

RSVpreF Vaccine, Preterm Birth, and Small for Gestational Age at Birth Preliminary Results from The Vaccine Safety Datalink

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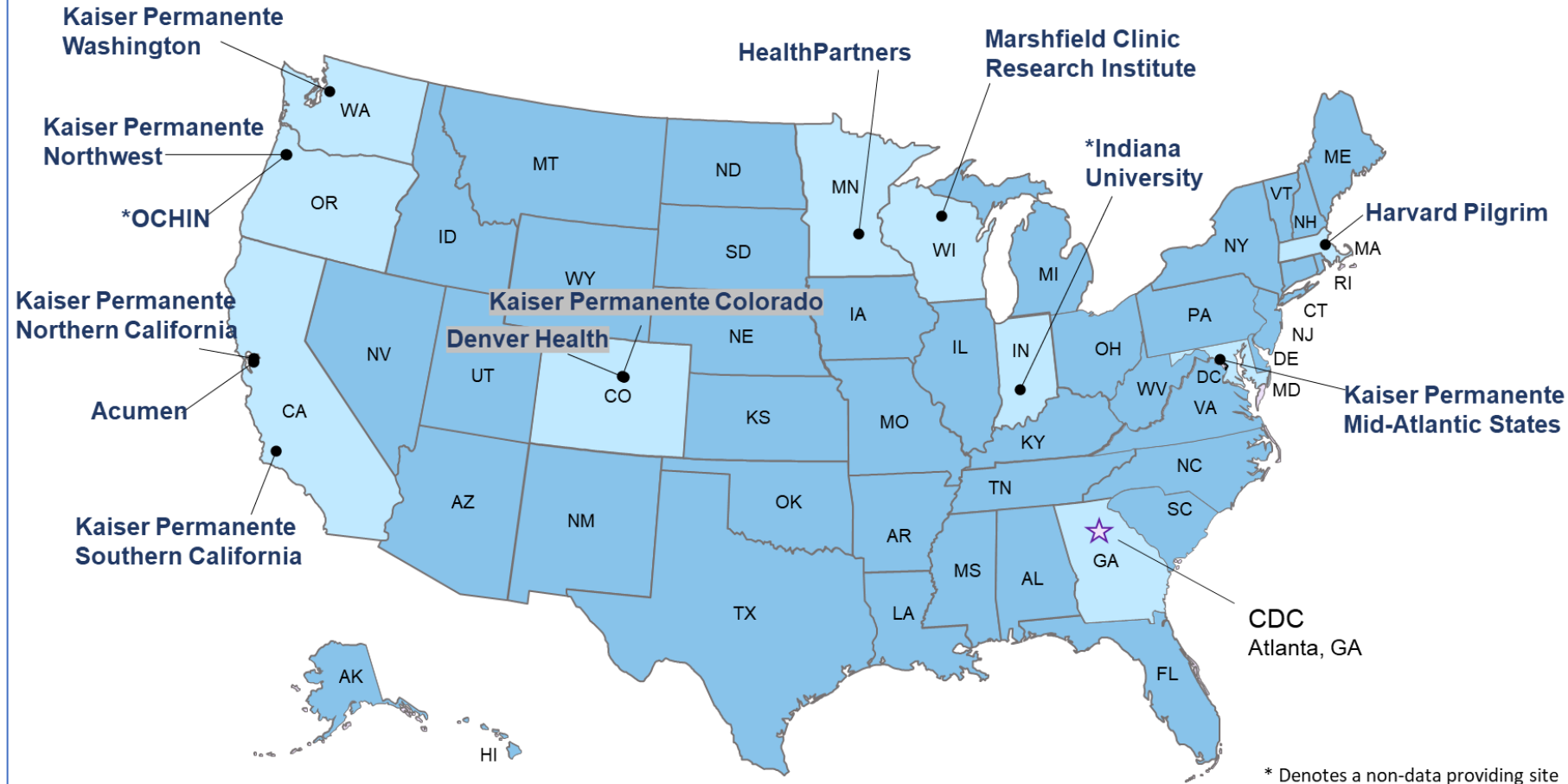
ACIP

October 23, 2024



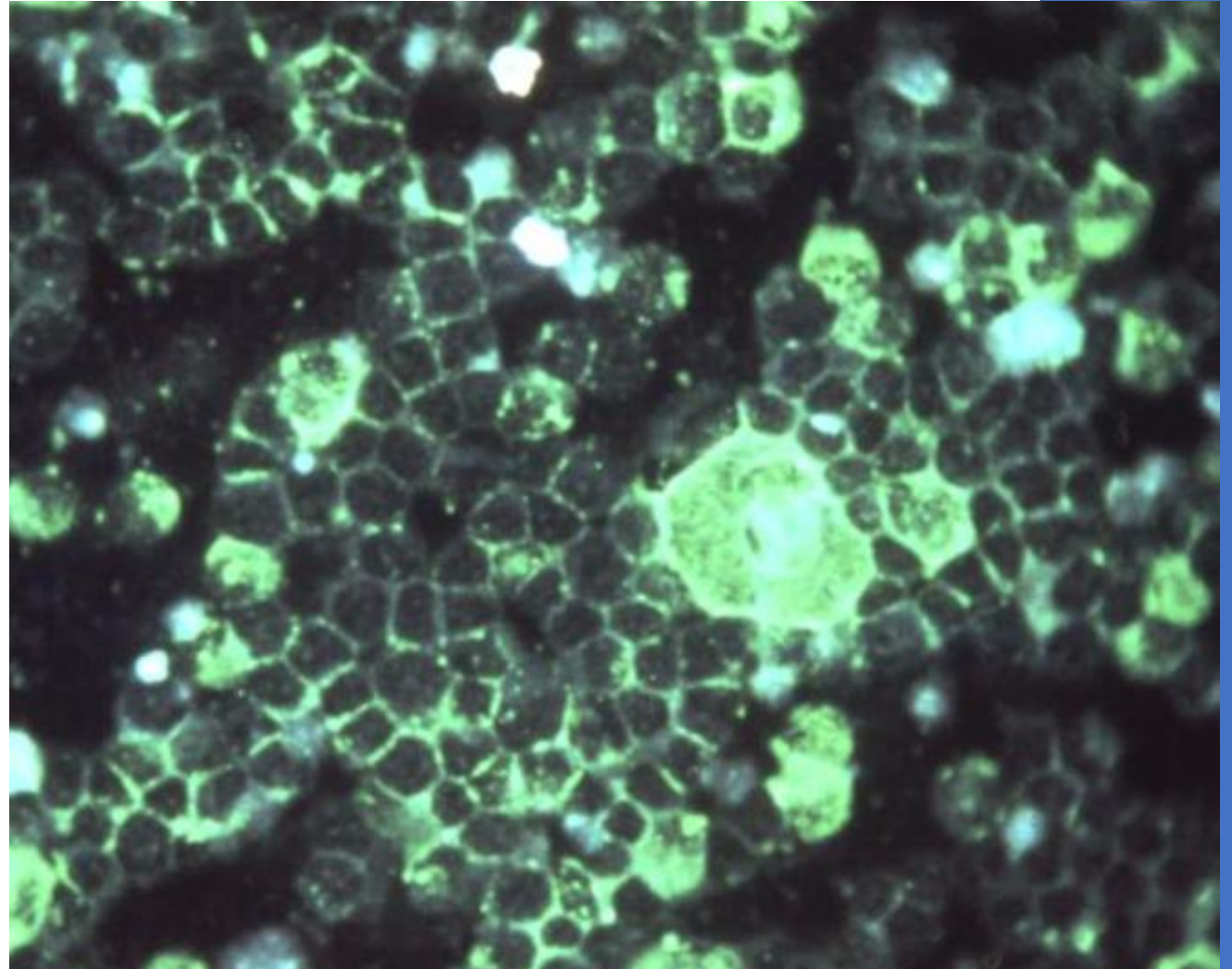
Vaccine Safety Datalink, 2024

- Collaborative project between CDC and 13 integrated healthcare organizations
- Monitors safety of vaccines used in the U.S., primarily through observational multisite studies of rare and serious events following vaccination
- Includes data on ~15.5 million individuals across all sites annually (~3-4% of U.S. population)
- **Annual birth Cohort ~ 115,000**
- Data is organized using a common data dictionary with standardized coding systems



Prenatal RSV Vaccine 2023–2024 season

- ACIP recommendation 9/22/23:
 - 32–36 weeks gestation
 - Seasonal administration
September – January
- Most VSD sites did not start vaccinating until late October or November 2023
- One VSD site did not administer vaccine in health system
- Two VSD sites continued administrations through 2/29/24



Evaluation of Preterm Birth and SGA at Birth following prenatal RSV vaccine

- **Perform a matched analysis comparing pregnant persons exposed to RSV vaccine with pregnant persons unexposed at the same gestational week to evaluate**
 - **Preterm birth (<37 weeks gestation)**
 - **Small for gestational age (SGA) at birth (<10th percentile)**

Preterm birth

- **Definition: live birth occurring prior to 37 weeks gestational age**
- **RSVpreF clinical trial identified an imbalance in preterm births in vaccinated group compared to placebo group¹**
 - **Most were late preterm (34–<37 weeks)**
 - **Most occurred >30 days after vaccination**
 - **Most prominent in a single country**
- **GSK RSV prenatal vaccine clinical trial halted due to imbalance in preterm birth in vaccinated²**

¹Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med*. 2023 Apr 20;388(16):1451-1464. doi: 10.1056/NEJMoa2216480. Epub 2023 Apr 5. PMID: 37018474.

²Dieussaert 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 Mar 14;390(11):1009-1021. doi: 10.1056/NEJMoa2305478. PMID: 38477988.

Small for Gestational Age (SGA) at birth

- **Definition: Birthweight below 10% for gestational age and sex**
- **Causes**
 - **Constitutionally small – parental genetics**
 - **Intrauterine growth restriction (IUGR) –**
 - **Placentation issues → decreased placental blood flow**
 - **Maternal conditions (chronic heart or lung disease, HTN, CKD, DM, infection, cigarette use, alcohol or drug use, malnutrition, infections)**
 - **Genetic or structural abnormalities**
- **Early onset IUGR <32 weeks gestational age usually more severe with higher morbidity/mortality**
- **SGA at birth not evaluated in clinical trial, but imbalance in low birth weight ($\leq 2500\text{g}$) among RSVpreF vaccinated**

Matched analysis methods

- **Pregnant persons 16–49 years with gestational age 30–<37 weeks during 9/22/2023–1/31/24 (2/29/24 for two sites)**
- **Target trial emulation design to compare vaccinated and unvaccinated persons at each gestational week**
 - **Pregnant persons exposed to RSVpreF vaccine matched 1:1 on VSD site and propensity to be vaccinated to unvaccinated pregnant persons during same gestational week**
 - **Unvaccinated index date = gestational day of vaccine**
 - **Matched pair censored if unvaccinated person later vaccinated**
- **Propensity to be vaccinated calculated individually for 2 sites and for all other sites combined**
 - **Maternal age at pregnancy start, calendar week at pregnancy start, number of weeks with prenatal care encounters, race/ethnicity, comorbidities (hypertension, diabetes mellitus, gestational hypertension, gestational diabetes, obesity, substance use), history of preterm labor, poor fetal growth, supervision of high-risk pregnancy, enrollment, and VSD site**

Analysis

- **For SGA at birth, matched sets excluded if infant weight not available for either infant in matched pair**
- **Log binomial model with robust variance to estimate risk ratios with 95% confidence intervals**
 - **Overall (30–<37 weeks gestational age)**
 - **Restricted to vaccines administered during 32–<37 weeks gestational age (ACIP recommendation)**

Matched Cohort* characteristics, N = 14,099

Age group	RSV Vaccinated, n(%)	Unvaccinated match, n(%)
• 16–24 years	1418 (10.1)	1607 (11.4)
• 25–29 years	3180 (22.6)	3471 (24.6)
• 30–34 years	5514 (39.1)	5325 (37.8)
• 35–39 years	3320 (23.5)	3050 (21.6)
• 40–49 years	667 (4.7)	646 (4.6)
Race/Ethnicity		
• Asian	3061 (21.7)	2651 (18.8)
• Black	873 (6.2)	1007 (7.1)
• Hispanic	4488 (31.8)	4730 (33.5)
• White	4604 (32.7)	4595 (32.6)
• Other/Unknown	1073 (7.6)	1116 (7.9)

*Not unique individuals due to crossover from unvaccinated to vaccinated

Preterm birth^a risk among pregnant persons receiving RSV vaccine and unvaccinated matches, 30–36 weeks GA

	Matched pairs, N	RSV vaccinated		Unvaccinated match		Risk Ratio (95% CI)
		N events*	Preterm birth %	N events*	Preterm birth %	
Overall ^b	14,099	571	4.0	637	4.5	0.90 (0.80–1.00)
32–36 weeks	13,965	563	4.0	628	4.5	0.90 (0.80–1.00)

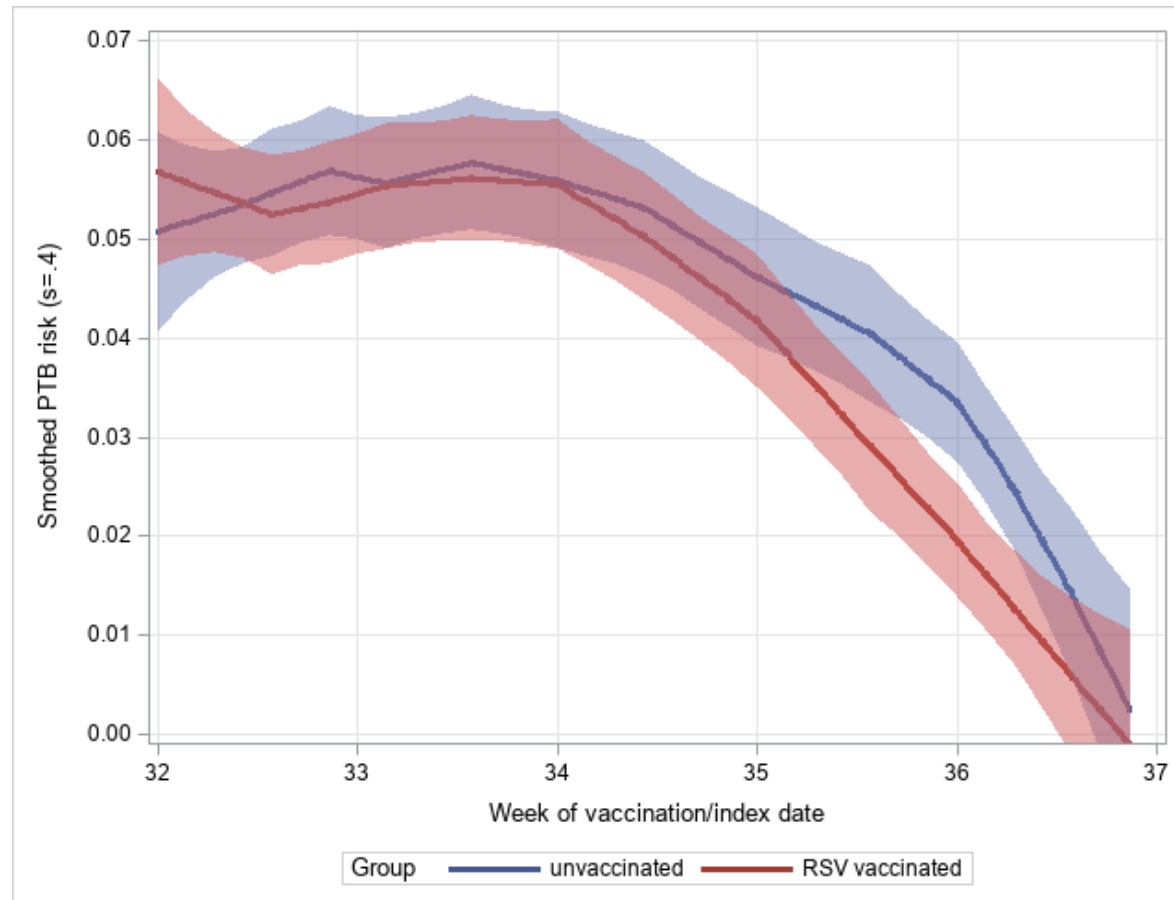
GA = gestational age

^aPreterm birth = birth <37 weeks gestational age

^bN RSV vaccines administered <32 weeks = 134 (0.95%)

*Events only included through date of censoring when unvaccinated pair crosses over to vaccinated

Preterm birth risk by GA* at vaccination or index date for matched sets 32–36 weeks GA*



Smoothed curve showing average preterm birth risk (line) by gestational age at vaccination or index date with 95% confidence band (shading)

*GA = gestational age

SGA^a at birth risk in infants born to RSV vaccinated pregnant person or unvaccinated pregnant matches, 30–36 weeks GA^b

	Matched pairs, N	RSV vaccinated		Unvaccinated match		Risk Ratio (95% CI)
		N events*	SGA at birth %	N events*	SGA at birth %	
Overall	11,920	800	6.7	781	6.6	1.02 (0.93–1.13)
32–36 weeks	11,819	799	6.8	774	6.5	1.03 (0.94–1.14)

^aSGA at birth = “Small for Gestational Age”; birthweight <10th percentile for gestational age compared with a U.S. reference population¹

^bGA = gestational age

*Events only included through date of censoring when unvaccinated pair crosses over to vaccinated

Note: 11,920 matched pairs with complete infant weight data (85%)

Conclusions and next steps

- **RSVpreF vaccine is not associated with increased risk for preterm birth or SGA at birth**
- **Currently working on analysis for acute safety outcomes, stillbirth, and preeclampsia/eclampsia/HELLP**
- **Chart review for stillbirths and some acute safety outcomes (i.e., anaphylaxis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, transverse myelitis, venous thromboembolism, pulmonary embolism, and myocarditis/pericarditis)**
- **Preeclampsia/eclampsia/HELLP – association with hypertensive disorders of pregnancy in recent study¹ and clinical trial**

¹Son M, Riley LE, Staniczenko AP, et al. Nonadjuvanted Bivalent Respiratory Syncytial Virus Vaccination and Perinatal Outcomes. *JAMA Netw Open*. 2024;7(7):e2419268. doi:10.1001/jamanetworkopen.2024.19268

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Other VSD sites

- Acumen
- Denver Health
- Harvard Pilgrim
- Indiana University
- Kaiser Permanente Northwest
- Kaiser Permanente Colorado
- Kaiser Permanente Southern California
- Kaiser Permanente Northern California
- Kaiser Permanente Washington
- Kaiser Permanente Mid-Atlantic States
- Marshfield Clinic
- OCHIN