



Published in final edited form as:

BMJ Public Health. 2024 July ; 2(1): . doi:10.1136/bmjph-2023-000770.

Evaluating COVID-19 vaccine effectiveness during pre-Delta, Delta and Omicron dominant periods among pregnant people in the U.S.: Retrospective cohort analysis from a nationally sampled cohort in National COVID Collaborative Cohort (N3C)

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Decision to submit manuscript- Qiuyuan Qin, Rena C. Patel

Transparency statement:

The lead author, Qiuyuan Qin, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

Conflicts of Interest and Disclaimers

APC helped to conceptualize this study while at Vanderbilt University. Following this contribution, APC joined the staff of AstraZeneca Pharmaceuticals, LP ("AZ"), which markets a COVID-19 vaccine in direct competition to other products considered in this manuscript. After joining AZ, APC did not participate in the conduct of this research, with his subsequent contributions limited to ad hoc consultation on methods for real-world data management, as part of routine meetings of the N3C Pregnancy Domain Team for which he is an advisor. APC did not provide any guidance on product-specific or advocacy topics. Similarly, AZ did not provide any data, funding, or scientific input towards the results herein.

The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, AZ, or the N3C program.

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Abstract

Objectives: To evaluate the effectiveness of COVID-19 vaccinations (initial and booster) during pre-Delta, Delta, and Omicron dominant periods among pregnant people via (1) COVID-19 incident and severe infections among pregnant people who were vaccinated vs. unvaccinated and (2) post-COVID-19 vaccination breakthrough infections and severe infections among vaccinated females who were pregnant vs. non-pregnant.

Design: Retrospective cohort study using nationally sampled electronic health records data from the National COVID Cohort Collaborative (N3C), December 10, 2020, to June 07, 2022.

Participants: Cohort 1 included pregnant people (15-55 years), and Cohort 2 included vaccinated females of reproductive age (15-55 years).

Exposures: (1) COVID-19 vaccination and (2) pregnancy.

Main outcome measures: Adjusted hazard ratios (aHRs) for COVID-19 incident or breakthrough infections and severe infections (i.e., COVID-19 infections with related hospitalizations).

Results: In Cohort 1, 301,107 pregnant people were included. Compared to unvaccinated pregnant people, the aHRs for pregnant people with initial vaccinations *during* pregnancy of incident COVID-19 were 0.77 (95% CI: 0.62, 0.96) and 0.88 (95% CI: 0.73, 1.07) and aHRs of severe COVID-19 infections were 0.65 (95% CI: 0.47, 0.90) and 0.79 (95% CI: 0.51, 1.21) during the Delta and Omicron periods, respectively. Compared to pregnant people with full initial vaccinations, the aHR of incident COVID-19 for pregnant people with booster vaccinations was 0.64 (95% CI: 0.58, 0.71) during the Omicron period. In Cohort 2, 934,337 vaccinated people

were included. Compared to vaccinated non-pregnant females, the aHRs of severe COVID-19 infections for people with initial vaccinations *during* pregnancy was 2.71 (95% CI: 1.31, 5.60) during the Omicron periods.

Conclusions: Pregnant people with initial and booster vaccinations during pregnancy had a lower risk of incident and severe COVID-19 infections compared to unvaccinated pregnant people across the pandemic stages. However, vaccinated pregnant people still had a higher risk of severe infections compared to non-pregnant females.

Keywords

vaccine effectiveness; pregnant people; COVID-19 pandemic

INTRODUCTION

COVID-19 vaccines are considered one of the best tools in the global fight against the COVID-19 pandemic. Increasing data suggest that the incidence and severity of COVID-19 infections are lower among vaccinated vs. unvaccinated people.[1] While breakthrough infections still occurred among vaccinated individuals, particularly during Delta and Omicron variant periods in the U.S., their lower frequency and severity may be attributable largely to vaccine effectiveness.[2], [3]

Pregnant people with COVID-19 infections appear to be at higher risk of severe COVID-19 outcomes, such as a higher risk of severe pneumonia and intensive care unit (ICU) admission, than non-pregnant people.[4], [5] Immunological and physiological changes during pregnancy may be driving factors for the overall increased risk.[6] Pregnant people with COVID-19 infection may also face a higher risk of adverse pregnancy outcomes, including preeclampsia/eclampsia, preterm birth, and mortality, than pregnant people without COVID-19 infection.[7], [8] Furthermore, infections during pregnancy may be associated with potentially adverse long-term outcomes in infants.[9] Thus, either avoiding or attenuating severe COVID-19 infections is important for pregnant people.

Generally, vaccinations are well tolerated, safe, and effective in pregnancy. For instance, influenza vaccinations have demonstrated effectiveness at preventing influenza infection and are not related to adverse maternal and infant outcomes, such as preterm birth or low birth weight.[10], [11], [12] Also, emerging data suggests COVID-19 vaccinations are safe for pregnant people without major adverse birth outcomes.[13], [14], [15], [16], [17] Studies in different settings have also shown COVID-19 vaccines had a protective effect on pregnant people.[18], [19], [20], [21] However, whether the COVID-19 vaccines work similarly for both pregnant and non-pregnant people has been rarely investigated. While previous research suggested that pregnant people had a higher risk of breakthrough infection compared to non-pregnant females, COVID-19 severity, the stage of the pandemic, and the timing of vaccination relative to pregnancy were not accounted for in the analysis. [22] With the emergence of different viral variants and evolving immunological changes during pregnancy, the pandemic stages and the timing of vaccination regarding pregnancy may impact the effectiveness of vaccines.

The National COVID Cohort Collaborative (N3C) was developed in 2020 to provide an aggregated and harmonized platform for de-identified electronic health record (EHR) data from numerous healthcare sites from all geographic regions in the U.S. for use in COVID-19 research. Our group has phenotyped pregnant people, their pregnancy episodes as well as gestational aging, and their COVID-19 outcomes in N3C.[23] With the largest harmonized EHR data in the U.S., we focused on two interconnected questions for this study. First, we aimed to evaluate the extent to which COVID-19 vaccination could reduce the risk of incident and severe COVID-19 infections among pregnant people who were vaccinated vs. unvaccinated. Second, we aimed to evaluate whether and how the risk of breakthrough and severe COVID-19 infections would vary among vaccinated females comparing those who were pregnant vs. non-pregnant. We stratified both analyses by the stages of the pandemic and vaccination timing regarding pregnancy.

MATERIALS AND METHODS

Overall study setting and design

We conducted a retrospective cohort analysis of a prospectively collected EHR repository. The N3C consortium is a high-granularity EHR data repository of de-identified, patient-level data from medical centers across the U.S. The overall N3C design, data ingestion and harmonization, and sampling approach have been described previously.[24], [25] Additional details about N3C and ethical review are in supplementary materials.

Our dataset included COVID-19 vaccines currently given Food and Drug Administration (FDA) authorization, including two mRNA vaccines (Pfizer-BioNTech [BNT162b2] and Moderna [mRNA-1273]) and a viral vector vaccine (Johnson & Johnson/Janssen [JNJ-784336725]), as well as other vaccines (e.g., AstraZeneca). We categorized initial full vaccination as completion of the recommended dosing regimen of any vaccine (i.e., at least two doses for mRNA or other vaccines and one dose for the Janssen vaccine) and partial vaccination as one dose of mRNA vaccine. We categorized any additional doses after 90 days of initial dosing (e.g., a 3rd mRNA dose) as booster vaccinations and only accounted for the first booster vaccination in this analysis.[26] The concepts and codes to define vaccinations can be found in supplementary table 1.

Study period and analytic cohort selection

Our study observation period occurred from December 10, 2020, to June 7, 2022. We used N3C data version 84 (released July 7, 2022), noting that we truncated the observation period one month earlier to allow for adequate time for data reporting. We defined the beginning of the observation period, December 10, 2020, based on the date the FDA first approved COVID-19 vaccination²⁷. We chose the end date, June 7, 2022, to allow 90 days prior to when the bivalent booster became available (September 9, 2022) so that this analysis amply precludes bivalent booster impact (separate analysis forthcoming).

We stratified the analysis by variants predominant during the pandemic: pre-Delta (December 10, 2020, to June 20, 2021), Delta (June 21, 2021, to December 25, 2021),

and Omicron (December 26, 2021, to June 7, 2022), with predominance periods defined based on CDC estimates for the US in general.[27]

Cohort construction and bias control

Figure 1 illustrates our cohort construction. We included data from 43 total contributing sites, excluding sites in the bottom quartile of vaccination rates. Next, we generated subsets of this cohort to identify pregnant people (Cohort 1) and vaccinated females (Cohort 2).

For the analysis of initial vaccinations with Cohort 1, we included pregnant people aged 15-55 with COVID-19 vaccinations *during or before* their pregnancy on or after December 10, 2020 (i.e., the earliest date that COVID-19 vaccination was approved by FDA). For unvaccinated pregnant people, we included those with pregnancy end dates after March 1, 2021. We used March 1, 2021, the first peak of the initial full vaccination date among vaccinated pregnant people, as the “proxy initial vaccination date.” Similarly, for the analysis of booster vaccinations with Cohort 1, we included pregnant people with a booster vaccination *during or before* their pregnancy after December 1, 2021. For unvaccinated pregnant people, we included those with pregnancy end dates after December 1, 2021. We used December 1, 2021, the peak of booster vaccination date among vaccinated pregnant people, as the “proxy booster vaccination date.” We defined proxy vaccination dates to avoid ascertainment bias in person-time at risk being longer in the unvaccinated vs. vaccinated groups.

For analysis of initial and booster vaccinations with Cohort 2, we included non-pregnant vaccinated (i.e., those initial vaccinations/ booster vaccinations) females of reproductive age to match with the pregnant vaccinated (i.e., those initial vaccinations/ booster vaccinations) females.

Cohort 1 analysis (all pregnant people)

In the analysis for initial and booster vaccinations in Cohort 1, we compared vaccinated vs. unvaccinated pregnant people aged 15-55 to evaluate the vaccine effectiveness in pregnancy via incident and severe COVID-19 infections. We categorized vaccinated pregnant people based on vaccination timing into four groups: received any initial or booster vaccination *during* pregnancy (vaccinated *during* pregnancy) and received all initial or booster vaccinations *before* pregnancy (vaccinated *before* pregnancy).

To further investigate the effectiveness of booster vaccinations, we compared pregnant people with full initial vaccinations and those with booster vaccinations via incident and severe COVID-19 infections.

Cohort 2 (all vaccinated females)

In the analysis for initial and booster vaccinations in Cohort 2, we compared pregnant people vaccinated *during or before* pregnancy (same as Cohort 1) vs. non-pregnant females aged 15-55 to examine the impact of pregnancy on COVID-19 vaccine effectiveness.

For both Cohorts 1 and 2, we excluded pregnant people with COVID-19 infections after their initial/booster vaccination (or proxy initial/booster vaccination dates) but before

pregnancy. In the analysis for booster vaccinations, the included people were a subsample of the analysis cohort for initial vaccination.

Exposures definitions

In the analysis with Cohort 1 (all pregnant people), vaccination status is the key exposure category. In the analysis with Cohort 2 (all vaccinated females), pregnancy is the key exposure category.

Outcomes definitions

Our first co-primary outcome was incident and breakthrough COVID-19 infections among vaccinated and unvaccinated people, respectively. Our incident or breakthrough COVID-19 positivity definition only included positive results based on: 1) PCR-positivity, 2) antigen-positivity, or 3) ICD diagnosis condition, in that hierarchical order.[24] Breakthrough infection was defined by incident COVID-19 positivity after 14 days of the last vaccine received for initial/booster vaccination.[2], [22]

Our second co-primary outcome was severe COVID-19 infections. We defined severe COVID-19 infections as incident or breakthrough COVID-19 infections with hospitalization records within 14 days before or 45 days after infections that do not overlap within 7 days before or after the recorded delivery or pregnancy end date (to avoid confounding of hospitalization due to deliveries or other pregnancy outcomes).[2], [28] The concepts and codes to define COVID-19 infections and hospitalizations can be found in supplementary table 1.

Person-time at-risk for vaccinated people accrued from 14 days after their last date of vaccination (initial/booster) until the earliest date of COVID-19 incident or severe infections, death, transfer to hospice, or the date of their last record in N3C. Person-time at-risk for unvaccinated pregnant people accrued similarly from 14 days after the proxy initial or booster vaccination date. More details on person-time at risk are illustrated in supplementary figure 1. In the comparison of pregnant people with booster vaccinations vs. those with full initial vaccinations, we used the full initial vaccination date plus 90 days as the start date to calculate person-time-at-risk for pregnant people without booster vaccinations to avoid ascertainment bias. The 90-day time window was based on the definition of booster vaccinations, as mentioned in the previous section.

Other outcomes included: (1) ICU admission within 45 days after COVID-19 infection; (2) severe COVID-19 disease with invasive ventilation or extracorporeal membrane oxygenation (ECMO) treatment within 45 days after COVID-19 infection; and (3) 30-day mortality after COVID-19 infection [2], [29]. Note that ICU admission, ventilation, and ECMO outcomes are hospital-based and, therefore, subsumed in the second co-primary outcome of severe COVID-19 infection.

Statistical analysis

We present summary characteristics at the time of the first initial COVID-19 vaccination date and proxy vaccination date for vaccinated and unvaccinated people, respectively. We used descriptive statistics only for outcomes with low counts in various groups.

We applied Cox proportional hazard models to estimate adjusted hazard ratios (aHR) with 95% confidence intervals (CI). We clustered standard errors at data partner sites to account for heterogeneity across sites. We adjusted for individual-level sociodemographic characteristics, including age, race, ethnicity, specific clinical comorbidities, Charlson Comorbidity Index (CCI), and whether people had any prior COVID-19 infections before initial/booster or proxy vaccinations.

We stratified the models by the variant predominance periods (i.e., pre-Delta, Delta, and Omicron) to allow for different hazard ratio estimations during our observation period, and we assessed model assumptions accordingly. Person-time at-risk was also calculated for each variant stratum (i.e., one within each stratum). We further separated the analysis for initial and booster vaccinations.

Of note, given the timing of booster vaccinations occurring mainly during the Omicron period, we only analyzed booster vaccinations during the Omicron period. Since we anticipated pregnant people to possibly undergo more frequent COVID-19 testing than non-pregnant people (for instance, for the delivery hospitalization), we conducted an *a priori* sensitivity analysis restricting non-pregnant people in Cohort 2 to people with at least one recorded COVID-19 test. Due to the concern of different effectiveness of mRNA and non-mRNA vaccines,[30] we additionally conducted sensitivity analyses only including people with mRNA vaccinations (i.e., Pfizer and Moderna).

Details about covariates and modeling can be found in the supplementary materials. All analyses were conducted in the N3C Data Enclave using PySpark and SparkR/R³¹.

Patient and Public Involvement: This is a retrospective observational study, patients were not involved.

RESULTS

Cohort characteristics

A total of over 12 million people had records included in N3C from December 10, 2020, to June 7, 2022 (Figure 1). We included 301,107 people in Cohort 1 and 934,337 people in Cohort 2.

Among Cohort 1 (pregnant people), 34,907 (11.6%) had any initial vaccination *during* pregnancy, another 34,538 (11.5%) had all initial vaccinations *before* pregnancy, and 231,662 (76.9%) did not have any COVID-19 vaccinations recorded (Table 1). The median age was around 32.0 years for pregnant people with vaccinations and 30.2 (IQR 25.0, 33.8) for those without vaccination. Among those who had any initial vaccination *during* pregnancy, 28,537 (81.8%) had full initial vaccinations, 8,415 (24.1%) had booster

vaccination, and 25,540 (73.2%) had received a Pfizer vaccine for their first dose. Among those who had all initial vaccinations *before* pregnancy, 31,530 (91.6%) had full initial vaccination, 14,730 (42.6%) had booster vaccination, and 23,547 (68.2%) had received a Pfizer vaccine for their first dose.

Among Cohort 2 (vaccinated females), 864,892 (92.6%) were non-pregnant vaccinated females (Table 1). The characteristics of the vaccinated pregnant groups were the same as above for Cohort 1. Among vaccinated non-pregnant females, the median age was 37.1 (IQR 28.1, 47.2) years, 765,929 (88.6%) had full initial vaccinations, 460,967 (53.3%) had booster vaccination, and 576,921 (66.7%) had received a Pfizer vaccine for their first dose.

Cohort 1 findings: Pregnant people with initial vaccinations had a lower risk of incident COVID-19 infections compared to unvaccinated pregnant people during pre-Delta and Delta periods, and they had a lower risk of severe infections consistently throughout the pandemic stages

In Cohort 1, 4,323 (12.4%) and 4,577 (13.3%) of pregnant people with initial vaccinations *during and before* their pregnancy had incident COVID-19 infections across the entire study period, and 352 (1.0%) and 185 (0.5%) of them had severe COVID-19 infections, respectively. Among unvaccinated pregnant people, 39,313 (17.0%) had incident COVID-19 infections, and 3,868 (1.7%) developed severe COVID-19 infections (Table 1).

The adjusted models for incident COVID-19 infections resulted in aHRs of 0.36 (95% CI: 0.25, 0.51), 0.77 (95% CI: 0.62, 0.96), 0.88 (95% CI: 0.73, 1.07) comparing pregnant people with any initial vaccination *during* their pregnancy with unvaccinated pregnant people during the pre-Delta, Delta, and Omicron periods, respectively (Table 2). For severe COVID-19 infections, the aHRs were 0.65 (95% CI: 0.47, 0.90) and 0.79 (95% CI: 0.51, 1.21) for the same group during the Delta and Omicron periods, respectively. The model results for both co-primary outcomes for pregnant people with initial vaccinations *before* their pregnancy and unvaccinated pregnant people were similar.

Compared with unvaccinated pregnant people, the aHR of incident COVID-19 infections for those with booster vaccinations *during* their pregnancy was 0.52 (95% CI: 0.47, 0.58) during the Omicron period, and the aHR of severe COVID-19 infections was 0.35 (95% CI: 0.22, 0.54). The result of the comparison between unvaccinated pregnant people and pregnant people with booster vaccinations *before* their pregnancy was similar. In addition, compared with pregnant people with full initial vaccinations during their pregnancy, the aHR of incident COVID-19 infections for pregnant people with booster during their pregnancy was 0.64 (95% CI: 0.58, 0.71), and the aHR of severe COVID-19 infections was 0.35 (95% CI: 0.24, 0.50).

Cohort 2 findings: Pregnant people had a lower risk of COVID-19 infections but a higher risk of severe COVID-19 infections compared to vaccinated non-pregnant people during the Delta and Omicron periods

In Cohort 2, among vaccinated non-pregnant females, 159,106 (18.4%) had breakthrough COVID-19 infections during the entire study period, of whom 3,717 (0.43%) developed severe COVID-19 infections (Table 1).

For breakthrough COVID-19 infections, the aHRs were 0.92 (95% CI: 0.61, 1.40), 0.79 (95% CI: 0.69, 0.91), and 0.61 (95% CI: 0.55, 0.69) comparing pregnant people with initial vaccinations *during* their pregnancy with vaccinated non-pregnant people for the pre-Delta, Delta, and Omicron periods, respectively (Table 3). For the same comparison, the aHRs for severe COVID-19 infections were 3.25 (95% CI: 1.76, 5.99) and 2.71 (95% CI: 1.31, 5.60) during the Delta and Omicron periods, respectively. The adjusted aHRs of breakthrough and severe COVID-19 infections for pregnant people with initial vaccinations *before* their pregnancy vs. vaccinated non-pregnant people were similar.

Compared with non-pregnant people with booster vaccinations, the aHRs for breakthrough infections during the Omicron period were 0.79 (95% CI: 0.69, 0.89) and 0.73 (95% CI: 0.64, 0.84) for pregnant people with booster vaccinations *during* and *before* their pregnancy, respectively. Furthermore, the aHRs for severe COVID-19 infections was 3.43 (95% CI: 2.59, 4.55) comparing non-pregnant people with booster vaccinations and pregnant people with booster vaccinations *during* their pregnancy.

More descriptive results on person-time at risk distribution, the timing of vaccinations, and incident/breakthrough infections can be found in supplementary figures 2 - 7. Full primary model results can be found in supplementary tables 2 and 3. The sensitivity analyses limiting the cohort to only people with at least one recorded COVID-19 test or those vaccinated receiving only mRNA vaccines showed similar results as our main analysis (supplementary tables 4 and 5). Descriptive numbers of included people stratified by pre-Delta, Delta, and Omicron predominant periods can be found in supplementary table 6.

DISCUSSION

In the U.S. nationally sampled cohort study, pregnant people who had initial vaccinations during or before their pregnancy were at a lower risk of incident and severe COVID-19 infection compared to unvaccinated pregnant people before the Omicron period. This reduction was more pronounced for severe COVID-19 infections with greater protection during the Delta period (nearly 60% lower risk for pregnant people with initial vaccination during pregnancy). The protective effect of initial vaccinations appeared to decrease during the Omicron period. However, booster vaccinations further protected pregnant people from incident and severe COVID-19 infections during the Omicron period compared to both unvaccinated and initial series only vaccinated pregnant people. Additionally, although vaccinated pregnant people did not appear to be at higher risk for incident COVID-19 infections compared to vaccinated non-pregnant females, they did face a higher risk of severe COVID-19 infections. Our findings suggested that vaccinated pregnant people continued to be at higher risk for severe COVID-19 infections and should be considered a priority population for further booster vaccinations. We also suggest pregnant people seek medical attention if they experience symptoms of COVID-19.

COVID-19 vaccination is advantageous for various groups of people to reduce the risk of incident and severe COVID-19 infections,[2], [29], and booster vaccinations could further protect pregnant people after initial vaccinations[31], [32], [33]. These observation holds for pregnant people, as we and others have found. Simultaneously, there is reassuring data on

the COVID-19 vaccine safety profile for maternal and newborn outcomes among pregnant people, as demonstrated by others and our team.[16], [17], [34] Our results suggest that vaccination during pregnancy or before the pregnancy could both be effective for preventing incident and severe COVID-19 infections. Thus, pregnant people (or those intending a pregnancy soon), their providers, and policymakers should feel confident in concluding that the currently known benefits of vaccination outweigh any known or hypothetical risks.

Our study also provides unique findings to date. We found a higher risk of severe COVID-19 infection post-COVID-19 vaccination among pregnant vs. non-pregnant people considering both initial vaccinations and booster vaccinations people across the pandemic stages. This higher risk may largely be driven by the underlying risk of COVID-19 infection severity among pregnant people, which is consistent with the findings from other studies.[22], [35] Relative to published reports, our study accounted for the potential variations in COVID-19 infection risk by the stage of the pandemic, the vaccination timing relative to the pregnancy, and vaccination status (full initial vs. booster). Though our data suggested that the monovalent boosters were less protective against incident COVID-19 infections during the Omicron predominance period than vaccinations for prior variants periods (30% vs. 60% risk reduction), our data demonstrate that booster, monovalent vaccinations still offered protection for vaccinated pregnant people. Bivalent booster vaccinations are hoped to offer even greater protection for pregnant people. We aim to better adjudicate booster vaccination effectiveness once more such records accrue in N3C.

Despite being the largest and first study of its kind, our study faces several limitations.

1) As with any dataset composed of EHR data, the risk of misclassification and the rate of missingness is high. We believe that the vaccination rates are likely underreported in N3C,[24] a non-differential misclassification biasing our results towards the null. By excluding data partner sites that reported vaccination rates less than the lowest quartile, we hope to have minimized potential bias from this misclassification. 2) Pregnant people may have received more frequent testing or more frequent monitoring for incident or severe COVID-19 infections than non-pregnant people. We attempted to ascertain this potential source of bias via a sensitivity analysis limiting the analytic group to only people with at least one COVID-19 test result recorded, and the attenuated point estimates still suggested similar findings. 3) Hospitalization rates are high within our pregnant cohorts, likely due to confounding of hospitalization due to delivery. To address this issue, we defined severe COVID-19 infections as any COVID-19-related hospitalization but not within 7 days of delivery. Relatedly, the overall rates of other severe COVID-19 outcomes are, fortunately, rare in this dataset, which could be secondary to underreporting. 4) As with all N3C data, source validation is not possible; our attempts at phenotyping the study population, healthcare sites, exposures, and outcomes have been established in other validated studies or published previously with N3C data.[2], [23] 5) As this is a retrospective cohort study, we are not able to obtain information about the way that COVID-19 testing was implemented. To address the potential bias in COVID-19 testing, we conducted a sensitivity analysis by limiting our dataset to only those with at least one COVID-19 test record. Notwithstanding these limitations, our work presents some of the most compelling data to date on understanding the real-world COVID-19 vaccine effectiveness through various variant periods among pregnant people.

Conclusion

In conclusion, we find that pregnant people who are vaccinated during or before their pregnancy had a lower risk of developing incident or severe COVID-19 infection compared to unvaccinated pregnant people, and booster vaccinations could provide further protection for pregnant people during the Omicron period after the initial series of vaccinations. However, vaccinated pregnant people still face a higher risk of severe COVID-19 infection post-vaccination compared to vaccinated non-pregnant females. Thus, pregnant people should continue to get vaccinated to protect against COVID-19 infections and should be considered a priority population for booster vaccinations. With increasingly reassuring data of no known adverse maternal or infant outcomes associated with COVID-19 vaccinations, pregnant people and their providers should feel confident about pursuing vaccinations during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was possible because of the patients whose information is included within the data, the organizations, and the scientists who have contributed to the ongoing development of this community resource.

N3C Attribution

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave covid.cd2h.org/enclave and supported by CD2H - The National COVID Cohort Collaborative (N3C) IDeA CTR Collaboration 3U24TR002306-04S2 NCATS U24 TR002306. This research was possible because of the patients whose information is included within the data from participating organizations (covid.cd2h.org/dtas) and the organizations and scientists (covid.cd2h.org/duas) who have contributed to the on-going development of this community resource (cite this <https://doi.org/10.1093/jamia/ocaa196>).

Individual Acknowledgements For Core Contributors

We gratefully acknowledge the following core contributors to N3C:

Adam B. Wilcox, Adam M. Lee, Alexis Graves, Alfred (Jerrod) Anzalone, Amin Manna, Amit Saha, Amy Olex, Andrea Zhou, Andrew E. Williams, Andrew Southerland, Andrew T. Girvin, Anita Walden, Anjali A. Sharathkumar, Benjamin Amor, Benjamin Bates, Brian Hendricks, Brijesh Patel, Caleb Alexander, Caroline Signore, Carolyn Bramante, Cavin Ward-Caviness, Charisse Madlock-Brown, Christine Suver, Christopher Chute, Christopher Dillon, Chunlei Wu, Clare Schmitt, Cliff Takemoto, Dan Housman, Davera Gabriel, David A. Eichmann, Diego Mazzotti, Don Brown, Eilis Boudreau, Elaine Hill, Elizabeth Zampino, Emily Carlson Marti, Emily R. Pfaff, Evan French, Farrukh M Korashy, Federico Mariona, Fred Prior, George Sokos, Greg Martin, Harold Lehmann, Heidi Spratt, Hemalkumar Mehta, Hongfang Liu, Hythem Sidky, J.W. Awori Hayanga, Jami Pincavitch, Jaylyn Clark, Jeremy Richard Harper, Jessica Islam, Jin Ge, Joel Gagnier, Joel H. Saltz, Joel Saltz, Johanna Loomba, John Buse, Jomol Mathew, Joni L. Rutter, Julie A. McMurry, Justin Guinney, Justin Starren, Karen Crowley, Katie Rebecca Bradwell, Kellie M. Walters, Ken Wilkins, Kenneth R. Gersing, Kenrick Dwain Cato, Kimberly Murray, Kristin Kostka, Lavance Northington, Lee Allan Pyles, Leonie Misquitta, Lesley Cottrell, Lili Portilla, Mariam Deacy, Mark M. Bissell, Marshall Clark, Mary Emmett, Mary Morrison Saltz, Matvey B. Palchuk, Melissa A. Haendel, Meredith Adams, Meredith Temple-O'Connor, Michael G. Kurilla, Michele Morris, Nabeel Qureshi, Nasia Safdar, Nicole Garbarini, Noha Sharafeldin, Ofer Sadan, Patricia A. Francis, Penny Wung Burgoon, Peter Robinson, Philip R.O. Payne, Rafael Fuentes, Randeep Jawa, Rebecca Erwin-Cohen, Rena Patel, Richard A. Moffitt, Richard L. Zhu, Rishi Kamaleswaran, Robert Hurley, Robert T. Miller, Saiju Pyarajan, Sam G. Michael, Samuel Bozzette, Sandeep Mallipattu, Satyanarayana Vedula, Scott Chapman, Shawn T. O'Neil, Soko Setoguchi, Stephanie S. Hong, Steve Johnson, Tellen D. Bennett, Tiffany Callahan, Umit Topaloglu, Usman Sheikh, Valery Gordon, Vignesh Subbian, Warren A. Kibbe, Wendy Hernandez, Will Beasley, Will Cooper, William Hilleagass, Xiaohan Tanner Zhang. Details of contributions available at covid.cd2h.org/core-contributors

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The following institutions whose data is released or pending:

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Pending: Arkansas Children’s Hospital — UL1TR003107: UAMS Translational Research Institute • Baylor College of Medicine — None (Voluntary) • Children’s Hospital of Philadelphia — UL1TR001878: Institute for Translational Medicine and Therapeutics • Cincinnati Children’s Hospital Medical Center — UL1TR001425: Center for Clinical and Translational Science and Training • Emory University — UL1TR002378: Georgia Clinical and Translational Science Alliance • HonorHealth — None (Voluntary) • Loyola University Chicago — UL1TR002389: The Institute for Translational Medicine (ITM) • Medical College of Wisconsin — UL1TR001436: Clinical and Translational Science Institute of Southeast Wisconsin • MedStar Health Research Institute — UL1TR001409: The Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS) • MetroHealth — None (Voluntary) • Montana State University — U54GM115371: American Indian/Alaska Native CTR • NYU Langone Medical Center — UL1TR001445: Langone Health’s Clinical and Translational Science Institute • Ochsner Medical Center — U54GM104940: Louisiana Clinical and Translational Science (LA CaTS) Center • Regenstrief Institute — UL1TR002529: Indiana Clinical and Translational Science Institute • Sanford Research — None (Voluntary) • Stanford University — UL1TR003142: Spectrum: The Stanford Center for Clinical and Translational Research and Education • The Rockefeller University — UL1TR001866: Center for Clinical and Translational Science • The Scripps Research Institute — UL1TR002550: Scripps Research Translational Institute • University of Florida — UL1TR001427: UF Clinical and Translational Science Institute • University of New Mexico Health Sciences Center — UL1TR001449: University of New Mexico Clinical and Translational Science Center • University of Texas Health Science Center at San Antonio — UL1TR002645: Institute for Integration of Medicine and Science • Yale New Haven Hospital — UL1TR001863: Yale Center for Clinical Investigation

Role of the funding source

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave <https://covid.cd2h.org> and N3C Attribution and Publication Policy v 1.2-2020-08-25b supported by NCATS U23 TR002306. Individual authors were supported by the following funding sources: NIMH R01131542 (Rena C. Patel), NICHD R21105304 (Anup P. Challa). The funding sources or study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Data sharing

Concept IDs, templates, or other specified data tools may be made available to others requesting them upon communication with the corresponding author, demonstration of appropriate ethic reviews (IRB approval), and establishment of data sharing agreements with N3C.

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Key messages:

- 1.** What is already known on this topic

Pregnant people are at higher risk of severe COVID-19 outcomes and adverse pregnancy outcomes (e.g., preeclampsia/eclampsia, preterm birth, or fetal death).

COVID-19 vaccination can reduce the risk of COVID-19 infection and severe COVID-19 outcomes and is safe for use among pregnant people.
- 2.** What this study adds

The protective effect of initial COVID-19 vaccines (i.e., two doses for mRNA or other vaccines and one dose for the Janssen vaccine) waned down during the Omicron period, but booster vaccines further protected pregnant people from incident and severe COVID-19 infection during the Omicron period.

Vaccinated pregnant people still had a higher risk of severe COVID-19 infections compared to vaccinated non-pregnant people during Delta and Omicron periods.
- 3.** How this study might affect research, practice, or policy

Pregnant people should continue to get booster COVID-19 vaccinations, and be considered as a priority group to get protection interventions during public health crises

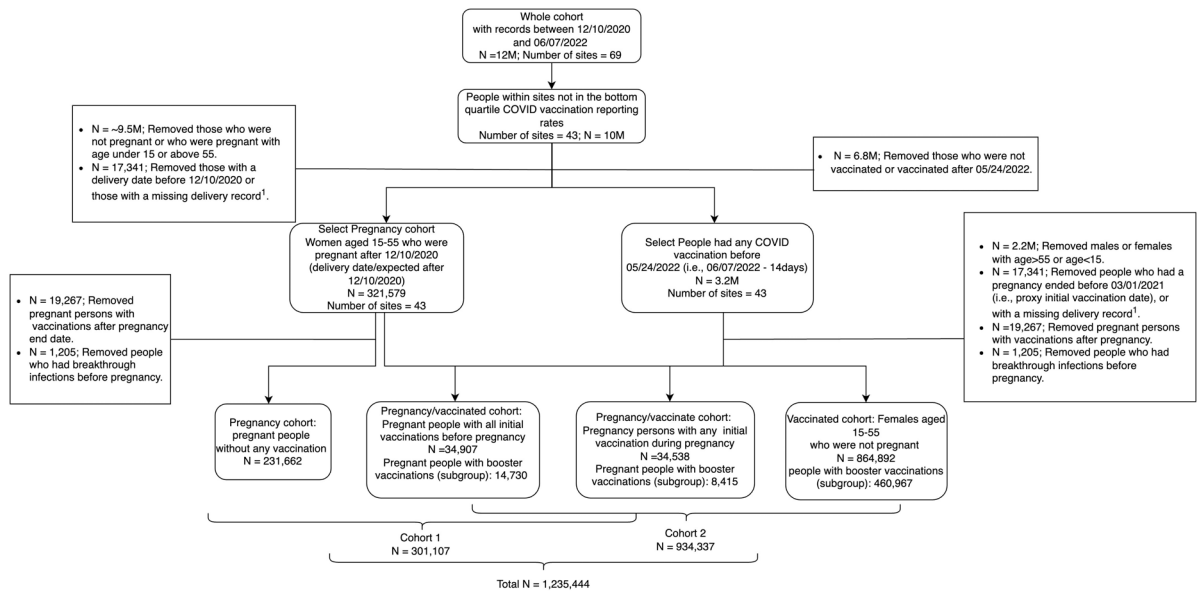


Figure 1.

Table 1: Characteristics of included people in N3C cohort, December 10, 2020 - June 07, 2022

	Cohort 1	Cohort II Cohort 2	Cohort II Cohort 2	Cohort 2
	Non-vaccinated pregnant people (n=231,662)	Pregnant people with initial vaccination <i>during</i> pregnancy (n=34,907)	Pregnant people with initial vaccination <i>before</i> pregnancy (n=34,538)	Non-pregnant vaccinated females aged 15 - 55 years old (n= 864,892)
Age (mean (IQR))	30.2 (25, 33.8)	31.9 (28.0, 36.1)	32.2 (28.2, 35.9)	37.1 (28.1, 47.2)
BMI				
BMI in kg/m ² , median (IQR)	27.5 (23.3, 33.5)	27.4 (23.3, 33.2)	27.5 (23.4, 33.2)	29.4 (24.3, 36.0)
Missing	166,165 (69.92%)	22,776 (65.25%)	18,986 (54.97%)	551,220 (63.7%)
Race/ethnicity				
White/non-Latinx	118,663 (51.22%)	18,731 (53.66%)	20,545 (59.49%)	514,957 (59.54%)
Black/non-Latinx	42,393 (18.30%)	4,574 (13.10%)	3,877 (11.23%)	120,639 (13.95%)
Any race/Latinx	38,382 (16.57%)	7,009 (20.08%)	5,699 (16.50%)	125,068 (14.46%)
Asian American	7,880 (3.40%)	1,850 (5.30%)	1,770 (5.12%)	30,391 (3.51%)
Other	3,376 (1.46%)	676 (1.94%)	578 (1.67%)	20,016 (2.31%)
Missing	20,968 (9.05%)	2,067 (5.92%)	2,069 (5.99%)	53,821 (6.22%)
Region				
Midwest	32,413 (13.99%)	2,914 (8.35%)	2,736 (7.92%)	63,146 (7.30%)
South	34,333 (14.82%)	8,284 (23.73%)	8,071 (23.37%)	159,907 (18.49%)
West	24,321 (10.50%)	3,951 (11.32%)	5,389 (15.60%)	102,324 (11.83%)
Northeast	21,006 (9.07%)	2,620 (7.51%)	2,125 (6.15%)	52,118 (6.03%)
Missing	119,589 (51.62%)	17,138 (49.10%)	16,217 (46.95%)	487,397 (56.35%)
Comorbidities				
Asthma	30,038 (12.97%)	4,719 (13.52%)	4,781 (13.84%)	112,973 (13.06%)
COPD	933 (0.40%)	144 (0.41%)	187 (0.54%)	12,467 (1.44%)
Chronic kidney disease	1,962 (0.85%)	353 (1.01%)	368 (1.07%)	17,242 (1.99%)
Hypertension	2,789 (1.20%)	424 (1.21%)	431 (1.25%)	10,338 (1.20%)
Cardiovascular disease	24,475 (10.56%)	3,362 (9.63%)	3,201 (9.27%)	89,477 (10.35%)
Type I diabetes	2,632 (1.14%)	427 (1.22%)	394 (1.14%)	8,743 (1.01%)
Type II diabetes	9,780 (4.22%)	1,749 (5.01%)	1,698 (4.92%)	73,814 (8.53%)
CCI Index				

	Cohort 1	Cohort II Cohort 2	Cohort II Cohort 2	Cohort 2
CCI=0	43,452 (18.76%)	6,785 (19.44%)	6,895 (19.96%)	165,799 (19.17%)
CCI=1	9,371 (4.05%)	1,600 (4.58%)	1,820 (5.27%)	63,926 (7.39%)
CCI=2	169,671 (73.24%)	25,068 (71.81%)	24,391 (70.62%)	571,002 (66.02%)
CCI=3+	9,168 (3.96%)	1,454 (4.17%)	1,432 (4.15%)	64,165 (7.42%)
First vaccine manufacturer				
Pfizer/BioNTech		25,540 (73.17%)	23,547 (68.18%)	576,921 (66.70%)
Moderna		8,026 (22.99%)	9,130 (26.43%)	239,928 (27.74%)
Janssen		1,195 (3.42%)	1,773 (5.13%)	46,919 (5.42%)
Other		146 (0.42%)	88 (0.25%)	1,124 (0.13%)
Insurance type				
Private insurance	32,791 (14.15%)	6,726 (19.27%)	7,819 (22.64%)	160,659 (18.58%)
Medicare/Medicaid	27,857 (12.02%)	3,843 (11.01%)	3,596 (63.24%)	83,347 (9.64%)
Missing	168,582 (72.77%)	23,293 (66.73%)	21,841 (3.71%)	596,701 (68.99%)
Other	2,432 (1.05%)	1,045 (2.99%)	1,282 (7.92%)	24,185 (2.80%)
Prior COVID-19 positive	4,747 (2.05%)	2,097 (6.01%)	1,512 (4.38%)	64,511 (7.46%)
First vaccination visit type				
Outpatient visit		17,373 (49.77%)	15,431 (44.68%)	345,383 (39.93%)
Emergency visit		131 (0.38%)	97 (0.28%)	1,729 (0.20%)
Other		153 (0.44%)	265 (0.77%)	6,406 (0.74%)
Vaccination status				
Full initial vaccination		28,537 (81.75%)	31,530 (91.29%)	765,929 (88.56%)
Partial initial vaccination		6,370 (18.25%)	3,008 (8.71%)	98,963 (11.44%)
Booster vaccination (with full initial vaccination)		8,415 (24.11%)	14,730 (42.6%)	460,967 (53.30%)
Outcomes				
COVID-19 infection with hospitalization	3,868 (1.67%)	352 (1.01%)	185 (0.54%)	3,717 (0.43%)
Breakthrough/incident COVID-19 infection	39,313 (16.97%)	4,323 (12.40%)	4,577 (13.30%)	159,106 (18.40%)
Ventilation and/or ECMO	162 (0.07%)	<20	<20	118 (0.01%)
ICU	52 (0.02%)	<20	<20	84 (0.01%)

Abbreviations: N3C=National COVID Cohort Collaborative; IQR= inter quartile range; CCI= Charlson Comorbidity Index; ER= emergency department; ECMO= extracorporeal membrane oxygenation; ICU= intensive care unit; COPD= Chronic obstructive pulmonary disease.

Prior COVID-19 positive was defined as whether they have prior COVID-19 diagnosis before the first vaccination date in Cohort 1 or before December 10, 2020 for unvaccinated pregnant people in Cohort 2.

COVID-19 severity outcomes include any hospitalization, including for a delivery, within 14 days before or 45 days after COVID-19 diagnosis; COVID-19-related hospitalization within 14 days before or 45 days after COVID-19 diagnosis but not within +/- 7 days of delivery date; ICU admission within 45 days after COVID-19 diagnosis; invasive ventilation or ECMO within 45 days after COVID-19 diagnosis.

Numbers in a category with number < 20 must be obfuscated to comply with the small number reporting rule for N3C.

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Table 2:

Risk of breakthrough or incident and severe COVID-19 infections among pregnant people (Cohort 1) by vaccination status and variant predominant periods in N3C Cohort, December 10, 2020- June 7, 2022

	Pre-Delta variant dominant period		Delta variant dominant period		Omicron variant dominant period	
	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³
Breakthrough or incident COVID-19 infection						
Initial vaccinations						
Unvaccinated pregnant people	0.36 (0.22, 0.5)	Ref.	1.36 (1.08, 1.63)	Ref.	4.16 (3.59, 4.74)	Ref.
Vaccinated pregnant people with initial vaccinations <i>during</i> pregnancy	0.12 (0, 0.42)	0.36 (0.25, 0.51)	0.91 (0.31, 1.51)	0.77 (0.62, 0.96)	3.7 (2.44, 4.96)	0.88 (0.73, 1.07)
Vaccinated pregnant people with initial vaccinations <i>before</i> pregnancy	-	0.07 (0.04, 0.14)	0.63 (0.16, 1.1)	0.60 (0.53, 0.68)	2.82 (1.79, 3.84)	1.05 (0.95, 1.16)
Booster vaccinations						
Unvaccinated pregnant people					4.16 (3.59, 4.74)	Ref.
Vaccinated pregnant people with booster vaccination <i>during</i> pregnancy					2.55 (1.05, 6.01)	0.52 (0.47, 0.58)
Vaccinated pregnant people with booster vaccination <i>before</i> pregnancy					3.21 (1.57, 4.85)	0.52 (0.41, 0.64)
Vaccinated pregnant people with initial vaccinations <i>during</i> pregnancy ^a					3.96 (0.99, 6.53)	Ref.
Vaccinated pregnant people with booster vaccination <i>during</i> pregnancy					2.55 (1.05, 6.01)	0.64 (0.58, 0.71)
Severe COVID-19 infection						
Initial vaccinations						
Unvaccinated pregnant people			0.15 (0.06, 0.23)	Ref.	0.37 (0.2, 0.54)	Ref.
Vaccinated pregnant people with initial vaccinations <i>during</i> pregnancy			0.08 (0, 0.26)	0.65 (0.45, 0.90)	0.29 (0, 0.64)	0.79 (0.51, 1.21)
Vaccinated pregnant people with initial vaccinations <i>before</i> pregnancy			0.03 (0, 0.12)	0.24 (0.15, 0.39)	0.12 (0, 0.32)	0.39 (0.27, 0.56)
Booster vaccinations						
Unvaccinated pregnant people					0.45 (0.23, 0.53)	Ref.

	Pre-Delta variant dominant period		Delta variant dominant period		Omicron variant dominant period	
	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model (M3) HR (95% CI) ³
Vaccinated pregnant people with booster vaccinations <i>during</i> pregnancy					0.14 (0, 0.58)	0.35 (0.22, 0.54)
Vaccinated pregnant people with full initial vaccinations <i>during</i> pregnancy ^a					0.43 (0, 1.36)	Ref
Vaccinated pregnant people with booster vaccination <i>during</i> pregnancy					0.14 (0, 0.58)	0.35 (0.24, 0.50)

Abbreviations: N3C=National COVID Cohort Collaborative; HR= hazard ratio; CI= confidence interval; Ref= reference; CCI= Charlson comorbidity index.

Model results were generated from Cox proportional hazard model with data partner site level clustered standard error stratified by pandemic variant periods.

Models were adjusted for sociodemographic variables such as age, race/ethnicity, region, clinical covariates such as comorbidities, CCI and prior COVID-19 positivity. Full model result was presented in supplementary table 2.

The number of people with records during variants periods is described in supplementary table 6.

Numbers in a category with number < 20 must be obfuscated to comply with the small number reporting rule for N3C.

^aWe used initial vaccination date plus 90 days as the start follow up time for vaccinated pregnant people with initial vaccinations during pregnancy to compare with those who had booster vaccinations during their pregnancy. We excluded those with COVID-19 incidence/severe infections during the 90 days.

Table 3:

Risk of breakthrough or incident and severe COVID-19 infections among vaccinated people (Cohort 2) by pregnancy status and variant predominant periods in N3C Cohort, December 10, 2020- June 7, 2022.

	Pre-Delta variant dominant period		Delta variant dominant period		Omicron variant dominant period	
	Events/100 women-months (95% CI)	Adjusted Model HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model HR (95% CI) ³	Events/100 women-months (95% CI)	Adjusted Model HR (95% CI) ³
Breakthrough COVID-19 infection						
Initial vaccinations						
Vaccinated non-pregnant females	0.13 (0.08, 0.18)	Ref.	1.34 (1.2, 1.48)	Ref.	5.19 (4.88, 5.49)	Ref.
Vaccinated pregnant people with initial vaccinations <i>during</i> pregnancy	0.12 (0, 0.42)	0.92 (0.61, 1.40)	0.91 (0.31, 1.51)	0.79 (0.69, 0.91)	3.7 (2.44, 4.96)	0.61 (0.55, 0.69)
Vaccinated pregnant people with initial vaccinations <i>before</i> pregnancy	-	0.86 (0.66, 1.13)	0.63 (0.16, 1.1)	0.76 (0.67, 0.87)	2.82 (1.79, 3.84)	0.71 (0.63, 0.80)
Booster vaccination						
Vaccinated non-pregnant females with booster vaccination					4.15 (3.70, 4.6)	Ref.
Vaccinated pregnant people with booster vaccination <i>during</i> pregnancy					3.53 (1.05, 6.01)	0.79 (0.69, 0.89)
Vaccinated pregnant people with booster vaccination <i>before</i> pregnancy					3.21 (1.57, 4.85)	0.73 (0.64, 0.84)
Severe COVID-19 infection						
Initial vaccinations						
Vaccinated non-pregnant females			0.03 (0.01, 0.06)	Ref.	0.11 (0.07, 0.16)	Ref.
Vaccinated pregnant people vaccinated <i>during</i> pregnancy			0.08 (0, 0.26)	3.25 (1.76, 5.99)	0.29 (0, 0.64)	2.71 (1.31, 5.60)
Vaccinated pregnant people vaccinated <i>before</i> pregnancy			0.03 (0, 0.12)	1.29 (0.88, 1.88)	0.12 (0, 0.32)	1.70 (1.08, 2.69)
Booster vaccinations						
Vaccinated non-pregnant females with booster vaccination					0.07 (0.01, 0.13)	Ref.
Vaccinated pregnant people with booster vaccination <i>during</i> pregnancy					0.14 (0, 0.58)	3.43 (2.59, 4.55)

Abbreviations: N3C=National COVID Cohort Collaborative; HR= hazard ratio; CI= confidence interval; Ref= reference; CCI= Charlson comorbidity index.

Model results were generated from Cox proportional hazard model with data partner site level clustered standard error stratified by pandemic variant periods.

Models were adjusted for sociodemographic variables such as age, race/ethnicity, region, clinical covariates such as comorbidities, CCI and prior COVID-19 positivity. Full model result was presented in supplementary table 3.

The number of people with records during variants periods is described in supplementary table 6.

Numbers in a category with number < 20 must be obfuscated to comply with the small number reporting rule for N3C.

We used initial vaccination date plus 90 days as the start follow up time for vaccinated pregnant people with initial vaccinations during pregnancy to compare with those who had booster vaccinations during their pregnancy. We excluded those with COVID-19 incidence/severe infections during the 90 days.

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