Effectiveness of COVID-19 vaccination during pregnancy by circulating viral variant



Ousseny Zerbo, PhD; G. Thomas Ray, MBA; Bruce Fireman, MA; Evan Layefsky, BA; Kristin Goddard, MPH; Pat Ross, BA; Mara Greenberg, MD; Nicola P. Klein, MD, PhD

BACKGROUND: SARS-CoV-2 infection in pregnancy can result in a spectrum of asymptomatic to critical COVID-19 outcomes, including hospitalization, admission to the intensive care unit, or death.

OBJECTIVE: This study aimed to investigate the effectiveness of messenger RNA COVID-19 vaccination during pregnancy against both hospitalization and infection, stratified by different variant circulations and by time since the last vaccine dose.

STUDY DESIGN: This was a retrospective cohort study among pregnant persons who were members of Kaiser Permanente Northern California and delivered between December 15, 2020, and September 30, 2022. Pregnant persons who received any vaccine dose before the pregnancy onset date were excluded. The primary outcome was hospitalization for COVID-19, and the secondary outcome was polymerase chain reaction—confirmed SARS-CoV-2 infection. Exposure was receipt of a messenger RNA vaccine during pregnancy. Poisson regression was used to estimate the risk ratio of hospitalization by comparing vaccinated pregnant persons with unvaccinated pregnant persons adjusted for sociodemographic factors and calendar time. Cox regression was used to estimate the hazard ratio of infection by comparing vaccinated pregnant persons with unvaccinated pregnant persons. Vaccine effectiveness was estimated as 1 minus the rate ratio or the hazard ratio multiplied by 100. Vaccine effectiveness was estimated overall and by variant periods (before Delta, Delta, Omicron, and subvariants).

RESULTS: Of 57,688 pregnant persons, 16,153 (28%) received at least 1 dose of a messenger RNA COVID-19 vaccine during pregnancy; moreover, 4404 pregnant persons tested positive for SARS-CoV-2 infection, and 108 pregnant persons were hospitalized during pregnancy. Overall, 2-dose vaccine effectiveness against hospitalization was 91% within <150 days of vaccination and 48% >150 days after vaccination. The 2-dose vaccine effectiveness within <150 days after vaccination was 100% during the original virus strain and Delta variant periods of the virus; vaccine effectiveness was 51% during the Omicron period. Of the hospitalization cases, 97% of pregnant persons were unvaccinated. During hospitalization, none of the vaccinated pregnant persons required ventilation or were admitted to the intensive care unit. Moreover, 2-dose vaccine effectiveness against infection was 54% within <150 days after vaccination and 26% \geq 150 days after vaccination.

CONCLUSION: Messenger RNA COVID-19 vaccination during pregnancy was effective against hospitalization for COVID-19 and SARS-CoV-2 infection. COVID-19 was mild among pregnant persons who were vaccinated compared with those who were unvaccinated. Thus, all pregnant persons should be strongly encouraged to receive messenger RNA COVID-19 vaccines to prevent severe disease.

Key words: COVID-19 vaccination, infection, pregnancy, SARS-CoV-2 variant period, severe COVID-19

Introduction

SARS-CoV-2 infection in pregnancy can result in a spectrum of asymptomatic to critical COVID-19.¹⁻⁵ Although pregnant persons are not more susceptible to SARS-CoV-2 infection than nonpregnant persons, unvaccinated pregnant persons are at higher risk of severe COVID-19.⁶ Pregnant persons with SARS-CoV-2 infection are more likely to be admitted to the intensive care unit (ICU), receive invasive

ventilation and extracorporeal membrane oxygenation, and die from complications than nonpregnant persons with SARS-CoV-2 infection.^{7–11} In addition, COVID-19 in pregnancy is associated with an increased risk of

From the Kaiser Permanente Northern California, Vaccine Study Center, Oakland, CA (Dr Zerbo, Mr. Ray, Fireman and Layefsky, Ms. Goddard, and Ross, and Dr Klein); Department of Obstetrics and Gynecology, Kaiser Permanente Northern California, Oakland, CA (Dr Greenberg); Regional Perinatal Service Center, Kaiser Permanente Northern California, Santa Clara, CA (Dr Greenberg).

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Preliminary data were presented as an oral presentation at the 2022 annual meeting of the Infectious Diseases Society of America (IDWeek 2022), Washington, DC, October 22, 2022. Patient consent is not required because no personal information or detail is included.

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Corresponding author: Ousseny Zerbo, PhD. Ousseny.x.zerbo@kp.org 2666-5778/\$36.00

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Why was this study conducted?

This study aimed to investigate the effectiveness of messenger RNA (mRNA) COVID-19 vaccination during pregnancy against both hospitalization and infection.

Key findings

Overall, 2-dose vaccine effectiveness (VE) against hospitalization was 91% within <150 days of vaccination and 48% >150 days after vaccination. VE within <150 days after vaccination was 100% during the original virus strain and Delta variant periods; VE was 51% during the Omicron period. Of the hospitalization cases, 97% of pregnant persons were unvaccinated. None of the vaccinated pregnant persons required ventilation during hospitalization or were admitted to the intensive care unit. Moreover, 2-dose VE against infection was 54% within <150 days after vaccination and 26% \geq 150 days after vaccination.

What does this add to what is known?

mRNA COVID-19 vaccination during pregnancy is effective against hospitalization. Although VE waned, COVID-19 was less severe among vaccinated persons than unvaccinated persons.

pregnancy-specific complications, including preeclampsia, cesarean delivery, preterm birth, low birthweight, and small for gestational age.^{8,10,12–16}

Vaccination offers the best way to protect against COVID-19 and its complications. Messenger RNA (mRNA) COVID-19 vaccines have demonstrated both high efficacy in clinical trials and high real-world effectiveness, especially against the original virus strain and Delta variant of the virus.^{17–25} Moreover, observational studies suggest that COVID-19 vaccine effectiveness (VE) in pregnant persons is broadly similar to that in nonpregnant persons.^{26–30}

Most COVID-19 VE studies among pregnant persons did not include the Omicron variant and its subvariant periods, and they were mostly limited to VE against infections. Previous VE studies^{25,29} against hospitalization using electronic health record data did not confirm hospitalization by medical record review to distinguish between COVID-19-related hospitalization and incidental COVID-19 cases found through infection control. This study aimed to investigate the effectiveness of 1, 2, or 3 doses of mRNA COVID-19 vaccines administered during pregnancy against both hospitalization for COVID-19 and infection among pregnant persons, stratified by different variant circulations and by time since the last vaccine dose. By comparing the clinical presentations of hospitalized pregnant persons who were vaccinated with that of those who were unvaccinated, our results provide additional information regarding the effectiveness of COVID-19 vaccination during pregnancy against hospitalization.

Materials and Methods

We conducted a retrospective cohort study among pregnant persons aged 16 to 49 years who were members of Kaiser Northern Permanente California (KPNC) and who delivered between December 15, 2020, and September 30, 2022. KPNC is an integrated healthcare delivery organization that provides comprehensive medical care to approximately 4.4 million members. In addition to the retrospective study design, we implemented a secondary test-negative design (TND),³¹ which is a case-control study design.

The exposure was 1, 2, or 3 doses of mRNA COVID-19 vaccine administered between pregnancy onset date and delivery. The primary outcome was COVID-19 hospitalization, and the secondary outcome was SARS-CoV-2 infection. We defined COVID-19 hospitalization cases as pregnant persons who tested positive for SARS-CoV-2 in a polymerase chain reaction (PCR) test and who were hospitalized for COVID-19. Infection was defined as a positive PCR test in any setting (outpatient, emergency department, or inpatient) after pregnancy onset and before delivery. Medical records of all potentially COVID-19—related hospitalization cases were reviewed by trained medical record abstractors using a medical record abstractors using a medical record reviews were adjudicated by an obstetrics and gynecology physician for a final determination of whether the cases were primarily the result of COVID-19 symptoms.

Of note, 4 variant periods were defined: the pre-Delta period from December 15, 2020, to June 30, 2021; the Delta period from July 1, 2021, to December 20, 2021; the Omicron period from December 21, 2021, to March 20, 2022; and the Omicron subvariant period from March 21, 2022, to September 30, 2022 (end of the study period). These periods were defined on the basis of genotyping data from the California Department of Public Health.

In the cohort analysis, we calculated the incidence rates (per 1000 person-years [PY]) of COVID-19 hospitalizations and positive PCR tests overall during the study period by vaccination status, by time since the last vaccine dose, and by the times associated with the 4 SARS-CoV-2 variant periods. For hospitalizations, we used the exact Poisson regression method to estimate the unadjusted risk ratio (RR) comparing vaccinated pregnant persons with unvaccinated pregnant persons. For infections, we used multivariable Cox proportional hazards models that allow for timevarying covariates to compare the hazards of a positive test among vaccinated pregnant persons with unvaccinated pregnant persons. VE was estimated as 1 minus the RR or the hazard ratio multiplied by 100.

In the TND, we used the multivariable logistic regression to determine the adjusted odds ratio of vaccination comparing cases with controls.

All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC), and statistical significance was assessed using a 2-sided P value of \leq .05. The study was approved by the KPNC Institutional Review Board.

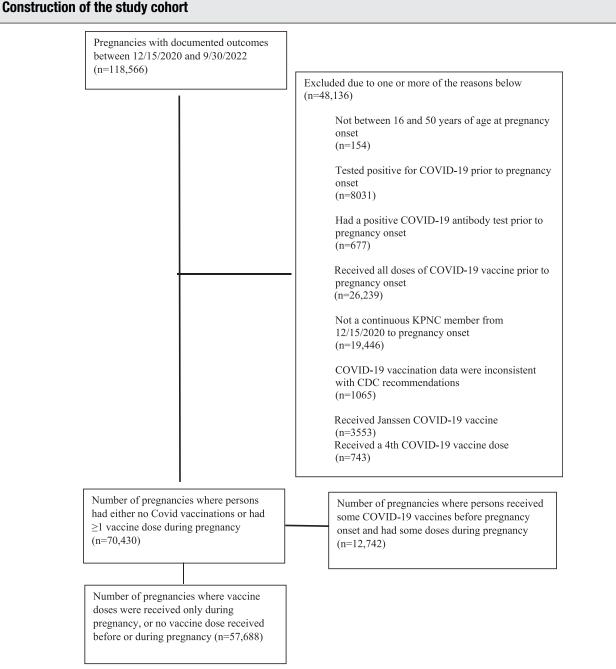
Results

FIGURE

From December 15, 2020, to September 30, 2022, 118,566 pregnant persons

delivered at KPNC facilities. We excluded 60,878 pregnant persons for a final study population of 57,688 pregnant persons (Figure). The mean age was 31 years, with 59% of the study population being between ages 25 and 34 years, and approximately 21.6% were Asian, 9.6% were Black, and 28.7% were Hispanic. In this population, 41,446

(71.9%) received no COVID-19 vaccine before or during pregnancy, 13,217 (22.9) received 2 doses during pregnancy, and 851 (1.5) received 3 doses (Table 1). During the follow-up period, 4404 (7.6%) tested positive for SARS-CoV-2 using the PCR test. Among 318 hospitalized pregnant persons with a positive PCR test, 108 (34%) were



The chart shows the pregnancies with delivery from December 15, 2020, to September 30, 2022, at Kaiser Permanente Northern California. *Zerbo. Messenger RNA COVID-19 vaccine effectiveness during pregnancy. Am J Obstet Gynecol Glob Rep 2023.*

Characteristics of pregnancies with a documented delivery from December 15, 2020, to September 30, 2022, at Kaiser Permanente Northern California

Characteristic	Pregnancies (N=57,688)		
Age group, n (%)			
16 to <25 y	8767 (15.20)		
25 to <35 y	34,362 (59.57)		
35 to <50 y	14,559 (25.24)		
Age, mean (median)	30.64 (31.00)		
Race and ethnicity, n (%)			
Asian	12,441 (21.57)		
Black	5527 (9.58)		
Hispanic	16,574 (28.73)		
Pacific Islander	541 (0.94)		
Multiracial	221 (0.38)		
Native American	1545 (2.68)		
Other or unknown	1386 (2.40)		
White	19,453 (33.72)		
Neighborhood deprivation, n (%)			
Quartile 1, least deprived	11,224 (19.46)		
Quartile 2	14,011 (24.29)		
Quartile 3	14,416 (24.99)		
Quartile 4, most deprived	17,997 (31.20)		
Missing	40 (0.07)		
Subsidized insurance: Medicare, Medicaid, or other, n (%)	8519 (14.77)		
Body mass index, n (%)			
Underweight	1209 (2.10)		
Normal	20,981 (36.37)		
Overweight	16,038 (27.80)		
Obese	16,888 (29.27)		
Unknown	2572 (4.46)		
Preexisting diabetes mellitus, n (%)	962 (1.67)		
Preexisting hypertension, n (%)	3844 (6.66)		
Parity, n (%)			
0	20,241 (35.09)		
1	18,954 (32.86)		
2	8311 (14.41)		
3	3053 (5.29)		
4+	1568 (2.72)		
Number of COVID-19 vaccines dose from pregnancy onset date to end of pregnancy			
0	41,446 (71.85)		
1	2174 (3.77)		
2	13,217 (22.91)		
3	851 (1.48)		
Received COVID-19 test during pregnancy	44,981 (77.97)		
Hospitalization because of COVID-19	108 (0.19)		
Positive COVID-19 test during pregnancy	4404 (7.63)		

medical record confirmed as hospitalized for COVID-19.

Of the 108 medical record-confirmed hospitalization cases, 105 pregnant persons (97%) were unvaccinated, and 3 pregnant persons (3%) were vaccinated. At admission, a higher proportion of unvaccinated individuals had shortness of breath than those who were vaccinated (81.9% vs 0%). During hospital stays, 9.5% of unvaccinated individuals required ventilation, and 18% of unvaccinated individuals were admitted to the ICU. However, none of the vaccinated pregnant persons required ventilation or were admitted to the ICU (Table 2).

Vaccine effectiveness against COVID-19 hospitalization

Across all variant periods, the incidence rates of hospitalization per 1000 PY were 4 persons among unvaccinated individuals, 0 among vaccinated with 2 doses within 150 days of vaccination, and 2 persons among persons who were vaccinated \geq 150 days from the date of their second dose (Table 3). VE of 2 doses against hospitalization within <150 days of vaccination was 91% (95% confidence interval [CI], 57%–100%), and VE after \geq 150 days of vaccination was 48% (95% CI, -61% to 97%). A third dose restored VE to 100% (95% CI, -90% to 100%).

VE varied by variant period. VE of 2 doses against hospitalization within <150 days of vaccination was 100% (95% CI, -6% to 100%) during the original virus strain period (pre-Delta period), 100% (95% CI, 88%-100%) during the Delta period, 51% (95% CI, -64% to 98%) during the Omicron period, and 100% (95% CI, -90% to 100%) during the Omicron subvariant period. During the Omicron period, VE for ≥150 days after vaccination decreased to -28% (95% CI, -87% to 94%).

During each period when a third dose was recommended, VE for the third dose was 100%, but measures were very imprecise because of small samples.

Effectiveness of COVID-19 vaccination during pregnancy against hospitalization by virus variant: cohort study design

			Number of		
SARS-CoV-2 variant period and vaccination status	Pregnancies ^a	РҮ	hospitalization cases	Crude incidence rates per 1000 PY	Vaccine effectiveness (95% Cl) ^b
Across all variant periods					
Unvaccinated	57,688	29,619	105	4	Reference
Vaccinated with 1 dose	14,913	836	1	1	66 (-41 to 98)
Vaccinated with 2 doses <150 d	13,239	3280	1	0	91 (57-100)
Vaccinated with 2 doses \geq 150 d	4276	545	1	2	48 (-61 to 97)
Vaccinated with 3 doses	825	64	0	0	100 (-90 to 100)
Original SARS-CoV-2 period					
Unvaccinated	50,832	23,753	36	2	Reference
Vaccinated with 1 dose	11,132	548	0	0	100 (-65 to 100)
Vaccinated with 2 doses <150 d	9609	1469	0	0	100 (-6 to 100)
Vaccinated with 2 doses \geq 150 d	231	8	0	0	100 (-100 to 100)
Delta variant period					
Unvaccinated	18,906	4040	51	13	Reference
Vaccinated with 1 dose	4016	224	0	0	100 (17-100)
Vaccinated with 2 doses <150 d	9573	1597	0	0	100 (88—100)
Vaccinated with 2 doses \geq 150 d	3666	446	0	0	100 (58—100)
Vaccinated with 3 doses	654	41	0	0	100 (78 to 100)
Omicron variant period					
Unvaccinated	6242	1092	13	12	Reference
Vaccinated with 1 dose	474	42	1	24	-49 (-91 to 91)
Vaccinated with 2 doses <150 d	1397	173	1	6	51 (-64 to 98)
Vaccinated with 2 doses \geq 150 d	842	61	1	16	-28 (-87 to 94)
Vaccinated with 3 doses	336	18	0	0	100 (-92 to 100)
Omicron subvariant period					
Unvaccinated	3546	735	5	7	Reference
Vaccinated with 1 dose	141	22	0	0	100 (-95 to 100)
Vaccinated with 2 doses <150 d	311	41	0	0	100 (-90 to 100)
Vaccinated with 2 doses \geq 150 d	310	31	0	0	100 (-93 to 100)
Vaccinated with 3 doses	65	5	0	0	100 (-99 to 100)
CL confidence interval: DV person vegra: I/E vegein	a offortivonogo				

Cl, confidence interval; PY, person-years; VE, vaccine effectiveness.

^a Vaccination status is a time-changing variable: the same person can contribute time to more than 1 category. Therefore, the sum of the number of pregnancies across the vaccination status categories totals more than the number of unique pregnancies in the study cohort; ^b Because of no count of hospitalization or very low counts of hospitalizations in unvaccinated persons, VE and VE confidence limits were unadjusted for any covariates and were established using exact Poisson methods.

Zerbo. Messenger RNA COVID-19 vaccine effectiveness during pregnancy. Am J Obstet Gynecol Glob Rep 2023.

Vaccine effectiveness against SARS-CoV-2 infection

Across all variant periods, the incidence rates of positive PCR tests (infection) per 1000 PY were 135 persons among unvaccinated individuals, 66 persons among vaccinated individuals with 2 doses within <150 days of vaccination, and 174 persons among persons who were vaccinated \geq 150 days from the date of their second dose (Table 4). VE of 2 doses against infection within

<150 days of vaccination was 54% (95% CI, 47%-60%), and VE was 26% (95% CI, 8%-40%) for \geq 150 days after vaccination.

VE against infection was higher during the original virus strain period than

Clinical presentation at admission, diagnoses, and treatment during hospital stay by COVID-19 vaccination status among COVID-19–related hospitalization cases

SARS-CoV-2 variant period and vaccination status	Unvaccinated (n=105) n (%)	Vaccinated (n=3) n (%)
Clinical presentation at admission		
Cough	88 (83.8)	1 (33.3)
Fever	61 (58.1)	2 (66.7)
Shortness of breath or respiratory distress	86 (81.9)	0 (0)
Trouble breathing	22 (21.0)	0 (0)
Treatment during hospital stay		
Ventilation	10 (9.5)	0 (0)
Oxygen support (but not ventilation)	78 (74.3)	0 (0)
Remdesivir	78 (74.3)	1 (33.3)
Extra corporeal membrane oxygenation	2 (1.9)	0 (0)
ICU admission	19 (18.1)	0 (0)
Diagnosis during hospital stay		
Acute respiratory distress syndrome	4 (3.8)	0 (0)
Sepsis	14 (13.3)	0 (0)
COVID-pneumonia	78 (74.3)	1 (33.3)

Zerbo. Messenger RNA COVID-19 vaccine effectiveness during pregnancy. Am J Obstet Gynecol Glob Rep 2023.

during subsequent periods. VE of 2 doses within <150 days after vaccination were 86% (95% CI, 70%-93%) during the original virus strain period, 78% (95% CI, 72%-83%) during the Delta period, 14% (95% CI, -5% to 30%) during the Omicron period, and -16% (95% CI, -60 to 43) during the Omicron subvariant period (Table 4). During each period, the VE of 2 doses decreased as the time from vaccination increased. VE of 3 doses were 100% (95% CI, 74%-100%) during the Delta period, 44% (95% CI, 5%-67%) during the Omicron period, and 100% (95% CI, -59 to 100) during the Omicron subvariant period.

In the TND, 44,981 pregnant persons were included. Overall VE of 2 doses against infection within <150 days after vaccination was 60% (95% CI, 53% -66%), and VE was 38% (95% CI, 21% -51%) for \geq 150 days after vaccination. VE of 2 doses within <150 after vaccination varied by variant periods. VE were 87% (95% CI, 73%-94%) during the original virus strain period (pre-Delta period), 77% (95% CI, 69%-82%) during the Delta period, 22% (95% CI, -7% to 44%) during the Omicron period, and 12% (95% CI, -48 to 59) during the Omicron subvariant period (Supplemental Table). In addition, VE decreased as the time from the last dose increased. During each period, a third dose increased VE against infections.

Comment Principal findings

In this large pregnancy cohort, receipt of 2 doses of mRNA COVID-19 vaccine during pregnancy was associated with a decreased risk of hospitalization for COVID-19. VE was higher during the pre-Delta and Delta periods than the Omicron period, and VE waned over time. Vaccinated pregnant persons were less likely to have severe disease after infection than unvaccinated pregnant persons.

Results in the context of what is known

Previous studies that evaluated VE suggested that mRNA COVID-19 vaccination of pregnant persons was associated with strong protection against COVID-19 and SARS-CoV-2 infections shortly after the second dose.^{23,25,26,28,32} However, these studies either preceded booster recommendations for this population or focused primarily on the pre-Delta, Delta, or early Omicron period. Our study provides more current and complete evidence regarding COVID-19 VE in this group by expanding into the Omicron subvariant period. Furthermore, unlike the previous studies, this study confirmed all hospitalization cases by medical record review; thus, all hospitalization cases were due to COVID-19.

Clinical implications

Among the vaccinated hospitalized pregnant persons, none were admitted to the ICU, had sepsis, or required mechanical ventilation or oxygen support. This important finding of decreased disease severity during hospitalization should strongly encourage both providers to recommend vaccination for their pregnant patients and pregnant persons to seek vaccination for themselves. Our finding of lower VE against a positive PCR test during the Omicron and Omicron subvariant periods suggests that these variants were efficient at escaping neutralizing antibodies after vaccination.³³⁻³⁶ Thus, efficient infection control during the Omicron variant and subvariant periods will require new-generation COVID-19 vaccines, such as bivalent vaccines, that are more adapted to the circulating virus strains.

In addition to preventing hospitalization, vaccination during pregnancy was also associated with a lower risk of a positive PCR test within 150 days after vaccination. However, effectiveness decreased as the time from the last vaccine dose increased. This supports the

Effectiveness of COVID-19 vaccination during pregnancy against testing positive for SARS-CoV-2 by virus variant: cohort study design

Across all variant periods Unvaccinated 57,688 29,619 4010 135 Reference Vaccinated with 1 dose 14,913 836 69 83 27 (7-42) Vaccinated with 2 doses <150 d 13,239 3280 215 66 54 (47-60) Vaccinated with 2 doses ≥150 d 4276 545 95 174 26 (8-40) Vaccinated with 3 doses 825 64 15 234 36 (-7 to 61) Original SARS-CoV-2 period Unvaccinated 50,832 23,753 2421 102 Reference Vaccinated with 1 dose 11,132 548 7 13 69 (35-85) Vaccinated with 2 doses <150 d 9609 1469 7 5 86 (70-93) Vaccinated with 2 doses <150 d 231 8 0 100 (-6 to 100) Delta variant period Unvaccinated 18,906 4039 855 212 Reference Vaccinated with 1 dose 4016 224 27 121 39 (11-59)	SARS-CoV-2 variant period and vaccination status	Pregnancies ^a	РҮ	Number of positive tests	Crude incidence rates per 1000 PY	Vaccine effectiveness (95% CI) ^b
Vaccinated with 1 dose14,913836698327 (7-42)Vaccinated with 2 doses <150 d	Across all variant periods					
Vaccinated with 2 doses <150 d13,23932802156654 (47-60)Vaccinated with 2 doses ≥150 d42765459517426 (8-40)Vaccinated with 3 doses825641523436 (-7 to 61)Original SARS-CoV-2 period </td <td>Unvaccinated</td> <td>57,688</td> <td>29,619</td> <td>4010</td> <td>135</td> <td>Reference</td>	Unvaccinated	57,688	29,619	4010	135	Reference
Vaccinated with 2 doses ≥150 d42765459517426 (8-40)Vaccinated with 3 doses825641523436 (-7 to 61)Original SARS-CoV-2 periodReferenceVaccinated with 1 dose11,13254871369 (35-85)Vaccinated with 2 doses <150 d	Vaccinated with 1 dose	14,913	836	69	83	27 (7-42)
Vaccinated with 3 doses825641523436 (-7 to 61)Original SARS-CoV-2 periodUnvaccinated50,83223,7532421102ReferenceVaccinated with 1 dose11,13254871369 (35-85)Vaccinated with 2 doses <150 d	Vaccinated with 2 doses <150 d	13,239	3280	215	66	54 (47-60)
Original SARS-CoV-2 period Unvaccinated 50,832 23,753 2421 102 Reference Vaccinated with 1 dose 11,132 548 7 13 69 (35–85) Vaccinated with 2 doses <150 d	Vaccinated with 2 doses \geq 150 d	4276	545	95	174	26 (8-40)
$\begin{tabular}{ c c c c c c } \hline Unvaccinated & 50,832 & 23,753 & 2421 & 102 & Reference \\ \hline Vaccinated with 1 dose & 11,132 & 548 & 7 & 13 & 69 (35-85) \\ \hline Vaccinated with 2 doses < 150 d & 9609 & 1469 & 7 & 5 & 86 (70-93) \\ \hline Vaccinated with 2 doses \geq 150 d & 231 & 8 & 0 & 0 & 100 (-65 to 100) \\ \hline Delta variant period & & & & & & & & & & & & & & & & & & &$	Vaccinated with 3 doses	825	64	15	234	36 (-7 to 61)
Vaccinated with 1 dose11,13254871369 (35-85)Vaccinated with 2 doses <150 d	Original SARS-CoV-2 period					
Vaccinated with 2 doses <150 d960914697586 (70-93)Vaccinated with 2 doses ≥150 d231800100 (-65 to 100)Delta variant periodUnvaccinated18,9064039855212ReferenceVaccinated with 1 dose40162242712139 (11-59)Vaccinated with 2 doses <150 d	Unvaccinated	50,832	23,753	2421	102	Reference
Vaccinated with 2 doses ≥150 d 231 8 0 0 100 (-65 to 100) Delta variant period Unvaccinated 18,906 4039 855 212 Reference Vaccinated with 1 dose 4016 224 27 121 39 (11-59) Vaccinated with 2 doses <150 d 9573 1597 66 41 78 (72-83) Vaccinated with 2 doses ≥150 d 3666 446 27 61 68 (52-78) Vaccinated with 3 doses 654 41 0 0 100 (74-100) Omicron variant period Unvaccinated with 1 dose 474 42 27 636 -6 (-37 to 28) Vaccinated with 2 doses <150 d 1397 173 133 769 14 (-5 to 30) Vaccinated with 2 doses <150 d 1397 173 133 769 14 (-5 to 30) Vaccinated with 2 doses ≥150 d 842 61 56 921 10 (-17 to 33) Vaccinated with 2 doses ≥150 d 842 61 56 921 10 (-17 to 33) Vaccinated with 3 doses 336 18 15 839 44 (5-67)	Vaccinated with 1 dose	11,132	548	7	13	69 (35-85)
Delta variant period Image: constraint period Unvaccinated 18,906 4039 855 212 Reference Vaccinated with 1 dose 4016 224 27 121 39 (11–59) Vaccinated with 2 doses <150 d	Vaccinated with 2 doses <150 d	9609	1469	7	5	86 (70-93)
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Vaccinated with 2 doses \geq 150 d	231	8	0	0	100 (-65 to 100)
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Delta variant period					
Vaccinated with 2 doses <150 d95731597664178 (72-83)Vaccinated with 2 doses ≥150 d3666446276168 (52-78)Vaccinated with 3 doses6544100100 (74-100)Omicron variant period1092598548ReferenceVaccinated with 1 dose62421092598548ReferenceVaccinated with 2 doses <150 d	Unvaccinated	18,906	4039	855	212	Reference
Vaccinated with 2 doses ≥150 d3666446276168 (52-78)Vaccinated with 3 doses6544100100 (74-100)Omicron variant periodUnvaccinated62421092598548ReferenceVaccinated with 1 dose4744227636-6 (-37 to 28)Vaccinated with 2 doses <150 d	Vaccinated with 1 dose	4016	224	27	121	39 (11-59)
Vaccinated with 3 doses6544100100 (74–100)Omicron variant periodUnvaccinated62421092598548ReferenceVaccinated with 1 dose4744227636 -6 (-37 to 28)Vaccinated with 2 doses <150 d139717313376914 (-5 to 30)Vaccinated with 2 doses ≥ 150 d842615692110 (-17 to 33)Vaccinated with 3 doses336181583944 (5–67)Omicron subvariant periodUnvaccinated with 1 dose3546735136185ReferenceVaccinated with 1 dose141228366 -47 (-77 to 20) -16 (-60 to 43)	Vaccinated with 2 doses <150 d	9573	1597	66	41	78 (72–83)
Omicron variant period Unvaccinated 6242 1092 598 548 Reference Vaccinated with 1 dose 474 42 27 636 6 (-37 to 28) Vaccinated with 2 doses <150 d	Vaccinated with 2 doses \geq 150 d	3666	446	27	61	68 (52-78)
Unvaccinated62421092598548ReferenceVaccinated with 1 dose4744227636 -6 (-37 to 28)Vaccinated with 2 doses <150 d	Vaccinated with 3 doses	654	41	0	0	100 (74–100)
Vaccinated with 1 dose 474 42 27 636 -6 (-37 to 28) Vaccinated with 2 doses <150 d	Omicron variant period					
Vaccinated with 2 doses <150 d 1397 173 133 769 14 (-5 to 30) Vaccinated with 2 doses ≥150 d 842 61 56 921 10 (-17 to 33) Vaccinated with 3 doses 336 18 15 839 44 (5-67) Omicron subvariant period Unvaccinated 3546 735 136 185 Reference Vaccinated with 1 dose 141 22 8 366 -47 (-77 to 20) Vaccinated with 2 doses <150 d	Unvaccinated	6242	1092	598	548	Reference
Vaccinated with 2 doses ≥150 d842615692110 (-17 to 33)Vaccinated with 3 doses336181583944 (5-67)Omicron subvariant periodUnvaccinated3546735136185ReferenceVaccinated with 1 dose141228366-47 (-77 to 20)Vaccinated with 2 doses <150 d	Vaccinated with 1 dose	474	42	27	636	-6 (-37 to 28)
Vaccinated with 3 doses 336 18 15 839 44 (5–67) Omicron subvariant period	Vaccinated with 2 doses <150 d	1397	173	133	769	14 (-5 to 30)
Omicron subvariant period 3546 735 136 185 Reference Vaccinated with 1 dose 141 22 8 366 -47 (-77 to 20) Vaccinated with 2 doses <150 d	Vaccinated with 2 doses \geq 150 d	842	61	56	921	10 (—17 to 33)
Unvaccinated 3546 735 136 185 Reference Vaccinated with 1 dose 141 22 8 366 -47 (-77 to 20) Vaccinated with 2 doses <150 d	Vaccinated with 3 doses	336	18	15	839	44 (5-67)
Vaccinated with 1 dose 141 22 8 366 -47 (-77 to 20) Vaccinated with 2 doses <150 d	Omicron subvariant period					
Vaccinated with 2 doses <150 d 311 41 9 220 -16 (-60 to 43)	Unvaccinated	3546	735	136	185	Reference
	Vaccinated with 1 dose	141	22	8	366	-47 (-77 to 20)
Vaccinated with 2 doses \geq 150 d 310 31 12 387 -33 (-65 to 24)	Vaccinated with 2 doses <150 d	311	41	9	220	-16 (-60 to 43)
	Vaccinated with 2 doses \geq 150 d	310	31	12	387	-33 (-65 to 24)
Vaccinated with 3 doses 65 5 0 0 100 (-59 to 100)	Vaccinated with 3 doses	65	5	0	0	100 (-59 to 100)

Cl, confidence interval; PY, person-years; VE, vaccine effectiveness.

^a Vaccination status is a time-changing variable: the same person can contribute time to more than 1 category. Therefore, the sum of the number of pregnancies across the vaccination status categories totals more than the number of unique pregnancies in the study cohort; ^b VE results adjusted for maternal age, race and ethnicity, neighborhood deprivation index quartile, insurance payor, Kaiser Permanente Northern California facility, prepregnancy body mass index, diabetes mellitus, hypertension, tobacco smoking status, and parity. Where VE was 100%, lower bound CIs were unadjusted for any covariates and established using exact Poisson methods.

Zerbo. Messenger RNA COVID-19 vaccine effectiveness during pregnancy. Am J Obstet Gynecol Glob Rep 2023.

need for pregnant persons to stay up to date on their vaccination schedule.

Research implications

Despite several studies showing that vaccination during pregnancy is safe

for pregnant persons,^{37–41} vaccine uptake has been suboptimal in this group. Here, only 23% of pregnant persons received 2 doses, and 1.5% of pregnant persons received 3 doses during pregnancy. These proportions

might not be representative of the proportion of all vaccinated pregnant persons within KPNC because of our exclusion criteria. However, more efforts are needed to promote COVID-19 vaccines for pregnant persons

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because vaccination provides protection to mothers and their infants until they are old enough to receive their COVID-19 vaccines.⁴²⁻⁴⁴

Strengths and limitations

A major strength of the study was that all hospitalization cases were confirmed by medical record review. In addition, the primary analysis for the risk of a positive PCR test used calendar days as the underlying scale, which ensured that vaccinated and unvaccinated pregnant persons were compared on the same calendar days. This was important because vaccination status during pregnancy and risk of infection varied over time during the study period. Furthermore, we used 2 study designs, and both (cohort design and TND) yielded similar VE estimates, providing greater confidence in our findings.

The study had some limitations worth noting. Our VE estimates against positive PCR tests during the Omicron and Omicron subvariant periods could have been subject to misclassification bias. At the beginning of the Omicron period, home tests became widely available. If unvaccinated pregnant persons were more likely to test at home and not report their results to the healthcare system than vaccinated persons, this could lead to a misclassification of infection status that can bias the VE estimate toward the null. However, such misclassification was less likely to affect our primary hospitalization outcome. Moreover, we did not confirm variants via genotyping because these data were not available. Alternatively, we relied on state data regarding circulating virus strain predominance in the Northern California region. In addition, the study did not evaluate the effectiveness of vaccines received before pregnancy. Our study was mainly interested in evaluating the effectiveness of vaccines received during pregnancy.

Conclusion

mRNA COVID-19 vaccination during pregnancy was effective against hospitalization for COVID-19 and SARS-CoV-2 infection. COVID-19 was mild among pregnant persons who were vaccinated compared with those who were unvaccinated. Thus, all pregnant persons should be strongly encouraged to receive mRNA COVID-19 vaccines to prevent severe disease.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xagr.2023.100264.

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