ARTICLE

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Critical care among newborns with and without a COVID-19 diagnosis, May 2020–February 2022

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OBJECTIVE: To assess COVID-19 association with newborn critical care outcomes, including nursery level of care and ventilation, during three time periods: Pre-delta (May 2020–June 2021), Delta (July–November 2021), and Omicron (December 2021–February 2022).
STUDY DESIGN: In a retrospective cohort of newborns born May 2020–February 2022 using the Premier Healthcare Database, we classified COVID-19 status and critical care using International Classification of Diseases 10th Revision and Current Procedural Terminology codes, laboratory data, and billing records and assessed for variation during three time periods.
RESULTS: Of 1,388,712 newborns, 0.06% had COVID-19 during the birth hospitalization (Pre-delta period: 0.03%; Delta: 0.07%; Omicron: 0.21%). Among newborns with COVID-19, the risks for admission to a higher-level nursery and for invasive or non-invasive ventilation were lower in the Omicron period compared to Pre-delta and Delta periods.
CONCLUSION: From May 2020–February 2022, COVID-19 in newborns was rare and cases were less severe during the period of Omicron predominance.

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INTRODUCTION

While Coronavirus disease 2019 (COVID-19) in newborns is uncommon, studies have reported 0.4–3.6% of infants born to mothers with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy test positive during the birth hospitalization or within 14 days of birth, depending on methodology, population, and period of the study [1–3]. Findings from the period when wild-type SARS-CoV-2 virus was predominant (March-December 2020) showed that late preterm and term newborns (≥34 gestational weeks) with COVID-19 had an increased risk of neonatal intensive care unit (ICU) admission and early preterm newborns (<34 gestational weeks) with COVID-19 had an increased risk of invasive ventilation support [4]. Further, COVID-19 was a leading cause of death for infants <1 year during 2021–2022 [5].

Although perinatal SARS-CoV-2 transmission to newborns is uncommon, emergence of new and more transmissible strains of the virus has reignited concerns around infant health, and there are particular concerns for infants who have immature immune systems. The Omicron variant (B.1.1.529 and BA sublineages) may be more infectious than the Delta (B.1.617.2) variant [6], possibly due to spike protein mutations leading to increased receptor binding and immune escape [7, 8]. Despite the Omicron variant being associated with record COVID-19 cases and hospitalizations in the U.S., early reports from December 2021–January 2022 using electronic health record data found a lower proportion of ICU admissions, lower mean hospital length of stay in adults, and a lower risk of ICU admission and mechanical ventilation in children aged <5 years than in prior peaks of the COVID-19 pandemic [9, 10]. However, children aged 0–4 years at the peak of the Omicron variant were hospitalized at 5 times the rate of the previous Delta variant peak, and infants <6 months had the highest rate of hospitalization. Approximately 12% of infants <6 months hospitalized with COVID-19 were diagnosed during their birth hospitalization, though 91% of the newborns with COVID-19 were asymptomatic [11].

With continued transmission and no COVID-19 vaccines for children <6 months [12], there is a need to assess critical care needs for newborns with COVID-19 and how they may vary based on predominant strains. To better understand the association of COVID-19 with newborn health, we sought to compare critical care (ICU admission and ventilation support) for newborns by COVID-19 status and gestational age prior to and during the time periods of the Delta variant and Omicron variant predominance.

MATERIALS AND METHODS

Data source

We performed a retrospective cohort analysis of birth hospitalizations using the Premier Healthcare Database Special COVID-19 Release (PHD) (release date: July 19, 2022), an all-payer, administrative database containing patient-level discharge records from nongovernmental, community, and teaching hospitals representing 20% of hospital admissions

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throughout the U.S [13]. We included data from 523 hospitals reporting birth hospitalizations for newborns during May 01, 2020–February 28, 2022.

Study population

We identified birth hospitalizations using *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) diagnostic codes (Supplementary Table). From May 2020–February 2022, 1,518,554 inpatient birth hospitalizations were reported in the PHD. We excluded 1094 duplicate birth records from 544 newborns, 118,329 newborns from 127 hospitals that did not report newborns in all comparison periods of this study, and 10,419 newborns who were born ≥35 gestational weeks and had charges for ventilation support and were discharged home with no evidence of being admitted to a higher-level nursery or ICU. The resulting study sample included 1,388,712 newborns (Supplementary Fig. 1).

Measures and outcomes

COVID-19 status during the birth hospitalization was based on ICD-10-CM code U07.1 (COVID-19, virus identified) during May 2020–February 2022 [14] or positive RNA laboratory test results for SARS-CoV-2 (available for 29.7% of hospitals). Time periods were defined using admission month and to reflect the times at which the Delta and Omicron variants became the predominant circulating variants of SARS-CoV-2: [15] Pre-delta (May 2020–June 2021), Delta (July–November 2021), and Omicron (December 2021–February 2022).

Ventilation support was defined through hospital chargemaster records, ICD-10-CM procedure codes, and Current Procedural Terminology codes and categorized to represent the highest level of ventilatory support received (invasive vs noninvasive) (Appendix 1). Nursery level of care (Level I, Level II, Level III, or higher) was defined using hospital chargemaster records (Appendix 1). Newborns with billing codes for admission to an ICU, step-down unit, or a Level III or Level IV nursery were considered to have admission to a Level III or higher nursery; newborns with chargemaster codes for admission to a Level II nursery were categorized accordingly; and newborns with codes for basic room and board or without codes for higher-level nurseries were categorized as admitted to a Level I nursery. Level of care was categorized to represent the highest level of care received (Level III + vs. Level II) (Appendix 1). There were 7656 newborns who had ventilation in the absence of specific charges for Level II or higher care. Of these, 1491 were discharged to another facility, discharged to hospice, or deceased within a day of birth; these newborns were included for analysis without imputing a higher-level nursery. For the remaining 6165 newborns, we backfilled Level III or higher care when [1] they were born ≤35 weeks' gestation (1876/6165) or [2] had a billing record that indicated likely ICU-level care (e.g., caffeine, surfactant, total parenteral nutrition, furosemide, lorazepam, nitric oxide, umbilical catheter) (4289/6165).

Newborn demographic and health characteristics (sex, race/ethnicity, payor, gestational age, small for gestational age, and discharge status) were described along with hospital characteristics (urbanicity and U.S. census region). Race and ethnicity were combined for this analysis: non-Hispanic Black, Hispanic, non-Hispanic Other/Unknown, and non-Hispanic White. Newborns with unknown Hispanic origin were assumed to be non-Hispanic if race was available. The non-Hispanic Other/Unknown category includes persons reported as a race other than Black or White for which sample size was too small to individually report and are combined into a single category to comply with the Health Insurance Portability and Accountability Act and other regulatory requirements: Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, persons of more than one race, and persons with missing race. Gestational age and small for gestational age were defined using ICD-10-CM codes in the newborn health record. Gestational weeks at the time of delivery are reported through ICD-10-CM codes for preterm newborns; newborns without an ICD-10-CM code for preterm birth were assumed to be born full-term (Appendix 1). Gestational age strata were chosen to reflect the critical threshold at which the majority of infants would not routinely receive respiratory support (32 gestational weeks) [16] nor require admission to an ICU after birth for prematurity (35 gestational weeks) [17].

Disposition was identified from the patient discharge status codes (home; other care [includes discharge/transfer to other facilities]; other/unknown [left against medical advice, information not available]; and death/discharge to hospice). Because data are not reported into the PHD until discharge, analyses of length of hospital stay are limited to newborns discharged within 90 days of birth.

Analysis

Pearson chi-squared tests were used to assess differences in infant and hospital characteristics by COVID-19 status. Median length of stay in days was calculated for newborns born ≥35 gestational weeks, the gestational age cutoff at which ICU admission is not routine, stratified by ICU admission. Levene's test for homogeneity of variance was used to verify the assumption of equal variance. Wilcoxon rank sum tests were used to compare length of stay by COVID-19 status. Poisson regression models with robust standard errors were used to calculate relative risks for critical care, accounting for within-hospital correlation. Relative risks were estimated controlling for race/ethnicity and provider U.S. census region and stratified by gestational age (<35/≥35 weeks for higher level nursery care and <32/≥32 weeks for ventilation support). A priori significance level was set to $p < 0.05$. Analyses of large datasets can result in statistically significant findings that may not be meaningful; consequently, we a priori chose to report significant results with a risk ratio (RR) indicating at least 5% difference for newborns with and without COVID-19 or for newborns with COVID-19 between time periods (Pre-delta: May 2020–June 2021; Delta: July–November 2021; Omicron: December 2021–February 2022). All analyses were performed in SAS® 9.4 (SAS Institute, Cary NC). The data that support the findings of this study are available from Premier Inc. and were used under license for the current study. Restrictions apply to the availability of these data, and so line-level data are not publicly available. Analytic code is available upon request to the first author.

We conducted five sensitivity analyses to assess the impact of exclusion criteria and definitions on the outcomes. First, we excluded all 7 656 newborns who received ventilation support with no indication of being admitted to a Level II nursery or higher level of care who were not discharged home. Second, to assess potential conflation of newborn infection with maternal infection, we excluded newborns with an ICD-10-CM COVID-19 code, no positive laboratory result when laboratory results were available, and an ICD-10-CM code for *Contact with and (suspected) exposure to COVID-19* (Z20.822) to account for the possibility that the COVID-19 diagnosis code on the newborn record was only indicative of a maternal infection. Because the Z20.822 ICD-10-CM code went into effect January 1, 2021, this sensitivity analysis was limited to newborns born after that date. Third, because newborns could be transferred to another facility to receive higher level care at the end of their birth hospitalization, we excluded newborns who were transferred to other facilities or had an unknown discharge status. Fourth, to address potential misclassification of newborns in time periods of variant predominance, we excluded newborns from June 2021 and December 2021 from the analysis because the Delta and Omicron variants rose to be the dominant circulating variants the weeks ending June 26, 2021 and December 25, 2021, respectively [15]. Fifth, in order to test a more generous threshold of when most newborns would be expected to require mechanical ventilation support due to their gestational age, we recalculated the risk for ventilation support, stratifying at 34 instead of 32 gestational weeks.

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy; the activity was determined to meet the requirements of public health surveillance as defined in 45 CFR 46.102(l) [2].

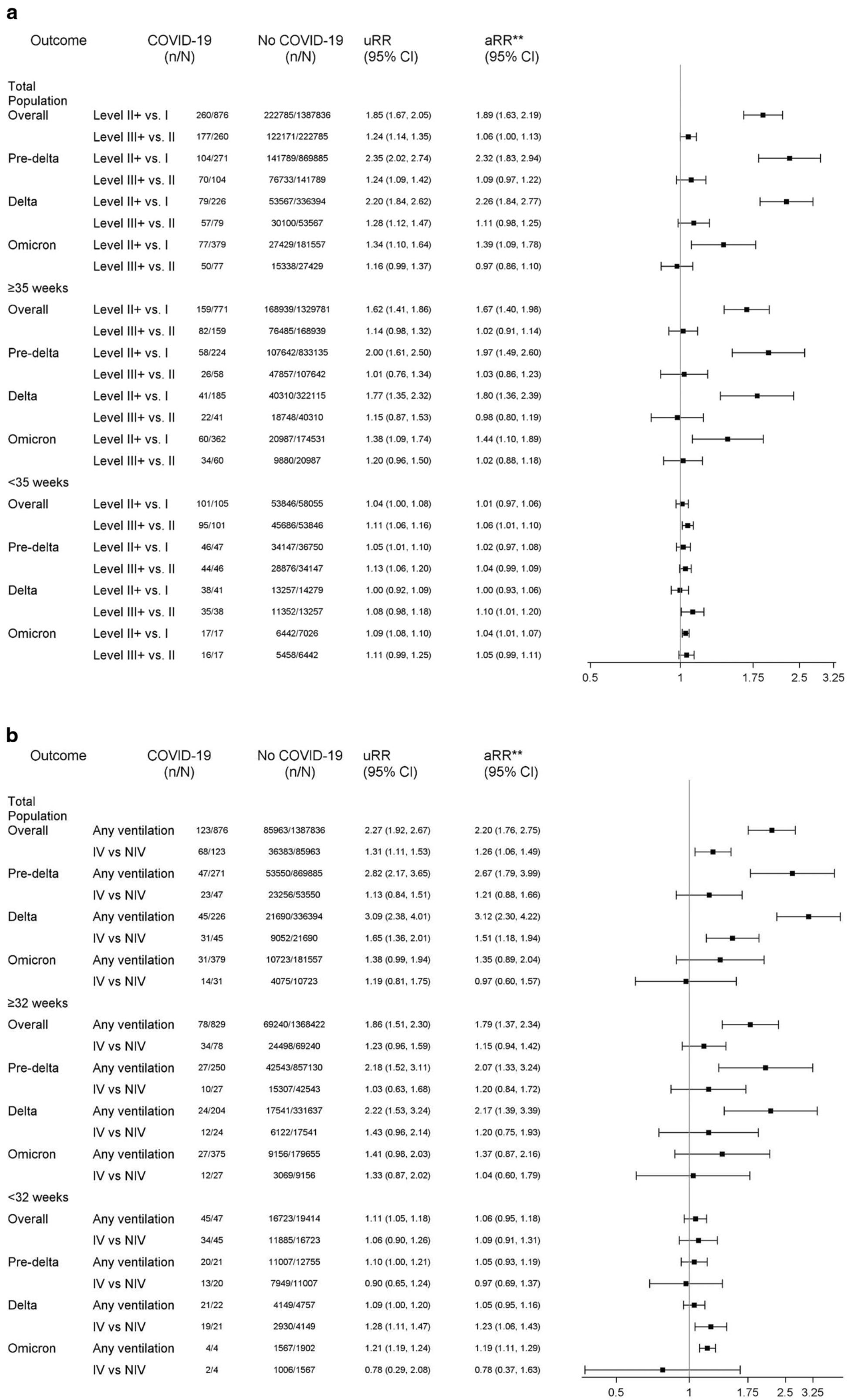
RESULTS

Among 1,388,712 newborns in 523 U.S. hospitals from May 2020–February 2022, 0.06% had COVID-19 during the birth hospitalization (Pre-delta: 0.03%; Delta: 0.07%; Omicron: 0.21%). In all newborns, 48.4% were non-Hispanic White, and 47.6% had Medicaid insurance. Nearly all newborns (97.1%) were discharged home, and 45.5% were born in the South census region. Among those born preterm (9.9% of all newborns), 19.3% were born <34 gestational weeks. Race and ethnicity differed by COVID-19 status overall, in the Pre-delta period, and in the Omicron period, but not in the Delta period; a higher proportion of newborns with COVID-19 were Hispanic compared those without COVID-19 overall (23.1 vs 16.9%), in the Pre-delta (24.0 vs. 15.8%), and in the Omicron period (24.3 vs. 19.0%). The distribution of public and private insurance significantly differed by COVID-19 status overall and in the Pre-delta and Omicron periods, with higher proportion of newborns with Medicaid insurance among those with COVID-19 compared to those without. A higher proportion of newborns with COVID-19 were born preterm (<37 gestational weeks) compared

Table 1. Newborn demographic and health characteristics and hospital characteristics among birth hospitalizations with and without a documented COVID-19 diagnosis, PHD[a], May 2020–February 2022[b].

Characteristics	Total (n = 1,388,712)	Overall COVID-19 (n = 876)	Overall No COVID-19 (n = 1,387,836)	Overall *p*-value[c]	Period 1- Pre delta COVID-19 (n = 271)	Period 1- Pre delta No COVID-19 (n = 855,613)	Period 1 *p*-value[c]	Period 2 - Delta COVID-19 (n = 226)	Period 2 - Delta No COVID-19 (n = 336,394)	Period 2 *p*-value[c]	Period 3 - Omicron COVID-19 (n = 379)	Period 3 - Omicron No COVID-19 (n = 178,596)	Period 3 *p*-value[c]
Infant Characteristics													
Gender													
Female	678,788 (48.88)	423 (48.29)	678,365 (48.88)	0.7675	132 (48.71)	425,031 (48.86)	0.9338	106 (46.90)	164,863 (49.01)	0.7839	185 (48.81)	88,471(48.73)	0.9177
Male	709,295 (51.08)	453 (51.71)	708,842 (51.08)		139 (51.29)	444,425 (51.09)		120 (53.10)	171,413 (50.96)		194 (51.19)	93,004 (51.23)	
Unknown	629 (0.05)	0 (0.00)	629 (0.05)		0 (0.00)	429 (0.05)		0 (0.00)	118 (0.04)		0 (0.00)	82 (0.05)	
Race and Ethnicity[d]													
Black, non-Hispanic	192,621 (13.87)	119 (13.58)	192,502 (13.87)	**<0.0001**	41 (15.13)	121,862 (14.01)	**0.0010**	31 (13.72)	45,763(13.60)	0.7086	47 (12.40)	24,877 (13.70)	**0.0345**
Hispanic	234,302 (16.87)	202 (23.06)	234,100 (16.87)		65 (23.99)	137,271 (15.78)		45 (19.91)	62,424 (18.56)		92 (24.27)	34,405 (18.95)	
Other Unknown, non-Hispanic	289,478 (20.85)	148 (16.89)	289,330 (20.85)		42 (15.50)	18,0986 (20.81)		40 (17.70)	69,923 (20.79)		66 (17.41)	38,421(21.16)	
White, non-Hispanic	672,311 (48.41)	407 (46.46)	671,904 (48.41)		123 (45.39)	429,766 (49.40)		110 (48.67)	158,284 (47.05)		174 (45.91)	83,854(46.19)	
Insurance													
Medicaid	661,584 (47.64)	481 (54.91)	661,103 (47.64)	**<0.0001**	139 (51.29)	415,988 (47.82)	0.0784	117 (51.77)	157,890 (46.94)	**0.0418**	225 (59.37)	87,225 (48.04)	**<0.0001**
Private[e]	615,355 (44.31)	333 (38.01)	615,022 (44.32)		104 (38.38)	385,989 (44.37)		100 (44.25)	150,312 (44.68)		129 (34.04)	78,721 (43.36)	
Self-pay, Other	111,773(8.05)	62 (7.08)	111,711 (8.05)		28 (10.33)	67,908 (7.81)		9 (3.98)	28,192(8.38)		25 (6.60)	15,611 (8.60)	
Infant Health Characteristics													
Gestational Age													
Full Term (37+ weeks)	1,251,732 (90.14)	698 (79.68)	1,251,034 (90.14)	**<0.0001**	195 (71.96)	784,176 (90.15)	**<0.0001**	168 (74.34)	302,937 (90.05)	**<0.0001**	335 (88.39)	163,921 (90.29)	0.2132
Preterm (<37 weeks)	136,980 (9.86)	178 (20.32)	136,802(9.86)		76 (28.04)	85,709 (9.85)		58 (25.66)	33,457 (9.95)		44 (11.61)	17,636 (9.71)	
34-<37 weeks	110,503 (80.67)	108 (60.67)	110,395 (80.70)	**<0.0001**	42 (55.26)	68,582 (80.02)	**<0.0001**	32 (55.17)	26,977 (80.63)	**<0.0001**	34 (77.27)	14,836 (84.12)	0.2145
<34 weeks	26,477 (19.33)	70 (39.33)	26,407 (19.30)		34 (44.74)	17,127 (19.98)		26 (44.83)	6480 (19.37)		10 (22.73)	2800(15.88)	
Small for Gestational Age													
Yes	64,593 (4.65)	37 (4.22)	64,556 (4.65)	0.5478	9 (3.32)	39,286 (4.52)	0.3434	14 (6.19)	16,163 (4.80)	0.3288	14 (3.69)	9107 (5.02)	0.2387
No	1,324,119 (95.35)	839 (95.78)	1,323,280 (95.35)		262 (96.68)	830,599 (95.48)		212 (93.81)	320,231 (95.20)		365 (96.31)	172,450 (94.98)	
Status at Discharge													
Deceased/ hospice	3800 (0.27)	3 (0.34)	3797(0.27)	**<0.0001**	1 (0.37)	2502 (0.29)	**0.0002**	1 (0.44)	847(0.25)	**<0.0001**	1(0.26)	448 (0.25)	0.9574
Home	1,347,745 (97.05)	825 (94.18)	1,346,920 (97.05)		251 (92.62)	843,485 (96.97)		205 (90.71)	326,812 (97.15)		369 (97.36)	176,623 (97.28)	
Other facility	36,068 (2.60)	47 (5.37)	36,021 (2.60)		19(7.01)	23,218 (2.67)		19 (8.41)	8465 (2.52)		9 (2.37)	4338(2.39)	
Other/Unknown	1099 (0.08)	1(0.11)	1098 (0.08)		0 (0.00)	680(0.08)		1 (0.44)	270 (0.08)		0 (0.00)	148 (0.08)	
Urbanicity													
Rural	182,010(13.11)	102 (11.64)	181,908 (13.11)	0.1995	29 (10.70)	114,217 (13.13)	0.2365	33 (14.60)	43,678(12.98)	0.4696	40 (10.55)	24,013(13.23)	0.1250
Urban	1,206,702 (86.89)	774 (88.36)	1,205,928 (86.89)		242(89.30)	755,668 (86.87)		193 (85.40)	292,716 (87.02)		339 (89.45)	157544 (86.77)	
US Census Region[f]													
Midwest	331,399 (23.86)	223 (25.46)	331,176 (23.86)	**<0.0001**	75 (27.68)	208,348 (23.95)	0.1612	47 (20.80)	79,777 (23.72)	**<0.0001**	101 (26.65)	43,051 (23.71)	0.1419
Northeast	179,650 (12.94)	90 (10.27)	179,560 (12.94)		27 (9.96)	112,974 (12.99)		13 (5.75)	43,513 (12.94)		50 (13.19)	23,073 (12.71)	
South	631,142 (45.45)	447 (51.03)	630,695 (45.44)		129 (47.60)	394,201 (45.32)		141 (62.39)	153,295 (45.57)		177 (46.70)	83,199 (45.83)	
West	246,521 (17.75)	116 (13.24)	246,405 (17.75)		40 (14.76)	154,362 (17.75)		25 (11.06)	59,809 (17.78)		51 (13.46)	32,234 (17.75)	

COVID-19 coronavirus disease 2019, *PHD* Premier Healthcare Database Special COVID-19 release.
[a]Premier Healthcare Database, 523 U.S. hospitals with birth hospitalizations.
[b]Pre-delta: May 2020–May 2021; Delta: June–November 2021; Omicron: December 2021–February 2022.
[c]P value associated with Pearson chi-square tests unless otherwise noted; significant results are bolded.
[d]Race and Hispanic origin were collected separately but combined for this analysis. Newborns who had unknown Hispanic origin were assumed to be non-Hispanic if race was available.
[e]Includes managed care and commercial indemnity.
[f]The U.S. Census defines an urban area as a territory whose core census block groups or blocks have a population density of at least 1000 people per square mile, and surrounding census blocks have an overall density of at least 500 people per square mile. Rural areas are considered territories outside the definition of urban.



to those without COVID-19 overall (20.3 vs. 9.9%) and in the Pre-delta and Delta periods (Pre-delta: 28.0 vs. 9.9%; Delta: 25.7 vs. 10.0%), and more preterm newborns with COVID-19 were born <34 gestational weeks overall (39.3 vs. 19.3%) and in the Pre-delta and Delta periods (Pre-delta: 44.7 vs. 20.0%, Delta: 44.8% vs. 19.4). Preterm birth was not significantly different by COVID-19 status in the Omicron period. The distribution of the census region of the hospital differed by COVID-19 status of the newborn overall (South: 51.0% with COVID-19 vs. 45.4% without COVID-19) and in the Delta period (South: 62.4 vs. 45.6%) (Table 1).

Overall, 70.1% of newborns with COVID-19 did not require ventilation support or admission to a higher-level nursery; 61.3%

Fig. 1 Relative risk estimates by COVID-19 status stratified by gestational age* and time period†, PHD, May 2020–February 2022§. Panel **a** is the relative risk for Level II or higher nursery admission. COVID-19 coronavirus disease 2019, PHD Premier Healthcare Database Special COVID-19 release, CI confidence interval, adjusted RR adjusted risk ratio, uRR unadjusted risk ratio. *Gestational age strata were chosen to reflect the critical threshold at which the majority of newborns would not routinely require admission to a higher-level nursery after birth for prematurity (35 gestational weeks). †Pre-delta: May 2020–May 2021; Delta: June–November 2021; Omicron: December 2021–February 2022. §Premier Healthcare Database, 523 hospitals with delivery hospitalizations. **Adjusted for hospital to account for within-facility correlation, provider region, and race and ethnicity. Panel **b** is the relative risk for ventilation support. COVID-19 coronavirus disease 2019, PHD Premier Healthcare Database Special COVID-19 release, IV invasive ventilation support, NIV non-invasive ventilation support, CI confidence interval, adjusted RR adjusted risk ratio, uRR unadjusted risk ratio. *Gestational age strata were chosen to reflect the critical threshold at which the majority of infants would not routinely receive respiratory support (32 gestational weeks). †Pre-delta: May 2020–May 2021; Delta: June–November 2021; Omicron: December 2021–February 2022. §Premier Healthcare Database, 523 hospitals with delivery hospitalizations. **Adjusted for hospital to account for within-facility correlation, provider region, and race and ethnicity.

of newborns with COVID-19 in the Pre-delta period, 64.6% in the Delta period, and 79.7% in the Omicron period did not require ventilation support or admission to a higher-level nursery (Pre-delta vs Delta: $p = 0.44$, Delta vs. Omicron: $p < 0.001$, Pre-delta vs Omicron: $p < 0.001$) (data not shown).

Risk for admission to a higher-level nursery by COVID-19 status

Among newborns ≥35 gestational weeks, there was an increased risk of admission to a Level II or higher nursery for those with COVID-19 compared to those without (overall [adjusted risk ratio (aRR): 1.67; 95% confidence interval (CI): 1.40–1.98]. This increased risk was present in all time periods: Pre-delta (aRR:1.97; 95% CI: 1.49–2.60); Delta (aRR:1.80; 95% CI: 1.36–2.39); and Omicron (aRR:1.44; 95% CI 1.10–1.89) (Fig. 1a).

Risk for ventilation support by COVID-19 status

Among newborns ≥32 gestational weeks, the risk for any ventilation support was increased for those with COVID-19 compared to those without overall (aRR: 1.79; 95% CI:1.37–2.34), in the Pre-delta period (aRR: 2.07; 95% CI:1.33–3.24), and in the Delta period (aRR: 2.17; 95% CI: 1.39–3.39). Among newborns born <32 weeks, the risk for any ventilation support was not different by COVID-19 status overall and in the Pre-delta and Delta periods, but newborns born during the Omicron period with COVID-19 had an increased risk for any ventilation support compared to newborns without COVID-19 (aRR: 1.19; 95% CI: 1.11–1.29); however, the number of newborns with COVID-19 who had any ventilation support in the Omicron period was small ($n = 4$) and should be interpreted with caution (Fig. 1b).

Risk for admission to a higher-level nursery among newborns with COVID-19 by time period

Among all newborns with COVID-19, the risk for admission to a Level II or higher nursery or ICU was lower in the Omicron period compared to the pre-Delta (aRR: 0.57; 95% CI: 0.42–0.77) and Delta periods (aRR: 0.64; 95% CI: 0.47–0.86). Among newborns with COVID-19 born ≥35 gestational weeks, the risk for admission to a Level II or higher nursery was also lower in the Omicron period compared to the Pre-delta period (aRR: 0.62; 95% CI:0.44–0.89) (Fig. 2a).

Risk for ventilation support among newborns with COVID-19 by time period

Among all newborns with COVID-19, the risk for any ventilation support was lower in the Omicron period compared to the Pre-delta (aRR: 0.47; 95% CI: 0.29–0.78) and Delta periods (aRR: 0.42; 95% CI: 0.28–0.65). Additionally, the risks for invasive ventilation support vs. non-invasive ventilation support were lower in the Omicron period compared to the Delta period for those with COVID-19 overall (aRR:0.58; 95% CI: 0.38–0.88) and <32 gestational weeks (aRR:0.41; 95% CI:0.17–0.98). Conversely, the risks for invasive ventilation support vs. non-invasive ventilation support were increased in the Delta period compared to the Pre-delta period for newborns with COVID overall (aRR:1.52; 95% CI:1.09–2.13) and for those born <32 weeks (aRR: 1.52; 95% CI:1.12–2.06) (Fig. 2b).

Length of stay

Among newborns born ≥35 gestational weeks and discharged from the hospital within 90 days, the median length of stay was longer for newborns with COVID-19 compared to those without COVID-19 in all periods and regardless of admission to a higher-level nursery. There were no differences in length of stay between time periods for newborns with COVID-19 (Table 2).

Sensitivity analyses

First, when excluding all newborns who received any ventilation support but did not have billing records for a higher-level nursery, no changes in trends or significance were observed. Second, when assuming that the COVID-19 diagnosis code on the newborn record could represent an exposure instead of a true diagnosis, we observed minor changes. The previously increased risks for invasive vs. non-invasive ventilation support in the Delta vs. Pre-delta periods were no longer significantly increased overall and among newborns born <32 weeks. Third, when excluding all newborns who were transferred out of a facility, the risk of any ventilation support was increased in the Omicron period and the risk for invasive ventilation support in the Pre-delta period was increased for those with COVID-19 compared to those without, while in the original analysis, they were not. As a result, the lower risk for any ventilation support among newborns with COVID-19 in the Omicron period compared to the Pre-delta period was no longer significant, and the increased risk for invasive vs. non-invasive ventilation support in the Delta period compared to the Omicron period was no longer observed. Despite these differences, the confidence intervals for the re-estimated risks and the original risks overlap (Supplementary File).

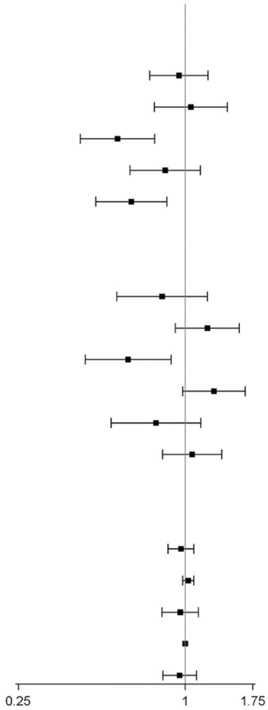
Fourth, when newborns born in June 2021 and December 2021 were dropped from the cohort, we observed minor changes in significance, but patterns remained consistent. The increased risks for higher-level nursery in the Omicron period overall and among newborns born ≥35 gestational weeks were no longer significant. Additionally, among newborns with COVID-19 born at or after 35 gestational weeks the trends of lower risk for any ventilation support in the Omicron period were strengthened. When adjusting the stratification for ventilation support from 32 weeks to 34 weeks, our results were impacted. Gestationally older newborns (≥34 weeks) were not at increased risk for ventilation support in the Pre-delta or Delta periods. Conversely, gestationally younger newborns (<34 weeks) were at increased risk for any ventilation support overall and in the Pre-delta period (Supplementary File).

DISCUSSION

In this observational cohort study including over 1.3 million newborns from 2020–2022, we found that 0.06% had a diagnosis of COVID-19. Newborns diagnosed with COVID-19 were more often born preterm and of Hispanic ethnicity. We found longer lengths of stay and increased risk of admission to a higher-level nursery among those ≥35 gestational weeks, consistent with a prior report [4]. There was also an increased risk of ventilation

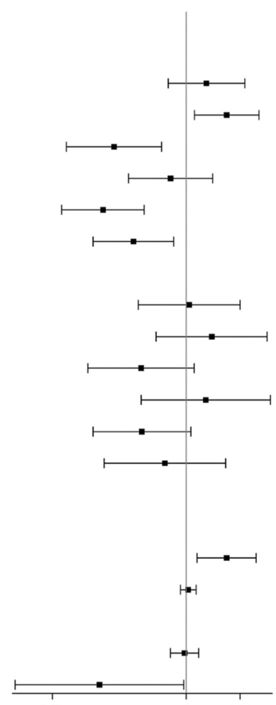
a

Outcome		Pre-delta (n/N)	Delta (n/N)	Omicron (n/N)	uRR (95% CI)	aRR** (95% CI)
Total Population						
Delta vs Pre-delta	Level II+ vs. I	104/271	79/226	77/379	0.91 (0.72, 1.15)	0.95 (0.74, 1.21)
	Level III+ vs. II	70/104	57/79	50/77	1.07 (0.89, 1.30)	1.05 (0.77, 1.42)
Omicron vs pre-delta	Level II+ vs. I	104/271	79/226	77/379	0.53 (0.41, 0.68)	0.57 (0.42, 0.77)
	Level III+ vs. II	70/104	57/79	50/77	0.96 (0.78, 1.19)	0.85 (0.63, 1.13)
Omicron vs Delta	Level II+ vs. I	104/271	79/226	77/379	0.58 (0.44, 0.76)	0.64 (0.47, 0.86)
	Level III+ vs. II	70/104	57/79	50/77	0.90 (0.73, 1.11)	. (. , .)
≥35 weeks						
Delta vs Pre-delta	Level II+ vs. I	58/224	41/185	60/362	0.86 (0.60, 1.21)	0.82 (0.57, 1.20)
	Level III+ vs. II	26/58	22/41	34/60	1.20 (0.80, 1.79)	1.20 (0.92, 1.56)
Omicron vs pre-delta	Level II+ vs. I	58/224	41/185	60/362	0.64 (0.46, 0.88)	0.62 (0.44, 0.89)
	Level III+ vs. II	26/58	22/41	34/60	1.26 (0.88, 1.81)	1.27 (0.98, 1.64)
Omicron vs Delta	Level II+ vs. I	58/224	41/185	60/362	0.75 (0.52, 1.07)	0.78 (0.54, 1.14)
	Level III+ vs. II	26/58	22/41	34/60	1.06 (0.74, 1.51)	1.06 (0.83, 1.35)
<35 weeks						
Delta vs Pre-delta	Level II+ vs. I	46/47	38/41	17/17	0.95 (0.86, 1.04)	. (. , .)
	Level III+ vs. II	44/46	35/38	16/17	0.96 (0.86, 1.08)	0.96 (0.87, 1.07)
Omicron vs pre-delta	Level II+ vs. I	46/47	38/41	17/17	1.02 (0.98, 1.07)	1.02 (0.98, 1.07)
	Level III+ vs. II	44/46	35/38	16/17	0.98 (0.86, 1.12)	0.96 (0.82, 1.12)
Omicron vs Delta	Level II+ vs. I	46/47	38/41	17/17	1.08 (0.99, 1.18)	1.00 (1.00, 1.00)
	Level III+ vs. II	44/46	35/38	16/17	1.02 (0.88, 1.19)	0.95 (0.83, 1.10)



b

Outcome		Pre-delta (n/N)	Delta (n/N)	Omicron (n/N)	uRR (95% CI)	aRR** (95% CI)
Total Population						
Delta vs Pre-delta	Any ventilation	47/271	45/226	31/379	1.15 (0.79, 1.66)	1.23 (0.83, 1.83)
	IV vs NIV	23/47	31/45	14/31	1.41 (0.99, 2.00)	1.52 (1.09, 2.13)
Omicron vs pre-delta	Any ventilation	47/271	45/226	31/379	0.47 (0.31, 0.72)	0.47 (0.29, 0.78)
	IV vs NIV	23/47	31/45	14/31	0.92 (0.57, 1.50)	0.85 (0.55, 1.32)
Omicron vs Delta	Any ventilation	47/271	45/226	31/379	0.41 (0.27, 0.63)	0.42 (0.28, 0.65)
	IV vs NIV	23/47	31/45	14/31	0.66 (0.42, 1.01)	0.58 (0.38, 0.88)
≥32 weeks						
Delta vs Pre-delta	Any ventilation	27/250	24/204	27/375	1.09 (0.65, 1.83)	1.03 (0.61, 1.75)
	IV vs NIV	10/27	12/24	12/27	1.35 (0.72, 2.54)	1.30 (0.73, 2.31)
Omicron vs pre-delta	Any ventilation	27/250	24/204	27/375	0.67 (0.40, 1.11)	0.63 (0.36, 1.09)
	IV vs NIV	10/27	12/24	12/27	1.20 (0.63, 2.29)	1.23 (0.63, 2.39)
Omicron vs Delta	Any ventilation	27/250	24/204	27/375	0.61 (0.36, 1.03)	0.63 (0.38, 1.05)
	IV vs NIV	10/27	12/24	12/27	0.89 (0.50, 1.59)	0.80 (0.43, 1.51)
<32 weeks						
Delta vs Pre-delta	Any ventilation	20/21	21/22	4/4	1.00 (0.88, 1.14)	. (. , .)
	IV vs NIV	13/20	19/21	2/4	1.39 (0.98, 1.98)	1.52 (1.12, 2.06)
Omicron vs pre-delta	Any ventilation	20/21	21/22	4/4	1.05 (0.95, 1.16)	1.02 (0.94, 1.11)
	IV vs NIV	13/20	19/21	2/4	0.77 (0.27, 2.16)	. (. , .)
Omicron vs Delta	Any ventilation	20/21	21/22	4/4	1.05 (0.96, 1.15)	0.98 (0.85, 1.14)
	IV vs NIV	13/20	19/21	2/4	0.55 (0.21, 1.49)	0.41 (0.17, 0.98)



support for newborns ≥32 gestational weeks with COVID-19. Together, these findings suggest that while COVID-19 among newborns is rare, the disease disproportionately affects preterm newborns and has an association with newborn critical care outcomes, even among those born at older gestations.

A significant strength of this study is the ability to assess for trends in the association of COVID-19 with newborn critical care outcomes across three variant periods. The highest proportion of cases occurred during the Omicron period, which was the shortest period of time (3 months), suggesting increased community

Fig. 2 Relative risk estimates between time periods* among newborns with COVID-19 stratified by gestational age*, PHD§, May 2020–February 2022§. Panel **a** is the relative risk for Level II or higher nursery admission. COVID-19 coronavirus disease 2019, PHD Premier Healthcare Database Special COVID-19 release, CI confidence interval, adjusted RR adjusted risk ratio, uRR unadjusted risk ratio. *Pre-delta: May 2020–May 2021; Delta: June–November 2021; Omicron: December 2021–February 2022. †Gestational age strata were chosen to reflect the critical threshold at which the majority of newborns would not routinely require admission to an ICU after birth for prematurity (35 gestational weeks). §Premier Healthcare Database, 523 hospitals with delivery hospitalizations. **Adjusted for hospital to account for within-facility correlation, provider region, and race and ethnicity. Panels **b** is the relative risk for ventilation support. COVID-19 coronavirus disease 2019, PHD Premier Healthcare Database Special COVID-19 release, IV invasive ventilation support, NIV non-invasive ventilation support, CI confidence interval, adjusted RR adjusted risk ratio, uRR unadjusted risk ratio. *Pre-delta: May 2020–May 2021; Delta: June–November 2021; Omicron: December 2021–February 2022. †Gestational age strata were chosen to reflect the critical threshold at which the majority of infants would not routinely receive respiratory support (32 gestational weeks). §Premier Healthcare Database, 523 hospitals with delivery hospitalizations. **Adjusted for hospital to account for within facility correlation, provider region, and race and ethnicity.

transmission of the Omicron variant. The risks for critical care relative to COVID-19 status varied by time period. Our results suggest that the risks for critical care for newborns with COVID-19 were lower in the Omicron period than in the preceding waves of the pandemic; we observed a decreased risk for any ventilation support in the Omicron period compared to prior periods for all newborns with COVID-19, and the risk of admission to a higher-level nursery was decreased in the Omicron period compared to prior periods in all newborns with COVID-19 and in newborns with COVID-19 born ≥35 gestational weeks when comparing the Omicron and pre-Delta periods. We did observe an increased risk for invasive ventilation support for newborns born <32 weeks who had COVID-19 in the Delta period compared to both the Pre-delta and Omicron periods. This suggests that the Delta strain may have been more virulent than the preceding SARS-CoV-2 variants. These results are consistent with prior reports which suggest that Omicron may be less severe in non-pediatric populations [18] and may be characterized by less involvement of the lower respiratory tract [19]. In a study looking specifically among pediatric hospitalizations with COVID-19, the proportion admitted to the ICU or who received invasive ventilation support was lower in the Omicron period than other periods [10]. Though the risk for critical care for newborns with COVID-19 were lower in the Omicron period, the higher rate of cases in this period may yield a higher public health burden. Our finding of decreased admissions to higher-level of nursery care and lower ventilation support in the Omicron period for newborns may be a product of decreased virulence of the Omicron SARS-CoV-2 strain, but may also be influenced by maternal COVID-19 antibody transfer, either through higher population seroprevalence through increased rates of maternal COVID-19 vaccination or increased SARS-CoV-2 infections [18]. Prior reports have described that maternal COVID-19 vaccination is associated with a reduced risk of COVID-19 associated hospitalizations in infants [20], and at the end of February 2022, 77.6% of pregnant females age 18–49 were fully vaccinated [21]. Unfortunately, we cannot ascertain maternal vaccination status from the PHD. Additionally, we do not have information on hospital policies, and it is possible that variation in hospital policies on breastfeeding and newborn isolation over time influence whether the newborn receives a higher-level of nursery care.

We previously observed a higher proportion of newborns with COVID-19 who were born preterm overall compared to newborns without COVID-19 [4], a trend which we continued to observe overall and in the Pre-delta and Delta periods in our current results. However, there was no difference in preterm birth in the Omicron period by COVID-19 status. Though pregnant persons with SARS-CoV-2, especially those with infection later in pregnancy, are at increased risk for preterm delivery [22–24], Olsen et al. [2] found that infants born preterm were more frequently tested for COVID-19, and neonatal positivity was correlated with neonatal testing. It is possible there is some misclassification of COVID-19 status, particularly for full term newborns, because of testing differences. Further studies that can control for differences in testing by time period and for differences between preterm and full-term newborns, that can control for maternal factors such as preeclampsia, and that can assess the impact of maternal vaccination status are needed to confirm whether risks for preterm delivery and birth are different in the Omicron period.

We report the risks for critical care in newborns throughout the COVID-19 pandemic, May 2020-February 2022, using a large, hospital-discharge dataset. Our results are subject to several limitations. Because we focus on the birth hospitalization alone, our results cannot be extrapolated to older infants. Also, maternal and infant records cannot be linked in the PHD; consequently, we were unable to report or control for maternal factors, including SARS-CoV-2 infection status, COVID-19 vaccination history, maternal age, maternal preeclampsia, or cause of preterm birth. Some of our findings may be due to the consequences of maternal SARS-CoV-2 infection and not the newborns' COVID-19 status. For instance, because pregnant women with COVID-19 have an increased risk for preeclampsia, it is possible that the newborns born to mothers with SARS-CoV-2 infection during pregnancy need more critical care or respiratory support due to perinatal stress or fetal acidosis related to maternal preeclampsia [25]. Though we cannot control for maternal infection, we did conduct a sensitivity analysis excluding newborns with an ICD-10-CM COVID-19 code, no positive laboratory result, and an ICD-10-CM code for *Contact with and (suspected) exposure to COVID-19* (Z20.822) to account for the possibility that the COVID-19 diagnosis code on the newborn record was only indicative of a maternal infection. While there were some statistically significant changes in risks, we did not observe any changes in trends over time. Further, our results cannot be extrapolated beyond the setting of the birth hospitalization. Cases in the PHD cannot be linked between hospital systems, which limited our ability to describe care received after transfer to other providers. When we excluded all newborns transferred to another facility at discharge, our results were impacted; this suggests there may be a bias in our data for newborns who were discharged and transferred to another facility to receive a higher level of care. The risks for ventilation support were sensitive to the threshold for stratification used for gestational age. It is possible that newborns age 32-34 weeks drive this risk, and unfortunately, the sample was not sufficient to explore this group as its own strata.

Our results may be influenced by misclassification bias. First, without genomic sequencing, there is likely misclassification of newborns by variants. We used time period as a proxy for COVID-19 variant – using the date that the variant exceeded 50% nationally from national genomic sequencing. However, there were geographic variations in when the Delta and Omicron variants became dominant in different regions of the U.S [15]. Despite this, when we excluded all newborns born in June (the month Delta rose to predominance) and December (the month Omicron rose to predominance) 2021, there were some statistically significant changes in risks, but we did not observe any changes in trends over time. Though our study period includes the time when the BA.1 Omicron variant was predominant, there may have been other sublineages of the Omicron variant in

Table 2. Length of stay among newborns born ≥35 gestational weeks by admission to higher level nursery, PHD[a], May 2020–February 2022[b].

Level II+ nursery		*Overall* n	Median (IQR)	p-value[c]	*Pre-delta* n	Median (IQR)	p-value[c]	*Delta* n	Median (IQR)	p value[c]	*Omicron* count	Median (IQR)	p-value[c]	*Pre-delta vs. Delta* p-valued	*Delta vs. Omicron* p-value[d]	*Omicron vs. Pre-delta* p-value[d]
Overall	**Overall**	1,330,376	2.0 (1.0–2.0)		833,228	2.0 (1.0–2.0)		322,260	2.0 (1.0–2.0)		174,888	2.0 (1.0–2.0)				
	COVID +	767	2.0 (2.0–3.0)	**<0.0001**	223	2.0 (2.0–3.0)	**<0.0001**	183	2.0 (2.0–3.0)	**<0.0001**	361	2.0 (2.0–3.0)	**<0.0001**	0.9244	0.3704	0.4069
	COVID-	1,329,609	2.0 (1.0–2.0)		833,005	2.0 (1.0–2.0)		322,077	2.0 (1.0–2.0)		174,527	2.0 (1.0–2.0)				
Yes	**Overall**	168,923	3.0 (2.0–5.0)		107,570	3.0 (2.0–5.0)		40,311	3.0 (2.0–5.0)		21,042	3.0 (2.0–5.0)				
	COVID +	155	4.0 (2.0–11.0)	**<0.0001**	57	4.0 (2.0–11.0)	**0.0097**	39	4.0 (3.0–13.0)	**0.0013**	59	3.0 (2.0–12.0)	**0.0421**	0.5273	0.2148	0.7281
	COVID-	168,768	3.0 (2.0–5.0)		107,513	3.0 (2.0–5.0)		40,272	3.0 (2.0–5.0)		20,983	3.0 (2.0–5.0)				
No	**Overall**	1,161,453	2.0 (1.0–2.0)		725,658	2.0 (1.0–2.0)		281,949	2.0 (1.0–2.0)		153,846	2.0 (1.0–2.0)				
	COVID +	612	2.0 (2.0–2.0)	**<0.0001**	166	2.0 (2.0–2.0)	**0.0036**	144	2.0 (2.0–2.0)	**0.0183**	302	2.0 (2.0–2.0)	**<0.0001**	0.9612	0.6674	0.6968
	COVID-	1,160,841	2.0 (1.0–2.0)		725,492	2.0 (1.0–2.0)		281,805	2.0 (1.0–2.0)		153,544	2.0 (1.0–2.0)				

COVID-19 coronavirus disease 2019, *PHD* Premier Healthcare Database Special COVID-19 release.
[a]Premier Healthcare Database, 523 hospitals with delivery hospitalizations.
[b]Pre-delta: May 2020-May 2021; Delta: June-November 2021; Omicron: December 2021–February 2022.
[c]P value associated with Wilcoxon rank sum test testing for differences by COVID-19 status; significant results are bolded.
[d]P value associated with Wilcoxon rank sum test testing for differences by time period; significant results are bolded.

circulation as well. Second, we use ICD-10-CM diagnosis codes as the primary identifier for COVID-19, in combination with COVID-19 laboratory testing which was only available for 0.47% of newborns. Though the ICD-10-CM code for COVID-19 has been found to be both sensitive and specific [26], it is likely that there is some misclassification of COVID-19 status, particularly for full term newborns, as preterm infants have been found to be more frequently tested for COVID-19 [2]. Additionally, testing practices likely varied throughout the outbreak and across hospitals, and because lab data were available for only a small portion of newborns, there could be additional misclassification of newborn COVID-19 status. This likely led to inclusion of asymptomatic infants who were not tested for COVID-19 to be included with other infants without a COVID-19 diagnosis and may overestimate effects. Third, nursery level of care was defined through hospital billing records, and we were unable to assess how the care facilities provided aligned with the AAP definition of levels of neonatal care [17]. There is jurisdictional variability in designation of the level of neonatal care [27], and in an analysis comparing facility self-reported level of neonatal care capacity to the level of neonatal care assessed by the CDC Levels of Care Assessment Tool[SM], 23.5% of facilities self-reported a higher level of care capacity than was assessed [28]. In this analysis, there might be misclassification of the level of nursery a newborn was admitted to. Fourth, we relied on ICD-10-CM codes on the newborn health record to define gestational age, and when a record did not have a code for preterm birth, we assumed the newborn was full-term; this may have led to some misclassification if newborns who are born preterm but are healthy are less likely to have an ICD-10-CM code indicating preterm birth. Fifth, no information was available on hospital policies and changes in higher-level of nursery care may be due to hospital policy including isolation of the neonate from the mother rather than because of neonatal infection.

Despite these limitations, we have used a robust cohort to describe the risk for critical care for newborns with COVID-19 with a comparison to newborns without COVID-19 using a large database of hospital-discharge data from geographically diverse hospitals across the United States. Our ventilation support risk analyses were sensitive to the threshold chosen for the gestational age strata, but there were not enough data to report the risk of ventilation support among newborns born 32–34 gestational weeks alone. Further analysis is needed to assess the risk of ventilation support for this group. Additionally, studies are needed to assess for potential additional long-term impacts of COVID-19 on newborns.

CONCLUSIONS

In this retrospective cohort study, COVID-19 during the birth hospitalization was rare, and the majority of newborns with COVID-19 did not require critical care in the Pre-delta, Delta, and Omicron periods. Further, for newborns with COVID-19, we observed decreased higher-level nursery admission and any ventilation risks in the Omicron period compared to prior waves of the COVID-19 pandemic, which may result from decreased disease severity from infection with the Omicron variant and increasing prevalence of maternal COVID-19 immunity. Despite this, the proportion of newborns with COVID-19 in the Omicron period was seven and three times the rates in the Pre-delta or Delta periods, respectively, and there was an increased risk for invasive ventilation for a small number of newborns which underscores the need for continued preventative measures, like maternal COVID-19 vaccination, to protect newborns against COVID-19.

DISCLAIMER/GRANT NUMBERS

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DATA AVAILABILITY

The data that support the findings of this study are available from Premier Inc. and were used under license for the current study. Restrictions apply to the availability of these data, and so line-level data are not publicly available.

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AUTHOR CONTRIBUTIONS

BW conceptualized and designed the study, carried out analyses, drafted the initial manuscript, and reviewed and revised the manuscript. DC replicated all analyses and reviewed and revised the manuscript. KW, SE, VT, EOO, and DF assisted with and approved study design and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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