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Association Between COVID-19 Vaccination During Pregnancy and Safety Among Infants

Elizabeth M. Quincer^{1,*}, Gabriela Vazquez-Benitez², Eric S. Weintraub¹, Kimp Walton¹, Lily Wang¹, Kimberly K. Vesco³, Michelle L. Henninger³, Matthew F. Daley⁴, Simon J. Hambidge⁵, Joshua T.B. Williams⁵, James G. Donahue⁶, Ousseny Zerbo⁷, Darios Getahun^{8,9}, Lisa A. Jackson¹⁰, Candace C. Fuller¹¹, Heather S. Lipkind¹², Allison L. Naleway³, Michael M. McNeil¹, Elyse O. Kharbanda²

¹Immunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA, United States;

²Pregnancy and Child Research Center, HealthPartners Institute, Minneapolis, MN, United States;

³Center for Health Research, Kaiser Permanente Northwest, Portland, OR, United States;

⁴Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, United States;

⁵Ambulatory Care Services, Denver Health, Denver, CO, United States;

⁶Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute, Marshfield, WI, United States;

⁷Vaccine Study Center, Kaiser Permanente Northern California, Oakland, CA, United States;

⁸Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States;

⁹Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, United States;

¹⁰Washington Health Research Institute, Kaiser Permanente Washington, Seattle, WA, United States;

¹¹Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, United States;

¹²Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY, United States

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*Corresponding author: Elizabeth M. Quincer, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop H16-3, Atlanta, GA 30329, United States (equincer@cdc.gov).

Author contributions

E.M.Q., E.O.K., G.V.B., E.S.W., and M.M.M. conceptualized the study and wrote the protocol. E.M.Q., G.V.B., K.W., E.S.W., and L.W. performed and reviewed the analyses. E.M.Q. wrote the initial draft of the manuscript. All authors helped interpret the findings and reviewed, edited, and approved the final version of the manuscript.

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Abstract

Background: Vaccination during pregnancy prevents disease in both the pregnant woman and infant via transplacental antibody transfer which may interfere with infant immune response to early childhood vaccination. Data on safety of COVID-19 vaccination during pregnancy in relation to non-targeted infant infections are lacking.

Methods: We conducted a retrospective cohort study of pregnancies from May 17, 2020, through February 15, 2021, across eight integrated healthcare systems in the Vaccine Safety Datalink to evaluate receipt of COVID-19 vaccination during second or third trimester of pregnancy on medically attended encounters for infections among infants up to 6 months. Adjusted incidence rate ratios (aIRRs) with 95% confidence intervals were estimated, controlling for potential confounders using inverse probability of treatment weighting.

Results: Among 42 940 pregnancies, 14 762 (34.4%) were exposed to COVID-19 vaccination during second or third trimester of pregnancy. COVID-19 vaccination during second or third trimester was not associated with an increase in non-targeted infant medically attended respiratory infections (aIRR 0.86, 95% CI 0.77, 0.95), including respiratory syncytial virus (RSV) (aIRR 0.78, 95% CI 0.65, 0.93) and was not associated with infant bloodstream (aIRR 1.03, 95% CI 0.77, 1.37) or meningial (aIRR 0.54, 95% CI 0.19, 1.56) infections up to 6 months of life.

Conclusions: We found no increased risk for non-targeted medically attended infant respiratory infections and no association with bloodstream or meningial infections from birth to 6 months of life following COVID-19 vaccination during second or third trimester of pregnancy. These findings support COVID-19 vaccination safety during pregnancy on the risk of non-targeted infant infections.

Lay summary

Among 42 940 pregnancies from eight health systems in the Vaccine Safety Datalink, receipt of COVID-19 vaccination during second or third trimester of pregnancy was not associated with increased rates of non-targeted infections among infants up to 6 months of life.

Keywords

vaccine safety; pregnancy; non-targeted infections; COVID-19

INTRODUCTION

Vaccines administered during pregnancy protect both the pregnant woman and infant against morbidity and mortality due to vaccine-targeted infections.¹ Vaccines are administered to healthy pregnant populations for this protection, and as such, rigorous assessment of benefits as well as local, systemic, pregnancy, birth, and infant safety outcomes is crucial.² It is critical that protection against vaccine-targeted infections does not come with an increase in non-vaccine-targeted (non-targeted) infections among infants.³ Antibodies produced in response to vaccination during pregnancy and transferred to the fetus may interfere with the infant's immune response to targeted vaccination during childhood.^{4,5} This blunting effect on infant response to vaccination following tetanus, diphtheria, and pertussis (Tdap) and influenza vaccines administered during pregnancy has been shown to have a negligible

impact on clinical outcomes including infant hospitalization and mortality.⁶ Childhood immune responses to vaccination for non-targeted infections may also be impacted by antibody interference from vaccination during pregnancy, but fewer data exist.⁷

The possibility that vaccination may increase general susceptibility to infection or have “non-specific effects” in the pregnant woman or infant is an evolving area of study.⁸ At least six non-live vaccines, including diphtheria-tetanus-pertussis and influenza vaccines, have shown a possible impact of non-specific effects among vaccinated children, particularly females.⁸ Meta-analyses across four randomized controlled trials in low- and middle-income countries of inactivated influenza vaccination among pregnant women have studied the potential that nonspecific effects could impact non-targeted infections in infants born to women vaccinated during pregnancy. An increase in non-influenza infections in both pregnant women and infants up to 6 months of life was found.⁹ Observational data on the risk for non-targeted infections following influenza vaccination administered during pregnancy have been inconsistent^{10,11,12} Additionally, inflammatory responses elicited by vaccination in pregnant women may have protective or adverse implications for the fetal immune system.^{3,13,14}

Receipt of COVID-19 vaccination during pregnancy protects infants up to 6 months of life from SARS-CoV-2 infection and hospitalization due to COVID-19.^{15,16} Data from numerous observational studies of antenatal COVID-19 vaccination have not indicated an adverse safety profile for local, systemic, pregnancy, birth, and perinatal outcomes.^{17–27} The few studies that have evaluated infant outcomes outside of the perinatal period have found no association between COVID-19 vaccination during pregnancy and hospital admission up to 6 months of life or neurodevelopment at 12 and 18 months of life.²⁸ Data on COVID-19 vaccination administered during pregnancy and safety in relation to non-targeted infant infections are lacking. We performed a study of infections from birth to six months of life following COVID-19 vaccination administered during second or third trimester of pregnancy among live-born infants in the Vaccine Safety Datalink (VSD).

METHODS

Study Design and Data Sources

We conducted a retrospective cohort study across eight integrated healthcare systems in the VSD to evaluate associations between receipt of COVID-19 vaccination during second or third trimester of pregnancy and medically attended encounters for infections among infants. The VSD is a collaboration between the Centers for Disease Control and Prevention (CDC) and several integrated healthcare organizations across the United States which aims to monitor the safety of vaccines and conduct studies of rare and serious adverse events following immunization, including vaccines administered during pregnancy, using electronic health data.^{29,30} While the VSD represents a highly insured population, as of 2023, it was estimated there were over 1.9 million Medicaid members in the VSD, which represents approximately 13.1% of the VSD population.³¹ This public health surveillance activity was reviewed by CDC and by the institutional review boards of all participating VSD sites, deemed not research, and was conducted consistently with applicable federal law and CDC policy.¹

Study Population and Follow-Up

Data for this cohort study came from eight VSD sites (Denver Health; HealthPartners Institute; Marshfield Clinic; and Kaiser Permanente: Colorado; Northern California; Northwest; Southern California; Washington). Women in the VSD aged 16–49 years at pregnancy start, with a pregnancy start date from May 17, 2020, through February 15, 2021, identified using a validated pregnancy episode algorithm, were included in the cohort.³⁰ Pregnant women were required to have at least one antenatal care, delivery, or postpartum visit; to be continuously enrolled from pregnancy start to pregnancy end; and to have their pregnancy end in a singleton, live birth, linked to an infant with enrollment in the first month of life, for at least 30 consecutive days, who had at least one inpatient or outpatient visit. Follow-up began on the infant's date of birth and continued up to 6 months of life.

Exposure

The exposure of interest was the receipt of one or more doses of any COVID-19 vaccination during second or third trimester of pregnancy, defined as week 14 through the end of pregnancy. The unexposed group included women who received COVID-19 vaccination pre- and post-pregnancy, during first trimester, and those who were unvaccinated for COVID-19. Those vaccinated in first trimester were considered unexposed, given minimal transplacental antibody transfer following first trimester vaccination.³² COVID-19 vaccination was identified from standardized VSD files, incorporating electronic health records, claims, and state and regional immunization information system data.

Safety Outcomes

Primary outcomes were incident, non-targeted respiratory, bloodstream, and meningeal diagnoses of respiratory syncytial virus (RSV), influenza, bronchiolitis, bacterial pneumonia, other lower respiratory tract illnesses, sepsis, and bacterial bloodstream infection, other bloodstream infections, bacterial meningitis, and other meningeal infections. COVID-19 was included as a proof-of-concept outcome, given the known infant protection conferred by COVID-19 vaccination during pregnancy.^{15,16} Outcomes were defined from the *International Classification of Disease, Tenth (ICD-10) Revision, Clinical Modification*. COVID-19, RSV and influenza were also identified via laboratory records, which included any available molecular, antigen, or viral culture-based test obtained at the discretion of the treating clinician. Outcomes and laboratory records were obtained from electronic health record data from inpatient, emergency department, and outpatient medically attended clinical encounters. If an infant had multiple codes for the same diagnosis, the earliest date was chosen as the incident date of onset. A single infant could have multiple diagnoses that were determined to be distinct clinical entities.

Covariates

Covariates were determined a priori and were included in propensity scores to account for potential sources of confounding. These included the pregnant woman's age and calendar week at pregnancy start, race and ethnicity, prenatal care adequacy, smoking status,

¹See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq

COVID-19 diagnosis in pregnancy, average state-level percentage of positive COVID-19 test results during pregnancy,³³ other vaccines received (Tdap vaccine during pregnancy and influenza vaccine during the influenza season proximally corresponding to pregnancy), neighborhood poverty index, and VSD site. Prenatal care adequacy was determined using the Kessner Adequacy of Prenatal Care Utilization Index, based on the timing of prenatal care initiation and the number of prenatal care encounters.³⁴ Neighborhood poverty level was measured as the percentage of households in an individual's Census tract whose income was below 100% of the federal poverty level, based on the American Community Survey 5-year summary for 2020.³⁵ Age and calendar week at pregnancy start were modeled using a smoothing parameter approach.

Statistical Analyses

Frequency distributions were used to describe baseline variables of interest. Standardized mean differences (SMDs) were compared for each variable by exposure status, with a difference of less than 0.1, considered well-balanced. A propensity score estimating the probability of receipt of a COVID-19 vaccine during the second or third trimester of pregnancy was determined for each pregnancy using logistic regression based on the covariates. Stabilized inverse probability weights were generated as the inverse of the propensity score for the exposed and the inverse of one minus the propensity score for the unexposed. The effectiveness of the stabilized weights in reducing potential confounding was assessed by applying the weights to the cohort and re-estimating the SMD for each covariate.

Incidence rates (IRs) up to 6-months of follow-up and 95% CIs were computed for the exposed and unexposed groups for all outcomes. Poisson regression with robust variance utilizing generalized estimating equations was used to estimate unadjusted incidence rate ratios (IRRs) and adjusted IRRs (aIRRs). These models incorporated the inverse probability of treatment weights to determine the association between receiving a COVID-19 vaccination during second or third trimester of pregnancy compared to not receiving a COVID-19 vaccine during these trimesters.

We performed a stratified analysis for RSV, considering the atypical circulation that occurred during the COVID-19 pandemic,³⁶ dividing the time for infant follow-up into four equal periods defined on the infant's date of birth. Subgroup analyses were conducted for specific outcomes, including laboratory-confirmed outcomes (COVID-19, RSV, and influenza), inpatient encounters, and encounters within the first month of life. We also performed secondary analyses utilizing exposure definitions excluding receipt of a COVID-19 vaccine administered within 6 weeks postpartum if the mother was breastfeeding, given this is another biologically plausible window for antibody transfer, and excluding those vaccinated in the first trimester.

RESULTS

We included 42 940 pregnancies (Supplement Figure S1); of these, 14 762 (34.4%) were exposed to COVID-19 vaccination during second or third trimester, and 28 178 (65.6%) were unexposed in second or third trimester. Those exposed were more likely to be older

at pregnancy start (median [interquartile range [IQR]]; 33[5] vs 31[6] years) and to have received Tdap (96.0% vs 87.0%) and influenza (86.0% vs 65.0%) vaccines, compared to those unexposed. The exposed group was less likely to live in an area with a higher neighborhood poverty index (median [IQR]; 0.05[0.06] vs 0.06[0.08]) and to have a higher average state-level percentage of COVID-19 test positivity during pregnancy (median [IQR]; 18.6[10.0] vs. 19.0[4.9]) than the unexposed group. Self-reported race and ethnicity of the pregnant woman also varied by exposure status, with those exposed more likely to be non-Hispanic Asian (27.7% vs 18.2%) or non-Hispanic White (40.7% vs 36.0%) and less likely to be non-Hispanic Black (3.4% vs 7.4%) or Hispanic (24.8% vs 35.0%) than those unexposed. After inverse probability of treatment weighting, all covariates were well-balanced across exposure groups and all SMDs were less than 0.1 (Table 1). Most COVID-19 vaccines used during the study period in the VSD population were mRNA COVID-19 vaccines, mRNA-1273 (Moderna) (33.6%) and BNT162b2 (Pfizer-BioNTech) (63.8%), with a minority of adenovirus-vectored COVID-19 Janssen (Johnson & Johnson) vaccine (2.7%) used.

We found no increased risk for non-targeted respiratory infections (aIRR 0.86 [95% CI, 0.77, 0.95]) up to 6 months of life comparing infants exposed to COVID-19 vaccination during second or third trimester to unexposed infants. This included no increased risk between COVID-19 vaccination during second or third trimester and RSV infection (aIRR 0.78 [95% CI, 0.65, 0.93]) up to 6 months of life as compared to those unexposed. There were also no statistically significant differences in respiratory infections, including influenza, bronchiolitis, bacterial pneumonia, and other lower respiratory illnesses up to 6 months of life among infants exposed to COVID-19 vaccination during second or third trimester compared to those unexposed (Table 2). We found no statistically significant association between COVID-19 vaccination during second or third trimester and bloodstream infections and meningial infections among infants up to 6 months of life as compared to those unexposed (Table 2).

Results of a stratified analysis for RSV showed few cases of RSV and no association with COVID-19 exposure during the second or third trimester of pregnancy from November 17, 2020, through February 21, 2021 (aIRR 0.00 [95% CI 0.00, -]) and from February 21, 2021, through May 28, 2021, (aIRR 0.89 [95% CI 0.55, 1.43]). Across the second two quartiles, May 28, 2021, through September 01, 2021 (aIRR 0.76 [95% CI 0.58, 0.99]) and September 01, 2021, through December 07, 2021, (aIRR 0.75 [95% CI 0.57, 0.98]) no increase in risk was observed (Table 3). Results of subgroup analyses of the association between COVID-19 vaccination during the second or third trimester of pregnancy and laboratory-confirmed outcomes (RSV and influenza), inpatient only encounters, and encounters within the first month of life were similar in magnitude and direction to those of the primary analyses (Table 4). Secondary analyses, excluding 6505 women vaccinated within 6 weeks postpartum while breastfeeding, and 2319 women vaccinated during the first trimester, found similar associations (Supplement Table S1, Table S2).

For the control outcome, we found a decrease in COVID-19 (aIRR 0.65 [95% CI, 0.57, 0.74]) among infants up to 6 months of life when exposed versus unexposed to COVID-19

vaccination during second or third trimester, including for laboratory-confirmed, inpatient, and infections within the first 6 months of life (Table 5).

DISCUSSION

In this large, multisite study of more than 42 940 pregnancies ending in singleton live birth, receipt of COVID-19 vaccination in second or third trimester of pregnancy was not associated with medically attended infant respiratory, bloodstream or meningial infections from birth to 6 months of life. Our findings were consistent in secondary analyses that evaluated receipt of COVID-19 vaccination during second or third trimester on laboratory confirmed outcomes, inpatient only encounters, encounters within the first month of life, and when excluding from analyses those vaccinated within 6 weeks postpartum while breastfeeding and those vaccinated in the first trimester.

Few studies have examined the safety of antenatal COVID-19 vaccination in relation to non-targeted infectious outcomes. There is biologic plausibility to suggest antenatal vaccination could impact susceptibility to infections in early life. Antibodies produced from vaccination during pregnancy may blunt the infant immune response to routine childhood vaccination for both vaccine-targeted and non-targeted pathogens.^{4,5,7} Non-specific effects from vaccination during pregnancy may increase the occurrence of non-vaccine-targeted infections in infants through the induction of innate immune tolerance and repression of non-specific T-cell reactivity.^{9,37} An excessive inflammatory response during pregnancy could impact fetal immune development through impaired expansion of fetal thymic cells, disturbance of Th1/Th2 balance, epigenetic modification of immune-related genes, and suppression of fetal lymphocyte proliferation.¹³ Our findings are reassuring and inform the safety for a range of respiratory, bloodstream, and meningial infections up to 6 months of life following COVID-19 vaccination during second or third trimester of pregnancy. Our results are in line with Norman et al. who in 2024 included infections in the broad range of neonatal outcomes examined following mRNA COVID-19 vaccination during pregnancy. Diagnoses of myocarditis and septicemia were included within the first 4 weeks of life and no cases of myocarditis and no association between mRNA COVID-19 vaccination during pregnancy and neonatal septicemia was found.²⁷ While our findings are reassuring, further study of non-targeted infections, immune and inflammatory outcomes following COVID-19 and other vaccines administered during pregnancy is needed.

The negative association we found for infant RSV infection may be due to residual confounding, resulting from healthy vaccinee bias, which suggests healthier individuals are more likely to be vaccinated, exaggerating the beneficial effects of vaccination,³⁸ or factors including breastfeeding, siblings in the home or household size, childcare attendance, parental educational status and workplace, masking, and other infectious risk mitigation behaviors.^{39,40} The decrease in infant COVID-19 disease we found is expected given known infant protection following COVID-19 vaccination during pregnancy^{15,16}; however, healthy vaccinee bias could also have impacted these findings. Our study partially addresses healthy vaccinee bias as both the unvaccinated and those vaccinated outside of the primary period for antibody transfer for infant infectious protection were included in our unexposed group; furthermore, healthy vaccinee bias in the obstetrical population may be less predictable

depending on local vaccine recommendations and practices that may impact vaccine uptake.³⁸

We attempted to address the atypical seasonality for RSV and other respiratory viruses that occurred during the COVID-19 pandemic³⁶ with stratified analyses. When RSV circulation was low, we found no association. When RSV circulation was generally similar to prior seasons, we found a negative association seen across the entire period of follow-up. Given the atypical respiratory viral seasonality that occurred during the COVID-19 pandemic, our findings would benefit from study during a period of more typical respiratory viral seasonality and a longer follow-up period. Given the evolving evidence base for vaccination during pregnancy, receipt of multiple recommended vaccines could contribute to the protective finding for RSV infection. Our study did not include the period when RSV vaccines were available for use during pregnancy. Medical practice can be informed by future studies that address how multiple vaccines interact when administered in a single pregnancy to understand the potential for effect modification and impact on early infant immune function.

Our study was subject to certain limitations. First, inherent differences in women who received vaccination while pregnant may exist, which we may not have been able to account for in our study, such as the healthy vaccinee bias, as noted above. Second, while it has been shown that the VSD population is representative of the general U.S. population on several key demographic and socioeconomic variables, differences still exist, which may limit the generalizability of our findings. Third, as a retrospective cohort study, data were limited to those attainable through automated electronic health records within the VSD. Given the complexity of the phased COVID-19 vaccination rollout based on high-risk groups in the United States,⁴¹ it is possible that some vaccines may have been missed or misclassified, potentially biasing results toward the null. Fourth, the potential for outcome misclassification exists, given that non-targeted infections were ascertained using electronically coded diagnoses and validated algorithms; chart review confirmation was not utilized. Our ability to confirm outcomes with laboratory data was limited to RSV, influenza, and COVID-19 given the complexity of attaining automated culture data for bloodstream and meningeal infections. Fifth, we only captured medically attended events, although the outcomes evaluated would generally involve medical encounters in infants less than 6 months of age. Sixth, while we were well-powered to assess more common outcomes, we had limited power to assess rare events such as bloodstream and meningeal infections, which would require a larger population to study. This limited our ability to determine the true association for outcomes where point estimates were elevated but had wide 95% CIs, and as such, these results should be interpreted with caution.

CONCLUSIONS

We found no increased risk for non-targeted medically attended infant respiratory infections and no association with bloodstream or meningeal infections from birth to 6 months of life following COVID-19 vaccination during the second or third trimester, supporting COVID-19 vaccination safety during pregnancy on the risk of non-targeted infant infections. Further study of childhood infections, the safety of multiple vaccines administered during

pregnancy, and longer-term immune and inflammatory outcomes following vaccination during pregnancy is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

K.K.V. has previously received grant funding from Pfizer Inc, for menopause-related research. D.G. received funding from NIH/NICHD, Garfield Memorial Fund, Bayer Pharma AG, Johnson & Johnson, and HOLOGIC Inc. for work unrelated to this manuscript. C.C.F. is employed at Harvard Pilgrim Health Care Institute, a non-profit organization that conducts work for government and private organizations, including pharmaceutical companies. H.S.L. was previously on the external independent Data Safety and Monitoring Board for Pfizer COVID-19 vaccine.

Data availability

Researchers outside of the Centers for Disease Control and Prevention and the Vaccine Safety Datalink (VSD) network may request access to VSD data to reanalyze specific datasets of published studies through the National Center for Health Statistics Research Data Center (NCHS RDC) for institutional review board approved projects. NCHS RDC will review the proposal and make a determination on the request based on the scientific and technical feasibility of the project.

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Table 1.

Baseline Characteristics by COVID-19 Vaccination Status Among 42 940 Pregnancies with Live Births with Pregnancy Episode start from May 17, 2020 to February 15, 2021 from Eight Vaccine Safety Datalink Sites

Characteristic	COVID-19 vaccination during pregnancy				
	Unweighted		IPTW		
	n (%), median (IQR)		%, median (IQR)		
	Exposed* (n = 14 762)	Unexposed† (n = 28 178)	Standardized difference (95% CI)	Exposed* (n = 14 762)	Unexposed† (n = 28 178)
Age (years)	33 (5)	31 (6)	0.322 (0.317, 0.327)	32 (7)	32 (7)
Race and Ethnicity					
Asian, non-Hispanic	4081 (27.7)	5138 (18.2)	0.225 (0.211, 0.240)	21.8	21.6
Black, non-Hispanic	500 (3.4)	2082 (7.4)	0.178 (0.158, 0.198)	5.8	6.0
Hispanic	3666 (24.8)	9852 (35.0)	0.223 (0.209, 0.237)	32.3	31.5
White, non-Hispanic	6004 (40.7)	10 148 (36.0)	0.0959 (0.0823, 0.109)	36.6	37.5
Unknown/other	511 (3.5)	958 (3.4)	0.00339 (−0.0188, 0.0256)	3.5	3.4
Poverty‡	0.05 (0.06)	0.06 (0.08)	0.209 (0.172, 0.245)	0.06 (0.07)	0.06 (0.07)
Prenatal care§					
Adequate	10 925 (74.0)	20 958 (74.4)	0.00846 (0.00584, 0.0228)	74.6	74.4
Intermediate	3614 (24.5)	6644 (23.6)	0.0211 (0.00666, 0.0356)	23.7	23.8
Poor	223 (1.5)	576 (2.0)	0.0404 (0.0144, 0.0664)	1.7	1.9
Smoking (any)	2430 (16.5)	5141 (18.2)	0.0471 (0.0317, 0.0625)	17.9	17.7
Maternal vaccines					
Tdap	14 177 (96.0)	24 533 (87.0)	0.327 (0.309, 0.345)	90.5	90.2
Influenza	12 693 (86.0)	18 319 (65.0)	0.503 (0.488, 0.518)	72.0	72.3
COVID-19 in pregnancy	781 (5.3)	2034 (7.2)	0.0797 (0.0604, 0.0989)	6.8	6.6
Percent high COVID-19 positivity ¶	18.6 (10.0)	19.0 (4.9)	0.213 (0.209, 0.217)	18.6 (7.3)	19.0 (5.6)
Propensity score mean (SD)	0.5 (0.2)	0.3 (0.2)	1.00 (0.977, 1.02)	0.3 (0.2)	0.3 (0.2)

Abbreviations: COVID-19, coronavirus disease 2019; IPTW, inverse probability of treatment weighting; IQR, interquartile range; CI, confidence interval; SD, standard deviation; Tdap, tetanus, diphtheria, and acellular pertussis.

* Vaccinated during the second or third trimester of pregnancy.

† Vaccinated pre-pregnancy, in the first trimester of pregnancy, post-pregnancy, and unvaccinated for COVID-19.

[‡]Neighborhood poverty level is measured as the percentage of households in an individual's Census tract whose income is below 100% of the federal poverty level, which came from the American Community Survey 5-year summary for 2020.

[§]Kessner Adequacy of Prenatal Care Utilization Index, which is based on the timing of the initiation of prenatal care and the number of prenatal care encounters¹.

//State-level percentage of positive COVID-19 test results during pregnancy, as defined by the average percent test positivity during a woman's pregnancy².

Table 2.

Association Between COVID-19 Vaccination During the Second or Third Trimester of Pregnancy and Infant Infectious Outcomes from Birth to 6 Months of Life Among 42 940 Pregnancies with Live Births with Pregnancy Episode Start from May 17, 2020 to February 15, 2021 from Eight Vaccine Safety Datalink Sites

Infectious outcome	COVID-19 vaccine exposed* (n = 14 762)		COVID-19 vaccine unexposed [†] (n = 28 178)		Incidence rate ratio	
	Events	IR per 6-months × 10 ⁻⁴ (95% CI) [‡]	Events	IR per 6-months × 10 ⁻⁴ (95% CI) [‡]	Crude IRR (95% CI)	Adjusted IRR (95% CI) [§]
Non-targeted respiratory infections	545	333 (305, 364) §	1052	389 (367, 413)	0.99 (0.89, 1.10)	0.86 (0.77, 0.95)
RSV	208	120 (110, 140)	409	150 (140, 170)	0.97 (0.82, 1.15)	0.78 (0.65, 0.93)
Influenza	15	9 (5, 15)	30	11 (7, 15)	0.95 (0.51, 1.77)	0.86 (0.45, 1.64)
Bronchiolitis	293	180 (160, 210)	563	210 (190, 230)	0.99 (0.86, 1.14)	0.88 (0.76, 1.02)
Bacterial pneumonia	41	28 (20, 38)	76	27 (21, 34)	1.03 (0.70, 1.51)	1.02 (0.70, 1.50)
Other lower respiratory	5	5 (2, 10)	9	3 (2, 6)	1.06 (0.36, 3.16)	1.62 (0.61, 4.29)
Bloodstream infections	68	49 (39, 62)	139	48 (40, 57)	0.93 (0.70, 1.25)	1.03 (0.77, 1.37)
Sepsis and bacterial	63	45 (36, 58)	127	44 (37, 52)	0.95 (0.70, 1.28)	1.03 (0.76, 1.39)
Other bloodstream	5	4 (2, 9)	13	4 (2, 8)	0.73 (0.26, 2.06)	0.94 (0.35, 2.52)
Meningeal infections	6	3 (1, 8)	18	6 (3, 9)	0.64 (0.25, 1.60)	0.54 (0.19, 1.56)
Bacterial meningitis	4	2 (1, 6)	11	3 (2, 6)	0.69 (0.22, 2.18)	0.59 (0.16, 2.26)
Other meningitis	2	1 (0, 5)	7	2 (1, 5)	0.55 (0.11, 2.63)	0.48 (0.087, 2.64)

Abbreviations: COVID-19, coronavirus disease 2019; IR, incidence rate; CI, confidence interval; IRR, incidence rate ratio; RSV, respiratory syncytial virus.

* Vaccinated during the second or third trimester of pregnancy.

[†] Vaccinated pre-pregnancy (n = 624), in the first trimester of pregnancy (n = 2319), post-pregnancy (n = 18836), and unvaccinated (n = 8865) for COVID-19.

[‡] Inverse probability of treatment weighting; incidence rates are presented per 6 months of follow-up multiplied by 10⁻⁴ given the rarity of some outcomes.

[§] Bold indicates significant difference between COVID-19 vaccine exposed and COVID-19 vaccine unexposed groups.

Table 3.

Association Between COVID-19 Vaccination During the Second or Third Trimester of Pregnancy and Infant Respiratory Syncytial Virus^I from Birth to 6 Months of Life Stratified by Infant Date of Birth Among 42 940 Pregnancies with Live Births with Pregnancy Episode Start from May 17, 2020 to February 15, 2021 from Eight Vaccine Safety Datalink Sites

Infant Date of Birth	Incidence rate ratio	
	<i>crude IRR (95% CI)</i>	<i>adjusted IRR (95% CI) *</i>
November 17, 2020 - February 21, 2021	0.00 (0.00, -)	0.00 (0.00, -)
February 21, 2021 - May 28, 2021	1.36 (0.86, 2.17)	0.89 (0.55, 1.43)
May 28, 2021 - September 01, 2021	0.75 (0.59, 0.96) †	0.76 (0.58, 0.99)
September 01, 2021 - December 07, 2021	0.71 (0.55, 0.92)	0.75 (0.57, 0.98)

Abbreviations: COVID-19, coronavirus disease 2019; IRR, incidence rate ratio; CI, confidence interval.

* Inverse probability of treatment weighting.

† Bold indicates significant difference between COVID-19 vaccine exposed and COVID-19 vaccine unexposed groups.

Table 4.

Association Between COVID-19 Vaccination during the Second or Third Trimester of Pregnancy and Laboratory-Confirmed and Inpatient-Only Infectious Outcomes from Birth to 6 Months of Life and Within the First Month of Life Among 42 940 Pregnancies with Live Births with Pregnancy Episode Start from May 17, 2020 to February 15, 2021 from Eight Vaccine Safety Datalink Sites

Infectious Outcome	COVID-19 vaccine exposed* (n = 14 762)		COVID-19 vaccine unexposed† (n = 28 178)		Incidence rate ratio	
	Events	IR per 6-months × 10 ⁻⁴ (95% CI)‡	Events	IR per 6-months × 10 ⁻⁴ (95% CI)‡	Crude IRR (95% CI)	Adjusted IRR (95% CI) §
Laboratory-confirmed infections						
RSV	173	99 (84, 120)	340	130 (120, 140)	0.97 (0.81, 1.17)	0.76 (0.63, 0.93)
Influenza	4	2 (1, 6)	8	3 (1, 6)	0.95 (0.29, 3.17)	0.75 (0.20, 2.80)
Inpatient infections						
RSV	82	47 (37, 59)	180	69 (60, 79)	0.87 (0.67, 1.13)	0.68 (0.52, 0.90)
Influenza	1	3 (1, 7)	3	1 (0, 3)	0.64 (0.066, 6.12)	2.81 (0.59, 13.37)
Bronchiolitis	17	12 (7, 19)	32	11 (8, 16)	1.01 (0.56, 1.83)	1.07 (0.60, 1.93)
Bacterial pneumonia	9	6 (3, 12)	17	7 (4, 11)	1.01 (0.45, 2.27)	0.92 (0.42, 2.04)
Other lower respiratory	0	0 (0, -)	3	1 (0, 3)	0.00 (0.00, -)	0.00 (0.00, -)
Sepsis and bacterial	59	43 (34, 55)	120	41 (35, 50)	0.94 (0.69, 1.28)	1.04 (0.77, 1.42)
Other bloodstream	3	3 (1, 8)	7	2 (1, 5)	0.82 (0.21, 3.16)	1.24 (0.37, 4.19)
Bacterial meningitis	4	2 (1, 6)	11	3 (2, 6)	0.69 (0.22, 2.18)	0.59 (0.16, 2.26)
Other meningitis	2	1 (0, 5)	6	2 (1, 5)	0.64 (0.13, 3.15)	0.56 (0.099, 3.18)
Infections within first month of life						
RSV	19	9 (5, 16)	33	15 (11, 20)	1.10 (0.63, 1.93)	0.62 (0.34, 1.15)
Influenza	0	0 (0, -)	2	1 (0, 3)	0.00 (0.00, -)	0.00 (0.00, -)
Bronchiolitis	13	8 (4, 14)	16	7 (4, 10)	1.55 (0.75, 3.22)	1.14 (0.54, 2.40)
Bacterial pneumonia	2	2 (1, 7)	6	2 (1, 4)	0.64 (0.13, 3.15)	1.30 (0.34, 4.92)
Other lower respiratory	1	0 (0, 5)	1	0 (0, 3)	1.91 (0.12, 30.52)	0.86 (0.040, 18.53)
Sepsis and bacterial	48	36 (27, 47)	105	36 (29, 43)	0.87 (0.62, 1.23)	1.01 (0.72, 1.41)
Other bloodstream	2	1 (0, 5)	2	1 (0, 3)	1.91 (0.27, 13.55)	1.35 (0.19, 9.72)
Bacterial meningitis	3	2 (0, 6)	9	3 (1, 5)	0.64 (0.17, 2.35)	0.59 (0.13, 2.66)
Other meningitis	2	1 (0, 5)	3	1 (0, 3)	1.27 (0.21, 7.62)	1.27 (0.18, 9.13)

Abbreviations: COVID-19, coronavirus disease 2019; IR, incidence rate; CI, confidence interval; IRR, incidence rate ratio; RSV, respiratory syncytial virus.

* Vaccinated during the second or third trimester of pregnancy.

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- [†] Vaccinated pre-pregnancy ($n = 624$), in the first trimester of pregnancy ($n = 2319$), post-pregnancy ($n = 18\,836$), and unvaccinated ($n = 8865$) for COVID-19.
- [‡] Inverse probability of treatment weighting; incidence rates are presented per 6 months of follow-up multiplied by 10^{-4} given the rarity of some outcomes.
- [§] Bold indicates significant difference between COVID-19 vaccine exposed and COVID-19 vaccine unexposed groups.

Table 5.

Association between COVID-19 Vaccination During the Second or Third Trimester of Pregnancy and Infant COVID-19 from Birth to 6 Months of Life among 42 940 Pregnancies with Live Births with Pregnancy Episode Start from May 17, 2020, to February 15, 2021, from 8 Vaccine Safety Datalink Sites

	COVID-19 vaccine exposed* (n = 14 762)		COVID-19 vaccine unexposed† (n = 28 178)		Incidence rate ratio	
	Events	IR per 6-months × 10 ⁻⁴ (95% CI)‡	Events	IR per 6-months × 10 ⁻⁴ (95% CI)‡	Crude IRR (95% CI)	Adjusted IRR (95% CI) §
COVID-19	300	190 (170, 210) §	775	290 (270, 310)	0.74 (0.65, 0.84)	0.65 (0.57, 0.74)
Laboratory-confirmed	189	120 (110, 140)	545	200 (180, 220)	0.66 (0.56, 0.78)	0.61 (0.52, 0.73)
Inpatient	11	12 (8, 19)	57	21 (16, 27)	0.37 (0.19, 0.70)	0.58 (0.34, 1.00)
First month of life	6	5 (3, 11)	56	20 (16, 27)	0.20 (0.088, 0.47)	0.27 (0.13, 0.56)

Abbreviations: COVID-19, coronavirus disease 2019; IR, incidence rate; CI, confidence interval; IRR, incidence rate ratio.

* Vaccinated during the second or third trimester of pregnancy.

† Vaccinated pre-pregnancy (n = 624), in the first trimester of pregnancy (n = 2319), post-pregnancy (n = 18 836), and unvaccinated (n = 8865) for COVID-19.

‡ Inverse probability of treatment weighting; incidence rates are presented per six months of follow-up multiplied by 10⁻⁴ given the rarity of some outcomes.

§ Bold indicates significant difference between COVID-19 vaccine exposed and COVID-19 vaccine unexposed groups.