy and 7 other prespecified safety outcomes, including preterm birth.

Meaning In this study, early postlicensure surveillance detected an association between maternal RSVpreF exposure during pregnancy and some safety outcomes, which should be investigated further in future epidemiological studies.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

hypertensive disorders (concurrent comparator: ARR, 1.14 [95% CI, 1.02-1.27]; historical comparator: ARR, 1.29 [95% CI, 1.24-1.34]), PROM (concurrent comparator: ARR, 1.09 [95% CI, 0.97-1.22]; historical comparator: ARR, 1.14 [95% CI, 1.09-1.19]), and preterm PROM (historical comparator: ARR, 1.18; 95% CI, 1.08-1.29). No other increased risks were observed.

CONCLUSIONS AND RELEVANCE In this study using a sequential surveillance design, there was no association between RSVpreF vaccination during pregnancy and preterm birth; however, potential increased risks of pregnancy-associated hypertensive disorders, PROM, and preterm PROM could not be ruled out, due to limited confounding control available in the early postlicensure period. Further epidemiological studies are needed to refine risk estimates and account for other confounding factors.

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Introduction

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease (LRTD) in infants globally and is associated with substantial morbidity and mortality in the first year of life.[1] In the US, RSV is the most common cause of hospitalization among infants,[2] leading to substantial economic burden on families.[3]

A bivalent RSV prefusion F subunit–based vaccine (Abrysvo, Pfizer; hereafter RSVpreF) was approved in August 2023 by the US Food and Drug Administration (FDA) for active immunization of pregnant individuals at 32 through 36 weeks' gestational age for the prevention of LRTD and severe LRTD in infants from birth through 6 months of age.[4] Pooled randomized clinical trial data from 18 countries[5,6] demonstrated vaccine efficacy of 56.8% in the full trial population (administered between 24 and 36 weeks' gestation) and 48.2% in the subset population (administered between 32 and 36 weeks' gestation) against infant hospitalization for RSV-associated LRTD.[2] This finding led to the Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) recommendation of seasonal administration (September to January in most of the continental US).[7] Although some statistically insignificant numerical imbalances in preterm birth and pregnancy-associated hypertensive disorders were observed among RSVpreF recipients in these same trials, ACIP determined that the benefits outweighed these potential risks. Recent observational case-control studies have continued to demonstrate RSVpreF effectiveness.[8,9]

This observational study is the first of many components to an FDA postmarketing requirement and was designed to regularly assess accumulating data using sequential surveillance methods and rapidly identify potential elevated risks while controlling for multiple hypothesis testing.[10] Herein, we aimed to report the sequential surveillance findings for 10 prespecified safety outcomes of exposure to RSVpreF during pregnancy over the course of its first vaccination season in the US.

Methods

Study Design

We retrospectively identified pregnancies with vaccinations from September 22, 2023, through August 9, 2024 (September 1, 2018, through January 31, 2023, for the historical comparator cohort) and analyzed them across 5 quarterly sequential surveillance periods between April 25, 2024, and April 10, 2025. The protocol was registered in the European Medicines Agency Catalogue (identifier: EUPAS10000000115)[11] and reviewed with the statistical analysis plan by the FDA. The Harvard Pilgrim Health Care Institute Institutional Review Board determined this cohort study to be nonhuman participant research and thus exempt from ethics review and informed consent

requirement. Research partners obtained local institutional review board approval and waivers of informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[12]

Setting and Population

We used health plan data from 5 research partners: Carelon Research, CVS Health, HealthPartners Institute, Kaiser Permanente Northwest, and Point32Health. We leveraged each organization's transformed and quality-controlled data in the Sentinel Common Data Model (SCDM), facilitating multisite standardized analyses.[13-15] The SCDM includes plan member demographic, enrollment, inpatient and outpatient visits, and pharmacy dispensing data[16] (eTable 1 in Supplement 1). Each research partner collects self-reported race and ethnicity and populates the SCDM categories (defined per federal guidance),[17] including American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, multiracial, and unknown and Hispanic origin. This information was included in the analysis because race and ethnicity are potentially confounding factors for important safety outcomes, such as stillbirth.

We included pregnancies culminating in a live birth or stillbirth and reaching 32 gestational weeks or later (based on the approved use of RSVpreF beginning at 32 weeks' gestation) among individuals aged 15 to 54 years at delivery, and we required them to have continuous enrollment with medical and pharmacy benefits for 90 days or more before the estimated last menstrual period through pregnancy end (allowing 45-day gaps). We excluded pregnancies from outcome-specific analyses if any diagnosis and/or procedure codes for that outcome occurred prior to RSVpreF or comparator vaccination (eTable 2 in Supplement 1). We identified pregnancies and estimated gestational ages using a claims-based algorithm adapted from validated methods and developed in the Sentinel System (FDA).[18-20]

The RSVpreF-exposed cohort included pregnancies that received RSVpreF during 32 through 36 weeks' gestation between September 22, 2023 (CDC and ACIP recommendation date), and 83 days before the data cutoff (end date: August 9, 2024), allowing pregnancies to reach 42 weeks' gestation after vaccination.[21] Two comparator cohorts included pregnancies receiving seasonal influenza, bivalent COVID-19, and/or Tdap (tetanus, diphtheria, and acellular pertussis) vaccinations during gestational weeks 32 through 36, with no RSVpreF exposure: (1) concurrent comparator cohort, vaccinated in the same time frame as the RSVpreF-exposed cohort, and (2) historical comparator cohort, vaccinated from September 1, 2018, through January 31, 2023 (5 seasons). Both RSVpreF-exposed and comparator pregnancies could receive multiple vaccines. Leveraging 2 comparator cohorts was essential. In addition to being the standard in vaccine safety surveillance,[22] a historical comparison supports early surveillance when accrual and small sample sizes limit concurrent analyses.[23,24]

We identified vaccine exposures using National Drug Codes, *Current Procedural Terminology* (Fourth Edition) codes, and Codes for Vaccines Administered (eTable 2 in the Supplement).

Outcomes

Primary outcomes included preterm birth and pregnancy-associated hypertensive disorders (composite of gestational hypertension; preeclampsia; eclampsia; hemolysis, elevated liver enzymes, and low platelets [HELLP] syndrome; or preexisting hypertension superimposed with preeclampsia or eclampsia). Secondary outcomes included preterm labor without preterm delivery, premature rupture of membranes (PROM), preterm PROM, stillbirth, and maternal Guillain-Barré syndrome (GBS). We assessed pregnancy-related outcomes from the day after vaccination through pregnancy end or through 42 days after vaccination for GBS,[25-27] and we assessed infant outcomes (large for gestational age [LGA], low birth weight, and small for gestational age) through 7 days after live birth (using maternal and, where available, linked infant records[28]). We defined outcomes with diagnosis and/or procedure codes in specified care settings (eTable 2 in Supplement 1).

Follow-Up for Outcomes With Potentially Elevated Risks

We reviewed outcomes with statistically elevated risks for data quality issues, misclassification, and residual confounding.[29,30] For a random subset of RSVpreF-exposed and concurrent comparator pregnancies with outcomes, we retrieved and reviewed deidentified patient profiles (line lists of all relevant claims or encounters)[31] from 90 days before pregnancy start through 56 days after delivery. We collected additional descriptive characteristics for vaccinated pregnancies with potentially elevated risks (eTable 2 in Supplement 1).

Statistical Analysis

We summarized demographic and other potential confounder variables for each cohort (eTable 2 in Supplement 1) and defined imbalance as a standardized mean difference greater than 0.1.[32] Consistent with vaccine safety surveillance practice, this analysis sought to identify any potential safety concerns as quickly as possible; adjusting for all possible confounding factors would limit the ability to do this by reducing power and creating instability in each estimate.[33-37] Therefore, we adjusted for confounding by stratifying outcomes by research partner and, when feasible without generating empty strata (eTable 3 in Supplement 1), by gestational age at vaccination, maternal age, high-risk status for preterm birth (eTable 2 in Supplement 1), and vaccination seasonality.

We conducted sequential surveillance with maximized sequential probability ratio testing (MaxSPRT) of the stratified outcomes.[34,38] The MaxSPRT statistic compares the observed outcomes in RSVpreF-exposed pregnancies against the expected outcomes in comparator pregnancies. We computed crude relative risks (RRs) from pooled incidence proportion (IP) ratios and adjusted RRs (ARRs) using the binomial MaxSPRT (concurrent comparator) and the Poisson or conditional Poisson MaxSPRT (historical comparator) (eTable 4 in Supplement 1). Infant outcome analyses used data from national research partners, regardless of infant linkage and required linkage from regional research partners. We calculated IPs restricted to linked records as a sensitivity analysis.

We monitored outcome accrual at each of 5 preplanned surveillance periods and performed hypothesis tests sequentially until we (1) rejected the null hypothesis of no increased risk in the RSVpreF-exposed cohort by surpassing a critical value or (2) failed to reject the null hypothesis by reaching the maximum duration of surveillance and/or end of all surveillance periods without surpassing the critical value (eTables 5 and 6 in Supplement 1).[38,39] We continued surveillance after formal sequential testing ended for contextualization (eTable 4 in Supplement 1). We reported nominal CIs without multiplicity adjustment, although the sequential testing procedure controlled for repeated evaluations of the same hypothesis in each surveillance period. For outcomes exhibiting historical temporal trends, we adjusted the detectable effect size in sensitivity analyses to test whether any identified increased risk would sustain even amid upward-trending background outcome rates.

We built analytic datasets using the Routine Querying Tool version 13.0.0 (Sentinel System),[40] with custom programming for SAS software[41] version 9.4 (SAS Institute Inc). We used the Sequential package version 4.3.4 (R Project for Statistical Computing)[42] for sequential statistical analyses.

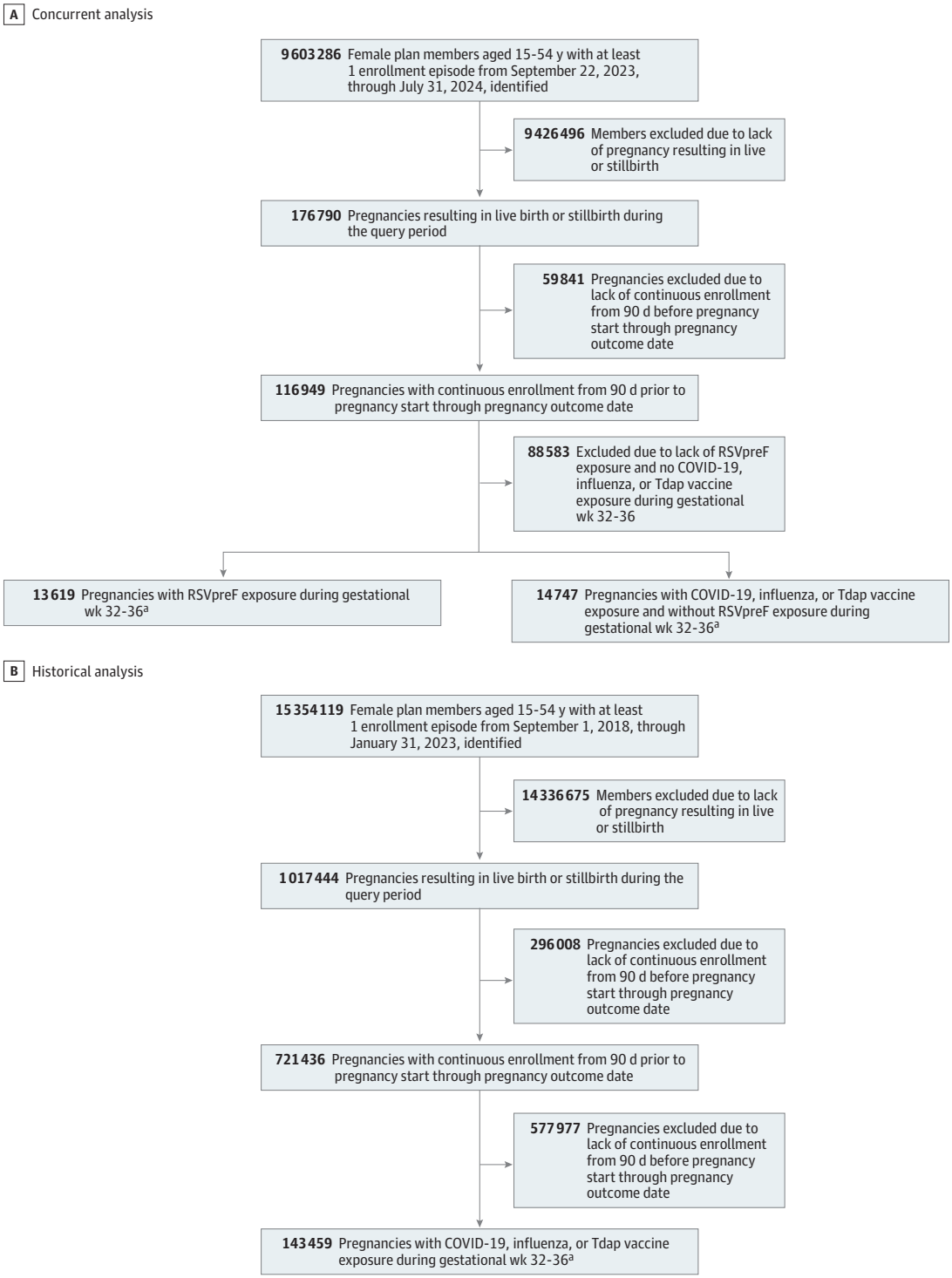
Results

We identified 116 949 eligible pregnancies during the concurrent period and 721 436 in the historical period (**Figure 1**). From these populations, we included 13 619 RSVpreF-exposed, 14 747 concurrent comparator, and 143 459 historical comparator pregnancies.

The RSVpreF-exposed cohort had a mean (SD) maternal age of 33.3 (4.6) years of age; 8026 (58.9%) of these individuals were aged 25 to 34 years (**Table 1**). Race was reported as follows: 60 American Indian or Alaska Native (0.4%), 1444 Asian (10.6%), 378 Black or African American (2.8%), 12 Native Hawaiian or Other Pacific Islander (0.1%), 6997 White (51.4%), and 287 multiracial individuals (2.1%); 4441 individuals (32.6%) were of unknown race. Hispanic origin was reported by 634 individuals (4.7%), while 7915 individuals (58.1%) reported non-Hispanic origin and 5070

individuals (37.2%) were of unknown ethnicity. Most vaccinations occurred during gestational weeks 33 through 35 (9046 pregnancies [66.5%]), and conditions marking the pregnancy at high risk for preterm birth were present in 7925 pregnancies (58.2%) (Table 1).

Figure 1. Flowcharts of Cohort Attrition



RSVpreF indicates bivalent respiratory syncytial virus prefusion F subunit–based vaccine, and Tdap indicates tetanus, diphtheria, and acellular pertussis.

[a] Number of pregnancies was equivalent to number of patients except in the historical analysis, which included 138 662 patients.

Table 1. Baseline Characteristics of RSVpreF-Exposed, Concurrent Comparator, and Historical Comparator Pregnancy Cohorts

Characteristic	Pregnancy cohorts				
	RSVpreF-exposed, No. (%) (n = 13 619)[a,b]	Concurrent comparator		Historical comparator	
		No. (%) (n = 14 747)[b]	SMD[c]	No. (%) (n = 143 459)[b]	SMD[c]
Maternal demographic					
Age at delivery, mean (SD), y	33.3 (4.6)	32.2 (5.0)	0.228	32.2 (5.0)	0.229
Age at delivery, y					
15-24	625 (4.6)	1301 (8.8)	−0.170	12 770 (8.9)	−0.173
25-34	8026 (58.9)	9085 (61.6)	−0.055	89 276 (62.2)	−0.068
35-54	4968 (36.5)	4361 (29.6)	0.147	41 413 (28.9)	0.163
Race[d]					
American Indian or Alaska Native	60 (0.4)	54 (0.4)	0.012	69 (0.0)	0.079
Asian	1444 (10.6)	1139 (7.7)	0.100	2172 (1.6)	0.385
Black or African American	378 (2.8)	703 (4.8)	−0.105	1502 (1.1)	0.123
Native Hawaiian or Other Pacific Islander	12 (0.1)	12 (0.1)	0.002	65 (0.0)	0.016
White	6997 (51.4)	6659 (45.2)	0.125	14 608 (10.5)	0.985
Multiracial	287 (2.1)	381 (2.6)	−0.031	2209 (1.6)	0.038
Unknown	4441 (32.6)	5799 (39.3)	−0.140	118 037 (85.1)	−1.262
Hispanic origin					
Yes	634 (4.7)	745 (5.1)	−0.018	2173 (1.6)	0.179
No	7915 (58.1)	7451 (50.5)	0.153	9778 (7.1)	1.299
Unknown	5070 (37.2)	6551 (44.4)	−0.147	126 711 (91.4)	−1.370
Year of delivery					
2018	NA	NA	NA	11 257 (7.8)	NA
2019	NA	NA	NA	29 692 (20.7)	NA
2020	NA	NA	NA	28 685 (20.0)	NA
2021	NA	NA	NA	37 648 (26.2)	NA
2022	NA	NA	NA	31 247 (21.8)	NA
2023	3850 (28.3)	6067 (41.1)	−0.273	4930 (3.4)	0.723
2024	9769 (71.7)	8680 (58.9)	0.273	NA	NA
Gestational age at delivery, mean (SD), wk[e]	38.8 (1.4)	38.8 (1.5)	−0.017	38.9 (1.5)	−0.069
Temporality of vaccine exposure					
Year and quarter of vaccine administration in GW 32-36					
2023, quarter 3	43 (0.3)	1509 (10.2)	−0.455	NA	NA
2023, quarter 4	7336 (53.9)	6087 (41.3)	0.254	NA	NA
2024, quarter 1	5837 (42.9)	4447 (30.2)	0.266	NA	NA
2024, quarter 2	394 (2.9)	2607 (17.7)	−0.502	NA	NA
2024, quarter 3	9 (0.1)	97 (0.7)	−0.099	NA	NA
Vaccine administration during RSV season[f]					
In season: September to January	11 288 (82.9)	8938 (60.6)	0.511	81 133 (56.6)	0.599
Out of season: February to August	2331 (17.1)	5809 (39.4)	−0.511	62 326 (43.4)	−0.599
Gestational age of vaccine administration, wk					
32	1971 (14.5)	4869 (33.0)	−0.447	47 614 (33.2)	−0.450
33	2721 (20.0)	3349 (22.7)	−0.067	33 421 (23.3)	−0.081
34	3198 (23.5)	2630 (17.8)	0.140	25 258 (17.6)	0.146
35	3127 (23.0)	1987 (13.5)	0.248	19 212 (13.4)	0.250
36	2602 (19.1)	1912 (13.0)	0.168	17 954 (12.5)	0.181

(continued)

Table 1. Baseline Characteristics of RSVpreF-Exposed, Concurrent Comparator, and Historical Comparator Pregnancy Cohorts (continued)

Characteristic	Pregnancy cohorts				
	RSVpreF-exposed, No. (%) (n = 13 619)[a,b]	Concurrent comparator		Historical comparator	
		No. (%) (n = 14 747)[b]	SMD[c]	No. (%) (n = 143 459)[b]	SMD[c]
High-risk conditions for preterm birth prior to vaccination					
Any occurrence of a high-risk condition for preterm birth[g]	7925 (58.2)	8237 (55.9)	0.047	75 179 (52.4)	0.117
Assisted reproduction[h]	966 (7.1)	648 (4.4)	0.116	5144 (3.6)	0.156
Cervical shortening	208 (1.5)	220 (1.5)	0.003	2035 (1.4)	0.009
Diabetes[i]	1943 (14.3)	1904 (12.9)	0.040	16 973 (11.8)	0.072
Hypertension[j]	1138 (8.4)	1187 (8.0)	0.011	9170 (6.4)	0.075
Infections[k]	2195 (16.1)	2655 (18.0)	−0.050	26 134 (18.2)	−0.056
Magnesium sulfate injection	44 (0.3)	50 (0.3)	−0.003	375 (0.3)	0.011
Multiple gestation	188 (1.4)	186 (1.3)	0.010	2204 (1.5)	−0.013
Placenta previa	1141 (8.4)	1167 (7.9)	0.017	10 869 (7.6)	0.030
Preterm labor	151 (1.1)	172 (1.2)	−0.005	2556 (1.8)	−0.056
Prior preterm birth or prior preterm labor[h]	302 (2.2)	381 (2.6)	−0.024	3031 (2.1)	0.007
Recent prior live birth delivery[l]	15 (0.1)	48 (0.3)	−0.046	400 (0.3)	−0.038
Substance use, alcohol use, or SUD	40 (0.3)	43 (0.3)	0.000	402 (0.3)	0.003
Supervision of high-risk pregnancy[m]	4409 (32.4)	4036 (27.4)	0.110	32 992 (23.0)	0.211
Tobacco or smoking cessation medications	595 (4.4)	720 (4.9)	−0.024	6315 (4.4)	−0.002
Any immunization recommended for adults until No. of d before estimated pregnancy start date[43]	10 551 (77.5)	10 183 (69.1)	0.191	NA	NA
Concomitant vaccinations within 14 d of the cohort entry vaccination					
COVID-19, bivalent	459 (3.4)	420 (2.8)	0.030	15 794 (11.0)	−0.299
Influenza, seasonal	836 (6.1)	4308 (29.2)	−0.635	41 033 (28.6)	−0.621
Tdap	2451 (18.0)	11 524 (78.1)	−1.508	103 840 (72.4)	−1.305

Abbreviations: GW, gestational week; NA, not applicable; RSV, respiratory syncytial virus; RSVpreF, bivalent RSV prefusion F subunit–based vaccine; SMD, standardized mean difference; SUD, substance use disorder; Tdap, tetanus, diphtheria, and acellular pertussis.

[a] RSVpreF-exposed pregnancy cohort data are from the concurrent comparator analysis. RSVpreF-exposed pregnancy cohort data from the historical comparator analysis are nearly identical.

[b] Percentages were calculated among total number of unique pregnancies, except for race and Hispanic ethnicity, which were calculated among total number of unique patients (equivalent to number of pregnancies for the RSVpreF-exposed and concurrent comparator cohorts; N = 138 662 for the historical comparator cohort).

[c] SMDs are compared with RSVpreF-exposed pregnancies and presented in SD units.

[d] Race data may not be completely populated at all data partners and therefore may be incomplete. Between data collection for the historical and concurrent analyses, race data capture improved substantially. Race and ethnicity were self-reported, and the categories are in accordance with federal guidance.

[e] Length of the pregnancy episode was estimated using a hierarchy of pregnancy markers. If overlapping pregnancy episodes were constructed in the same patient due to observation of multiple pregnancy markers, then the markers providing more reliable estimation of pregnancy start were selected for estimation of pregnancy start date. If no pregnancy markers were observed, then a fixed pregnancy duration was assigned by pregnancy outcome type, as described in the Sentinel Routine Querying Tool documentation.[34]

[f] Because the window of eligible vaccinations in the data by the fourth analysis was from September 2023 through May 2024, most vaccinations occurred in the fourth quarter of 2023 and first quarter of 2024 and were thus in season.

[g] Unless otherwise indicated, evaluated from estimated pregnancy start date until the day before vaccination.

[h] Evaluated in all available enrollment history until the day before estimated pregnancy start date.

[i] Includes gestational diabetes, preexisting diabetes, and antidiabetic medications.

[j] Includes hypertension, gestational hypertension, eclampsia, preeclampsia, and antihypertensive medications.

[k] Includes COVID-19, urinary tract infections, sexually transmitted infections, and certain vaginal infections.

[l] Evaluated in the 90 days before and not including estimated pregnancy start date.

[m] Required 2 occurrences of qualifying codes.

The RSVpreF-exposed cohort, compared with the concurrent comparator cohort, was older (4968 of 13 619 [36.5%] vs 4361 of 14 747 [29.6%] aged 35-54 years), less likely to include Black or African American individuals (378 [2.8%] vs 703 [4.8%]), vaccinated at later gestational ages (8927 [65.6%] vs 6529 [44.3%] in ≥34 gestational weeks), more likely to have encounters indicating the pregnancy was high risk (4409 [32.4%] vs 4036 [27.4%]), more likely to have evidence of assisted

reproduction (966 [7.1%] vs 648 [4.4%]), and more likely to have evidence of prior recommended immunizations (10 551 [77.5%] vs 10 183 [69.1%]). The characteristics of the historical comparator cohort resembled those of the concurrent comparator cohort.

Safety Outcomes

We identified the primary outcomes of preterm birth and pregnancy-associated hypertensive disorders in RSVpreF-exposed pregnancies (IP, 3.0% [95% CI, 2.7%-3.3%] and 17.3% [95% CI, 16.6%-17.9%], respectively), concurrent comparators (IP, 4.0% [95% CI, 3.6%-4.3%] and 13.1% [95% CI, 12.6%-13.6%], respectively), and historical comparators (IP, 3.6% [95% CI, 3.5%-3.7%] and 12.5% [95% CI, 12.4%-12.7%], respectively). Less common outcomes included PROM in 14.1% (95% CI, 13.5%-14.7%), 13.1% (95% CI, 12.6%-13.6%), and 12.5% (95% CI, 12.4%-12.7%) of the RSVpreF-exposed, concurrent comparator, and historical comparator cohorts, respectively (**Figure 2** and eTable 7 in Supplement 1). We observed an increasing temporal trend in the prevalence of pregnancy-associated hypertensive disorders, which necessitated a sensitivity analysis (eTable 5 in Supplement 1). There were no maternal GBS cases.

The LGA outcome was observed in 1.2% (95% CI, 1.0%-1.4%) of RSVpreF-exposed pregnancies (Figure 2). Incidence was higher when assessed only among pregnancies from research partners with available linkages to infant records (eTable 7 in Supplement 1).

Sequential Surveillance

We ended sequential hypothesis testing by our failure to reject the null hypothesis of no increased risk for preterm birth in the third surveillance period when using a historical comparator (ARR, 0.87; 95% CI, 0.78-0.96) and in the fifth or final surveillance period with a concurrent comparator (ARR, 0.79; 95% CI, 0.65-0.98) (**Table 2**, **Figure 3**). Starting in the second surveillance period and throughout the rest of the analysis, we detected a potential elevated risk for pregnancy-associated hypertensive disorders associated with RSVpreF vaccination (concurrent comparator: ARR, 1.14 [95% CI, 1.02-1.27]; historical comparator: ARR, 1.29 [95% CI, 1.24-1.34]). This potential risk persisted in sensitivity analyses accounting for temporal trends in historical comparator pregnancies, although it was not detected until the third surveillance period (eFigure 1 in Supplement 1).

We additionally detected a potentially elevated risk of PROM after the second hypothesis test with a historical comparator and the third hypothesis test with a concurrent comparator, which persisted through the end of analyses (concurrent comparator: ARR, 1.09 [95% CI, 0.97-1.22]; historical comparator: ARR, 1.14 [95% CI, 1.09-1.19]) (eFigure 1 in Supplement 1). Similarly, we were able to reject the null hypothesis of no excess risk for preterm PROM in the third surveillance period with a historical comparator (ARR, 1.18; 95% CI, 1.08-1.29) (eFigure 2 in Supplement 1); while the concurrent comparator analysis continued to show ARRs above the null for this outcome, the criteria for rejecting the null were not met (1.08; 95% CI, 0.87-1.36). We failed to reject the null hypothesis of no excess risk for the LGA outcome with both comparators, although the ARRs remained above the null with a concurrent comparator (1.18 [95% CI, 1.08-1.29]; historical: 0.96 [95% CI, 0.82-1.13]).

We found no excess risk for the secondary outcomes of preterm labor without delivery, stillbirth, low birth weight, and small for gestational age after 5 sequential surveillance periods. Crude RRs were similar to adjusted estimates for all outcomes (Table 2).

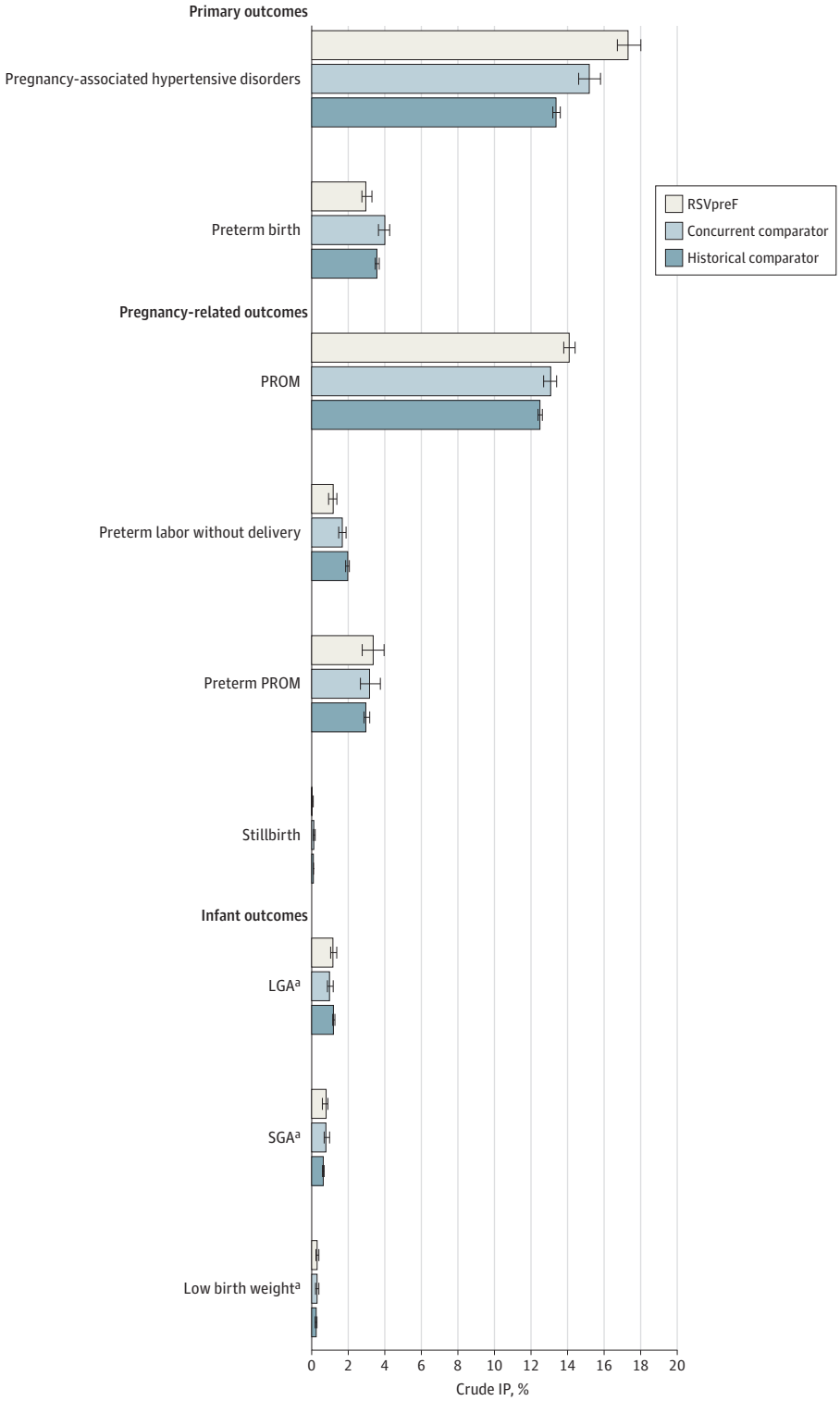
Follow-Up for Potentially Elevated Risks

Pregnancy-Associated Hypertensive Disorders

The most frequent diagnosis within the composite hypertension outcome was inpatient gestational hypertension (1387 [61.3%] of 2263 RSVpreF-exposed pregnancies with a pregnancy-associated hypertensive disorder; 1236 [57.4%] of 2152 concurrent comparator pregnancies with a pregnancy-associated hypertensive disorder) (eTable 8 in Supplement 1). Almost all outcomes occurred on the same day as the pregnancy delivery visit (3671 of 3951 pregnancy-associated hypertensive disorder

diagnosis codes [92.9%] among RSVpreF-exposed pregnancies; 3591 of 3944 pregnancy-associated hypertensive disorder diagnosis codes [91.0%] among concurrent comparator pregnancies). Patient profile reviews revealed that the mean (SD) lengths of delivery inpatient stay were shorter for pregnancies with only gestational hypertension codes (2.8 [1.5] days) compared with pregnancies

Figure 2. Horizontal Bar Graph of Crude Incidence Proportions (IPs) for Safety Outcomes



Error bars represent 95% CIs. LGA indicates large for gestational age; PROM, premature rupture of membranes; SGA, small for gestational age.

[a] eTable 7 in Supplement 1 shows the infant outcome IPs calculated only among pregnancies linked to an infant.

with other components of this outcome (3.3 [1.6] days for gestational hypertension plus preeclampsia or eclampsia; 3.8 [1.7] days for preeclampsia or eclampsia or preexisting hypertension superimposed with preeclampsia or eclampsia; 5.0 [1.4] days for HELLP syndrome, regardless of other components). RSVpreF-exposed and concurrent comparator cohorts were generally well balanced on the many prevaccination covariates collected to understand the potential for residual confounding in the elevated risk for pregnancy-associated hypertensive disorders (eTable 8 in Supplement 1), although RSVpreF-exposed pregnancies compared with comparator pregnancies had more evidence of prior immunizations recommended for adults (1689 of 2263 [74.6%] vs 1454 of 2152 [67.6%]) and assisted reproduction in the current pregnancy (198 of 2263 [8.7%] vs 102 of 2152 [4.7%]).

Table 2. Sequential Testing Results of RSVpreF Vaccine Safety After 5 Surveillance Periods in Historical and Concurrent Comparator Analyses[a]

Outcome	RSVpreF-exposed		Expected outcomes under null hypothesis	Met statistical threshold for excess risk	RR (95% CI)	
	Pregnancies, total No.	Observed outcomes, No. (%)			Crude[b]	Adjusted[c]
Preterm birth						
Concurrent comparator analysis	13 022	392 (3.0)	437.2	No	0.76 (0.67-0.87)	0.79 (0.65-0.98)
Historical comparator analysis	12 879	384 (3.0)	443.0	No	0.83 (0.75-0.92)	0.87 (0.78-0.96)
Pregnancy-associated hypertensive disorders						
Concurrent comparator analysis	13 099	2262 (17.3)	2144.4	Yes	1.14 (1.08-1.20)	1.14 (1.02-1.27)
Historical comparator analysis	12 955	2243 (17.3)	1740.1	Yes	1.29 (1.24-1.34)	1.29 (1.24-1.34)
PROM						
Concurrent comparator analysis	13 563	1914 (14.1)	1848.4	Yes	1.08 (1.02-1.14)	1.09 (0.97-1.22)
Historical comparator analysis	13 412	1888 (14.1)	1655.7	Yes	1.13 (1.08-1.18)	1.14 (1.09-1.19)
Preterm labor without delivery						
Concurrent comparator analysis	13 463	159 (1.2)	175.7	No	0.69 (0.56-0.83)	0.82 (0.65-1.01)
Historical comparator analysis	13 311	158 (1.2)	244.9	No	0.58 (0.49-0.68)	0.65 (0.55-0.75)
Preterm PROM						
Concurrent comparator analysis	13 577	459 (3.4)	444.2	No	1.05 (0.93-1.20)	1.08 (0.87-1.36)
Historical comparator analysis	13 426	454 (3.4)	385.0	Yes	1.12 (1.02-1.23)	1.18 (1.08-1.29)
Stillbirth[d]						
Concurrent comparator analysis	13 619	6 (<0.1)	13.6	No[d]	0.30 (0.12-0.73)	0.25 (0.08-0.57)
Historical comparator analysis	13 467	6 (<0.1)	11.1	No[d]	0.45 (0.20-1.03)	0.16 (0.07-0.38)
LGA						
Concurrent comparator analysis	12 399	154 (1.2)	136.3	No	1.20 (0.96-1.50)	1.33 (1.03-1.67)
Historical comparator analysis	12 248	151 (1.2)	156.7	No	1.02 (0.87-1.21)	0.96 (0.82-1.13)
Low birth weight						
Concurrent comparator analysis	12 407	35 (0.3)	36.2	No	0.84 (0.54-1.30)	0.93 (0.56-1.45)
Historical comparator analysis	12 256	28 (0.2)	33.9	No	1.06 (0.75-1.49)	0.83 (0.57-1.19)
SGA						
Concurrent comparator analysis	12 395	98 (0.8)	93.6	No	0.97 (0.74-1.27)	1.11 (0.81-1.48)
Historical comparator analysis	12 244	88 (0.7)	79.3	No	1.29 (1.05-1.59)	1.11 (0.90-1.37)

Abbreviations: LGA, large for gestational age; PROM, premature rupture of membranes; RR, relative risk; RSVpreF, bivalent respiratory syncytial virus prefusion F subunit–based vaccine; SGA, small for gestational age.

[a] Sequential testing was not performed for Guillan-Barré syndrome as no cases were identified in historical or concurrent analyses.

[b] Crude RRs were computed from pooled incidence proportions and are provided for descriptive comparison. Reported 95% CIs are nominal and do not account for multiple hypothesis testing (eTable 4 in Supplement 1).

[c] Adjusted RRs were covariate-stratified using outcome-specific strategies (eTable 3 in Supplement 1). Reported 95% CIs are nominal and do not account for multiple hypothesis testing (eTable 4 in Supplement 1).

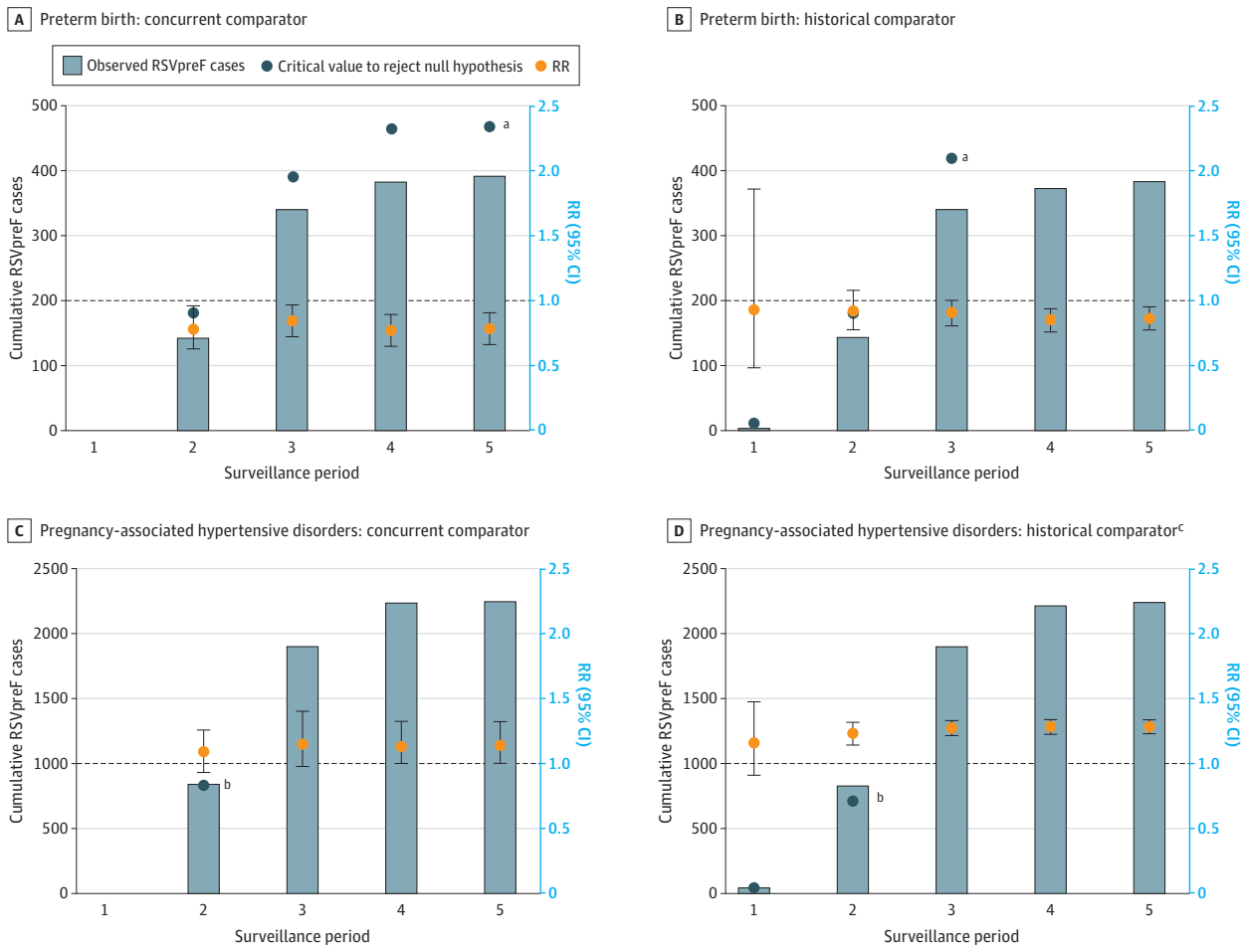
[d] No additional RSVpreF-exposed stillbirth cases were identified in the fifth or final surveillance period; thus, hypothesis tests could not be run. Reported RRs are from the fourth surveillance period.

Premature Rupture of Membranes

In both the RSVpreF-exposed and comparator cohorts, most PROM codes occurred on the date of delivery (2624 of 2754 [95.3%] and 2577 of 2746 [93.4%], respectively), and most pregnancies with PROM had *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* codes indicating that the pregnancy was full term (1400 of 1916 [73.1%] and 1386 of 1925 [72.0%], respectively) (eTable 9 in Supplement 1). The remaining pregnancies either had codes solely indicating a preterm delivery, both full-term and preterm codes, or no codes indicating pregnancy term.

In patient profile reviews, RSVpreF-exposed and comparator pregnancies with PROM were balanced on the evaluated risk factors (eTable 9 in Supplement 1). RSVpreF-exposed pregnancies with PROM, however, were more likely than comparator pregnancies with PROM to have evidence of prior immunizations recommended for adults (1464 of 1916 [76.4%] vs 1295 of 1925 [67.3%]).

Figure 3. Bar Graphs Showing Summary of Sequential Surveillance Results for Primary Outcomes Across Surveillance Periods



Concurrent comparisons were not performed during the first surveillance period while the study team assessed its feasibility. The use of a concurrent comparator requires a minimum number of outcomes (N = 6) during the course of planned surveillance in order for a 1:1 matched binomial probability model to find a solution using the MaxSPRT methods. After the first surveillance period, the study team determined a concurrent comparison was feasible and continued forward with both concurrent and historical comparisons. Error bars represent 95% CIs, which are nominal and do not account for multiple hypothesis testing. See eTable 5 in Supplement 1 for more information. Dashed line represents a relative risk of 1 (no association).

[a] Hypothesis testing ended in in given surveillance period without rejecting the null hypothesis.

[b] Null hypothesis of no increased risk rejected in given surveillance period.

[c] eFigure 1 in Supplement 1 provides the sequential monitoring results of the sensitivity analysis that adjusted detection criteria for the observed temporal pattern.

Discussion

In this sequential surveillance of RSVpreF vaccination safety during pregnancy in its first US vaccination season, we ruled out an increased risk for preterm birth as early as the third surveillance period with a historical comparator cohort. We did observe possible increased risks for pregnancy-associated hypertensive disorders, PROM, and preterm PROM with at least 1 comparator cohort. While sequential surveillance analyses provide information on the safety of vaccines during initial uptake,[10] confounding control is notably limited without additional follow-up and larger cohorts.[34]

Our findings are consistent with available data from other postmarketing observational studies. For instance, we found the incidence of preterm birth was 3.0% (95% CI, 2.7%-3.3%), comparable to the rate in a CDC Vaccine Safety Datalink (VSD) analysis of 10 295 pregnancies exposed to RSVpreF during the 2023 to 2024 vaccination season (expected 4.1%; 95% CI, 3.1%-6.1%).[44] Other observational studies[45,46]—including a VSD propensity score–matched analysis,[47] an exact-match analysis from France,[48] and our companion study using both matching techniques[49]—confirm these findings of numerically lower incidence and no statistically significant increased risk. Differing implications for early vs later vaccine adopters and the potential that pregnancies exposed to RSVpreF soon after vaccine approval may have other characteristics associated with lower risk of key outcomes, such as preterm and stillbirth delivery, and will continue to be explored in an ongoing companion study as more data accrue.

The small elevated risk of pregnancy-associated hypertensive disorders identified in this study has been observed in other studies that have used an unvaccinated comparator matching design, including a VSD study (ARR, 1.09; 95% CI, 1.03-1.15)[50] and a companion study (adjusted hazard ratio, 1.07; 95% CI, 0.92-1.24),[49] although the results of the latter were not statistically significant. Other studies have reported mixed findings both in terms of magnitude and statistical significance.[45,46,51] Composite outcome definition heterogeneity may contribute to the mixed findings about risk for pregnancy-associated hypertensive disorders. To prioritize timeliness of results, we did not include postpartum hypertension in the composite, which is known to occur in more than 10% of pregnancies,[52,53] whereas other studies do include this safety concern in their definition. When we reviewed a subset of health records for pregnancies through 8 weeks post partum, we found stark differences in trajectories for different components of this composite outcome: gestational hypertension (the most observed component) typically surfaced at delivery and resolved post partum, whereas HELLP and similar diagnoses were associated with prolonged hospitalization. Future studies should analyze individual components to further quantify potential risks.

Where available, we used validated outcome algorithms with high positive predictive value,[54,55] but none existed for PROM, preterm PROM, or LGA, leaving room for outcome misclassification. Another study that used an algorithm similar to ours reported a positive predictive value of only 54.9%,[56] suggesting that the outcome algorithm for preterm PROM may have been inadequate to measure preterm status. PROM incidence in this study (14.1% vs 13.1%) was slightly higher than some reported estimates (8%-11%),[57,58] and our record review follow-up indicated that some PROM cases had both codes for preterm birth and full-term status. Our use of nominal CIs that did not adjust for multiple testing may explain the discrepancies between exceeding statistical thresholds for detection and CI estimates for some of these outcomes.

The MaxSPRT statistics used in each sequential analysis were 1-sided and optimized to detect elevated risks.[34] Thus, estimates falling below the null (such as for preterm birth, preterm labor without delivery, and stillbirth) were interpreted as not meeting the predefined thresholds for elevated risk. Generally, RRs below the null are important and deserve more specific attention, particularly with respect to ruling out potential biases and competing explanations for the observed associations. While crude and adjusted estimates were similar (possibly suggesting that measured stratification covariates had limited impact), differences between crude and adjusted estimates may reflect confounding control and do not, on their own, establish the presence or lack of unmeasured confounding.

This cohort study is only 1 analysis in a multiphase approach to monitoring the safety of RSVpreF vaccination during pregnancy. Accordingly, the present findings should be interpreted as hypothesis generating and are intended to inform ongoing surveillance rather than serving as definitive causal estimates. Preliminary results of a companion cohort study, with effect estimates for these outcomes with different control groups and improved confounding control, were recently published,[49] and additional studies with larger and more diverse populations of pregnancies[11] are planned.

Strengths and Limitations

Including 2 different comparator cohorts, both of whom were actively vaccinated, strengthened this study. First, it ensured that statistical analyses could be performed in the first surveillance period with a historical comparator; sample sizes were insufficient to begin concurrent comparator analyses until the second surveillance period, resulting in signals typically associated with historical comparator analyses by at least 1 surveillance period. Second, it reduced confounding by indication.[59] Third, it reduced anchoring bias.[60]

Nevertheless, limitations stemming from our sequential analysis framework remain. The historical analysis may have been susceptible to secular patterns, although the sensitivity analysis added confidence because even increasing the detection criteria to account for this potential bias still resulted in a statistically significant increased risk of pregnancy-associated hypertensive disorders. Additionally, consideration of multiple comparator vaccines may have introduced the potential for effect modification.

We used outcome-specific covariate stratification to address as much confounding as possible, and all pregnancy-related outcomes were stratified on high-risk status for preterm birth. Groups were well balanced on this composite metric, but pregnancies receiving RSVpreF were more likely than comparator cohorts to have evidence of assisted reproduction (an independent risk factor for pregnancy-associated hypertensive disorders[43]). Additionally, the small sample sizes early in the postapproval period meant that broader strata than ideal were necessary and some outcomes (including infant outcomes and stillbirth) could not undergo additional stratification. This may have allowed the residual imbalance in characteristics, such as maternal age, gestational week at RSVpreF exposure, and vaccination season, to affect the findings. While other confounding control techniques (such as propensity score matching) are advantageous for many questions on drug safety, they are often not appropriate when assessing rare events during the initial uptake of a new drug or vaccine due to their instability in these settings and the resulting potential loss of information on serious adverse effects.[61] Furthermore, having such small sample sizes in the first surveillance period precluded the use of propensity score techniques, but the companion study that applied 1:1 propensity score matching to unexposed pregnancies[49] did not confirm these findings of statistically significant increased risks for certain safety outcomes.

Other limitations related to our use of health plan data include that nonmedically attended events and differences in documentation and coding practices may lead to outcome misclassification and that key clinical measurements (such as blood pressure) were not available. Race and ethnicity were not adjusted for due to large data missingness at the research partner sites, which may have led to potentially artifactual risk estimates for outcomes (eg, stillbirth[62,63]) that have clear confounding among racial and/or ethnic minority individuals; a future study including Medicaid data will better capture these important confounders. Including data from several sites increased sample sizes and improved generalizability, and leveraging the Sentinel System infrastructure ensured the data adhered to the highest quality standards[64,65]; we mitigated potential intersite differences by performing outcome-specific stratification on research partner site. We did not require mother-infant linkages when estimating infant outcomes, which lowered their reported incidence, but the supplemental analysis restricted to research partners with available linkages produced IPs similar to the published estimates.[47,66]

Conclusions

In this cohort study of a large and diverse population of pregnancies using sequential surveillance methods, we did not observe an increased risk of preterm birth associated with RSVpreF vaccination during pregnancy. However, we did identify potential increased risks of pregnancy-associated hypertensive disorders and PROM. While these findings provide a preliminary estimate of the magnitude of potential risks, evaluation of potential risks should always occur within the framework of a vaccine's overall risk-benefit assessment. Statistically significant findings in these sequential analyses cannot confirm a causal association, given limited confounding control. A full epidemiological study, including adjustment for immunocompromising conditions, risk factors for pregnancy-associated hypertensive disorders and PROM, and finer control for gestational age at vaccination, is forthcoming and is expected to yield more precise and robust risk estimates for RSVpreF vaccination during pregnancy.

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SUPPLEMENT 1.

SUPPLEMENT 2.