Epidemiology of Neonatal COVID-19 in the United States

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abstract

OBJECTIVES: Data on coronavirus disease 2019 (COVID-19) infections in neonates are limited. We aimed to identify and describe the incidence, presentation, and clinical outcomes of neonatal COVID-19.

METHODS: Over 1 million neonatal encounters at 109 United States health systems, from March 2020 to February 2021, were extracted from the Cerner Real World Database. COVID-19 diagnosis was assessed using severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) laboratory tests and diagnosis codes. Incidence of COVID-19 per 100 000 encounters was estimated.

RESULTS: COVID-19 was diagnosed in 918 (0.1%) neonates (91.1 per 100 000 encounters [95% confidence interval 85.3–97.2]). Of these, 71 (7.7%) had severe infection (7 per 100 000 [95% confidence interval 5.5–8.9]). Median time to diagnosis was 14.5 days from birth (interquartile range 3.1–24.2). Common signs of infection were tachypnea and fever. Those with severe infection were more likely to receive respiratory support (50.7% vs 5.2%, $P < .001$). Severely ill neonates received analgesia (38%), antibiotics (33.8%), anticoagulants (32.4%), corticosteroids (26.8%), remdesivir (2.8%), and COVID-19 convalescent plasma (1.4%). A total of 93.6% neonates were discharged home after care, 1.1% were transferred to another hospital, and discharge disposition was unknown for 5.2%. One neonate (0.1%) with presentation suggestive of multisystem inflammatory syndrome in children died after 11 days of hospitalization.

CONCLUSIONS: Most neonates infected with SARS-CoV-2 were asymptomatic or developed mild illness without need for respiratory support. Some had severe illness requiring treatment of COVID-19 with remdesivir and COVID-19 convalescent plasma. SARS-CoV-2 infection in neonates, though rare, may result in severe disease.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2022-056297

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DOI: https://doi.org/10.1542/peds.2022-056297

Accepted for publication Jul 19, 2022

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WHAT'S KNOWN ON THE SUBJECT: Data on neonatal coronavirus disease 2019 (COVID-19) is limited. Most studies are based on case series or on neonates born to mothers with COVID-19. Rates of severe infection, geographic distribution, mode of transmission, and outcomes are unclear.

WHAT THIS STUDY ADDS: We found 91.1 neonatal COVID-19 cases per 100 000 encounters. Most neonates were asymptomatic or developed mild illness. Few required treatment with remdesivir and COVID-19 convalescent plasma. COVID-19 in neonates, though rare, may result in severe disease.

To cite: Devin J, Marano R, Mikhael M, et al. Epidemiology of Neonatal COVID-19 in the United States. *Pediatrics.* 2022;150(4):e2022056297

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was declared an international public health emergency by the World Health Organization in January 2020.[1] Since March 2020, there have been >520 million confirmed cases of COVID-19 and 6.2 million reported COVID-19–related deaths globally.[2]

In the United States, 3.3% of total cases to date have been in patients aged 0 to 4 years, whereas the United Kingdom and Global Pregnancy and Neonatal Outcomes in COVID-19 study puts the rate in neonates across both countries at 0.9%.[3,4] The rate of COVID-19 infection in neonates is lower than in the adult and pediatric populations, possibly because of inherent protective factors.[5,6] Although symptomatic neonates may require admission to the ICU,[7] most present with mild COVID-19 symptoms, maintain spontaneous respiration, and have good overall prognosis.[8,9] Vertical transmission appears to be rare,[9,10] but the rate of community-acquired COVID-19 in neonates is rising because of highly transmissible variants,[11,12] with the geographic areas most affected by COVID-19 changing over time.[13–15]

To our knowledge, existing data on neonatal COVID-19 infections and outcomes in the United States are derived from case studies, voluntary census,[16] or focused on neonates born to SARS-CoV-2–positive mothers.[17,18] The aims of this study are to identify and describe the incidence, geographic distribution, severity, features of presentation, and clinical outcomes of neonatal COVID-19 in the United States using a large, deidentified electronic health record (EHR) database.

METHODS

Study Design and Data Sources

We conducted a cross-sectional study using retrospective neonatal encounter data from the Cerner Real-World Database (CRWD). CRWD is a large, fully deidentified database collated by Cerner Corporation that consists of EHR-agnostic data from >120 United States health systems. It consists of clinical data encompassing demographics, encounters, conditions, laboratory tests, and clinical events.[19] The 2021 third-quarter version of CRWD was used and included >153 million patients and 1.5 billion encounters across all care settings and ages.

We extracted data on neonates aged ≤28 days with positive diagnosis of COVID-19 between March 1, 2020, and February 28, 2021. Variables and outcomes previously identified in studies of COVID-19 in neonates[17,20,21] were used as starting points for data collection. Data were retrieved using the Cerner Corporation-managed data science platform HealtheDataLab,[19] a cloud-based, parallel-distributed computational engine.[19]

This study was approved by the institutional review board of the corresponding author's institution (institutional review board no. 2109133).

Inclusion Criteria

Neonates aged ≤28 days were eligible for inclusion (as positive for SARS-CoV-2 infection) if they had a positive, laboratory-confirmed COVID-19 test or a COVID-19 International Classification of Diseases, 10th Revision diagnosis code of U07.1.[22] Neonates were tested and coded for SARS-CoV-2 according to the guidelines of the individual health system. Refer to Supplemental Table 5 for list of laboratory tests. Patients with missing age were excluded.

Variables and Outcomes

Outcomes of interest were the incidence of COVID-19 infection in neonates in the United States as captured within the CRWD, incidence of severe illness, geographic distribution of infection, and treatment received.

Among several definitions for COVID-19 severity used by pediatricians,[20,23–25] we chose a definition for severe illness that has been previously used in neonates and includes both severe and critical outcomes.[20,25,26] Severe illness was therefore classified as cases that met at least 2 of the following 3 categories[1]: any of fever (>37.5°C), apnea, cough, tachypnea, respiratory distress or recession, supplemental oxygen requirement, vomiting or diarrhea[2]; any of low white blood cell count ($<5 \times 10^9$ per L), low lymphocyte count ($<1 \times 10^9$ per L), or raised C-reactive protein concentration (CRP) (>5 mg per L); and[3] an abnormal chest x-ray.[20,25,26] Diagnosis of pneumonia was used as a proxy for abnormal chest x-ray. The laboratory reference ranges represent the cutoffs for severe COVID-19 classification.[20]

In this study, we used the term "vertical transmission" instead of "congenital infection" used by the World Health Organization.[27] Maternal COVID-19 status could not be ascertained because the data source for this study is deidentified. We used timings and tests defined by Shah et al and in previous studies of neonatal COVID-19[20,28] to identify potential vertical transmission because a 12-hour window for neonatal diagnosis was a more conservative cutoff in the absence of maternal COVID-19 status.

Demographics and comorbidities were retrieved. Geographic distribution of neonatal COVID-19 was determined by patient zip code prefix. Medications of interest included antiviral agents, COVID-19 convalescent plasma (CCP), antibiotics, corticosteroids, immunoglobulins, and inotropes/vasopressors.

Statistical Analysis

Descriptive and inferential statistics were used to describe the population and generate hypotheses on clinical presentation. Incidence of COVID-19 per 100 000 encounters was calculated using the total neonatal population in the database for the study period. Categorical variables were analyzed via Pearson's $\chi 2$ test or Fisher's exact test. Normally distributed continuous variables, presented with means and SDs, were analyzed using student t tests; variables with nonnormal distributions, presented using medians and interquartile ranges (IQRs), were analyzed using Wilcoxon rank-sum tests. A Bonferroni correction set statistical significance at $P < .001$. R version 4.1.0 was used to perform statistical analyses.[29]

RESULTS

Demographics

Positive SARS-CoV-2 diagnoses between March 2020 and February 2021 were identified for 918 of 1 007 269 (0.1%) neonatal encounters with incidence rate of 91.1 (95% confidence interval [CI] 85.3–97.2) neonatal COVID-19 cases per 100 000 encounters (Table 1). Of these, 71 (7.7%) met the criteria for severe COVID-19 infection (7.0 per 100 000 encounters, 95% CI 5.5–8.9).

Overall, 46.5% were female, but most neonates with severe COVID-19 were male (55.0%). The study population was 36.7% Hispanic/Latinx, 27.0% non-Hispanic White, 7.6% non-Hispanic Black or African American, 1.7% non-Hispanic American Indian or Alaskan Native, and 1.0% non-Hispanic Asian American. The most common type of insurance was Medicaid or other government-sponsored insurance (37.4%). Median weight at admission was 3.40 kg (IQR 2.93–3.88). Median age at admission to hospital was 11 days (IQR 1–22) for all neonates and 15 days (IQR 1–22) for those with severe COVID-19. Only 209 patients had mode of delivery recorded, indicating that most neonates presented with COVID-19 at a subsequent encounter after delivery. For neonates with mode of delivery recorded, cesarean delivery rates were 57.1% in the severe COVID-19 category and 37.9% in the nonsevere category.

Diagnosis and Mode of Transmission

A positive laboratory test for SARS-CoV-2 was documented for 440 neonates; the remaining cases were identified using diagnosis codes. One neonate was diagnosed with COVID-19 within 12 hours of birth, suggesting possible vertical transmission or perinatal colonization. The median time to diagnosis was 14.5 days from birth (IQR 3.1–24.2) for all neonates and 20.0 days (IQR 10.8–20.7) for those with severe infection.

Prematurity and Comorbidities

Severe COVID-19

There was a higher proportion of low birth weight (<2500 g) or premature neonates in the severe category than in the nonsevere category ($P < .001$). Comorbidities were more likely in this category ($P < .001$) (Table 1). Among patients with severe COVID-19, 46.5% had at least 1 comorbidity, the most prevalent being a congenital abnormality (38%). Cardiac abnormalities excluding patent ductus arteriosus accounted for 17% of comorbidities. Suspected sepsis was observed in 24%, jaundice in 28.2%, and anemia requiring transfusion in 7.0%.

Nonsevere COVID-19

A total of 7.4% of neonates with nonsevere COVID-19 were premature, with birth weight from 500 to 2499 g. Overall, 25.5% had 1 or more comorbidities, including congenital abnormality (8%).

Clinical Presentation

Neonates were generally asymptomatic at initial presentation for care, with no reported signs of infection in 63.5% (Table 2). The most common signs of infection were tachypnea and fever (Fig 1). Pneumonia was present in 28.2% neonates with severe COVID-19 infection.

Laboratory Findings

Hematologic and biochemical findings were averaged over all results for each encounter in the severe and nonsevere COVID-19 categories (Table 3).

A total of 86% of neonates with severe COVID-19 underwent CRP measurement, in contrast with 12% of those with nonsevere COVID-19. Those with severe COVID-19 were more likely to have higher CRP (median 2 mg per L, IQR 1–8 versus median 0 mg per L, IQR 0–5, $P < .001$). They were also more likely to have lower albumin levels (median 3.2 g per dL, SD 0.5 versus median 3.6 g per dL, SD 0.5, $P < .001$) and decreased platelets (median 267 × 10^3 per μL, IQR 194–342 versus median 305 × 10^3 per μL, IQR 247–381, $P = .003$).

Respiratory Support

Severe COVID-19

There was a higher rate of respiratory support among neonates with severe COVID-19 (50.7% vs 5.2%, $P < .001$). Invasive mechanical

TABLE 1 Demographics, Medical History, and Exposures of Study Participants

	Total Neonates With COVID-19 (n = 918)	Neonates With Severe COVID-19 (n = 71)	Neonates with Nonsevere COVID-19 (n = 847)	Unadjusted P*
Incidence rate per 100 000 encounters (CI)	91.1 (85.3–97.2)	7.0 (5.5–8.9)	84.1 (78.5–90.0)	—
Age at admission, d, median (IQR)	11 (1–22)	15 (1–22)	11 (1–22)	.41
Sex, No. (%)				.02
Female	427 (46.5)	32 (45.1)	395 (46.6)	
Male	418 (45.5)	39 (55.0)	379 (44.8)	
Unknown	73 (8.0)	0 (9.9)	73 (8.6)	
Race/ethnicity, No. (%)				.13
Hispanic/Latinx	337 (36.7)	33 (46.5)	304 (35.9)	
Non-Hispanic American Indian or Alaska Native	12 (1.3)	2 (2.8)	10 (1.2)	
Non-Hispanic Asian American	9 (1.0)	1 (1.4)	8 (0.9)	
Non-Hispanic Black or African American	70 (7.6)	6 (8.5)	64 (7.6)	
Non-Hispanic Native Hawaiian or Pacific Islander	4 (0.4)	0 (0)	4 (0.5)	
Non-Hispanic White	247 (27.0)	19 (26.8)	228 (26.9)	
Other/unknown	239 (26.0)	10 (14.1)	229 (27.0)	
Medical insurance, No. (%)				.08
Commercial	211 (23.0)	22 (31.0)	189 (22.3)	
Medicaid/other governmental	343 (37.4)	29 (40.8)	314 (37.1)	
Other/unknown	364 (39.7)	20 (28.2)	344 (40.6)	
Weight at admission, g, No. (%)				<.001
<1000 (ELBW)	23 (2.5)	2 (2.8)	21 (2.5)	
1000–1499 (VLBW)	7 (0.8)	4 (5.6)	3 (0.4)	
1500–2499 (LBW)	45 (4.9)	6 (8.5)	39 (4.6)	
2500–3999	496 (54.0)	42 (59.2)	454 (53.6)	
4000–4499	94 (10.2)	11 (15.5)	83 (9.8)	
≥4500	31 (3.4)	5 (7.0)	26 (3.1)	
Unknown	222 (24.2)	1 (1.4)	221 (26.1)	
Mode of delivery, No. (%)				.35
Cesarean	82 (9.0)	8 (11.4)	74 (8.7)	
Vaginal (including instrumental)	127 (13.8)	6 (8.6)	121 (14.3)	
Unknown[a]	709 (77.2)	56 (80.0)	653 (77.0)	
LOS, d, median (IQR)	1 (1–2)	5 (2–11)	1 (1–2)	<.001
Neonates with comorbidities, total No. (%)[b]	249 (27.1)	33 (46.5)	216 (25.5)	<.001
Anemia requiring transfusion, No. (%)	8 (0.9)	5 (7.0)	3 (0.4)	
Birth trauma, No. (%)	4 (0.4)	0 (0)	4 (0.5)	
Chronic lung disease, No. (%)	4 (0.4)	4 (5.6)	0 (0)	
Congenital abnormality, No. (%)				
Cardiac (excluding PDA)	43 (4.7)	12 (17.0)	31 (3.7)	—
PDA	6 (0.7)	2 (2.8)	4 (0.5)	—
Other congenital abnormalities	46 (5.0)	13 (18.3)	33 (3.9)	—
Hypoxic ischemic encephalopathy, No. (%)	2 (0.2)	1 (1.4)	1 (0.1)	—
Intraventricular hemorrhage, No. (%)	4 (0.4)	4 (5.6)	0 (0)	—
Hyperbilirubinemia/jaundice, No. (%)	107 (11.7)	20 (28.2)	87 (10.3)	—
Pneumothorax, No. (%)	1 (0.1)	1 (1.4)	0 (0)	—
Retinopathy of prematurity, No. (%)	5 (0.5)	3 (4.2)	2 (0.2)	—
Seizure disorder, No. (%)	17 (1.9)	2 (2.8)	15 (1.8)	—
Sepsis, No. (%)	50 (5.4)	17 (24.0)	33 (4.0)	—

Percentages may not add to 100 because of rounding. ELBW, extremely low birth weight; VLBW, very low birth weight; LBW, low birth rate; PDA, patent ductus arteriosus; —, not applicable.

* Bonferroni-corrected P set significance at <.001.

[a] Mode of delivery present only for 209 neonates.

[b] Four neonates had >3 comorbidities.

ventilation (IMV) was used in 11.3% of these neonates. The majority were premature and had congenital abnormalities. An additional 36.6% of neonates with severe COVID-19 received other forms of respiratory support. One neonate (1.4%) with severe infection and presentation suggestive of multisystem inflammatory syndrome in children (MIS-C) received extracorporeal membrane oxygenation (ECMO) (Table 4).

Nonsevere COVID-19

Among neonates with nonsevere COVID-19, 1.2% received IMV and 3.2% received unspecified respiratory support. Three IMV neonates were term babies,

TABLE 2 Vital Signs at Admission

	Total Neonates With COVID-19 (n = 918)	Neonates With Severe COVID-19 (n = 71)	Neonates With Nonsevere COVID-19 (n = 847)	Unadjusted P*
Heart rate, median (IQR)	152 (140–165)	159 (143–170)	151 (140–164)	.10
Respiratory rate, median (IQR)	44 (36–51)	41 (35–52)	44 (36–50)	.84
Systolic blood pressure, median (IQR)	86 (74–96)	85 (71–96)	87 (74–96)	.69
Diastolic blood pressure, median (IQR)	50 (41–60)	52 (43–60)	50 (41–60)	.71
Sp02, median (IQR)	99 (97–100)	99 (96–100)	99 (97–100)	.15
Temperature, °C, median (IQR)	37.0 (36.6–37.5)	37.2 (36.7–37.9)	37.0 (36.7–37.4)	.07

Sp02, pulse oxygen saturation. * Bonferroni-corrected P set significance at <.001.

admitted with suspected sepsis or respiratory distress.

Medications

Severe COVID-19

Among neonates with severe COVID-19, 2.8% (n = 2) received remdesivir and 1.4% (n = 1) received CCP. This group of patients also received analgesia (38.0%), antibiotics (33.8%), anticoagulants (32.4%), corticosteroids (26.8%), and antiarrhythmics (11.3%).

Nonsevere COVID-19

In the nonsevere group, antibiotic treatment was the most frequently administered medication (7.1%), followed by vitamins (5.7%) and analgesia (5.3%). There were no administrations of immunoglobulin or CCP in this group, although 0.7% received antiviral agents (0.35% remdesivir and 0.35% acyclovir).

Multisystem Inflammatory Syndrome in Children (MIS-C)

One neonate in the severe COVID-19 category presented at 17 days old with normal heart rate, respiratory distress, hypotension, and mild hypothermia. The patient had no diagnosed congenital abnormalities or bacterial infection. Hematologic and biochemistry findings included normal total white blood cells (11.5×10^3 per μL), borderline lymphocytes (2×10^3 per μL), and raised CRP (8.4 mg per L). Anemia and thrombocytopenia were present, with lowest hemoglobin level 8.3 g per dL (average 13.0 g per dL) and lowest platelet level 10×10^3 per μL (average 70×10^3 per μL). Transaminases were highly elevated with aspartate aminotransferase 410 U per L and alanine aminotransferase 518 U per L, indicating severe liver damage. Maximum total bilirubin was 31.7 mg per dL. Coagulation studies showed prolonged prothrombin time of 18 seconds and prolonged activated partial thromboplastin time of 56 seconds.

The patient was administered antibiotics, antiarrhythmics, anticoagulants, vasopressors, analgesia, and vitamins. Although fever was not documented, the overall presentation suggests MIS-C, a rare hyperinflammatory response resulting from exposure to SARS-CoV-2.[30–33] This neonate received ECMO and died after length of stay (LOS) of 11 days.

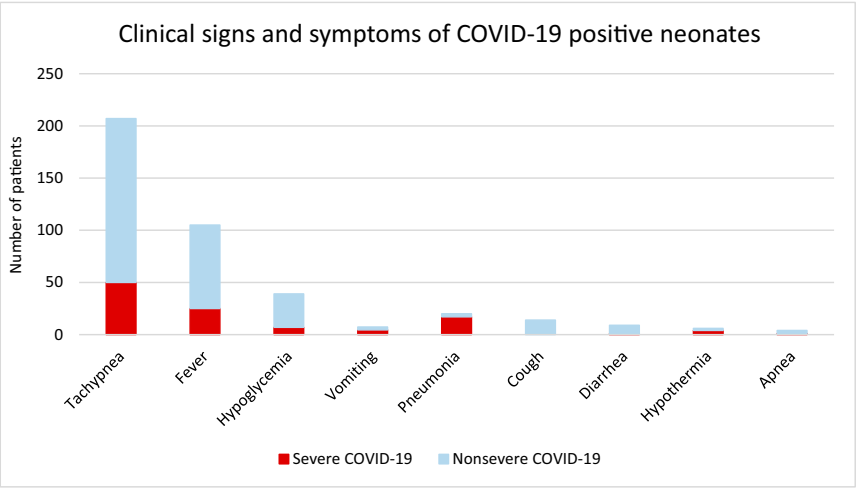

FIGURE 1
Clinical signs and symptoms of COVID-19 infection in neonates.

Discharge Disposition

Most neonates with COVID-19 were discharged home after care (93.6%), with 1.1% transferred to another facility. Median LOS was 5 days in the severe category (IQR 2–11), and 1 day (IQR 1–2) in the nonsevere category. Discharge disposition was unknown for 5.2% participants. The single death represents an overall case fatality rate of 0.1%.

Geographic Distribution

The CRWD contains zip code prefixes so geographic description of cases was restricted to the 10 United States zip code regions. The highest rate of total neonatal COVID-19 cases occurred in zip code region 0 (Connecticut,

TABLE 3 Laboratory Findings of Study Participants

	Neonates With Test Performed, No. (%)	Total Neonates With COVID-19 (n = 918)	Neonates With Severe COVID-19 (n = 71)	Neonates With Nonsevere COVID-19 (n = 847)	Unadjusted P*
Hemoglobin, g per dL, mean (SD)	138 (13.2)	15.0 (3)	14.5 (2)	15.1 (3)	.06
Platelet count, 10^3 per μL, median (IQR)	192 (18.3)	294 (233–376)	267 (194–342)	305 (247–381)	.003
PT, s, median (IQR)	32 (3.1)	13.5 (12.5–14.7)	13.6 (12.6–15.7)	13.2 (12.2–14.1)	.22
aPTT, s, median (IQR)	34 (3.2)	35.7 (30.0–44.4)	35.8 (31.1–48.6)	31.6 (28.8–38.6)	.30
INR, median (IQR)	30 (2.9)	1.0 (1.0–1.2)	1.1 (1.0–1.3)	1.0 (1.0–1.1)	.28
Albumin, g per L, mean (SD)	48 (4.6)	3.5 (0.5)	3.2 (0.5)	3.6 (0.5)	<.001
Ammonia, μg per dL, median (IQR)	10 (1.0)	78.4 (37.8–99.4)	88.2 (23.8–103.6)	68.6 (60.2–84.0)	.99
ALT, U per L, median (IQR)	67 (6.4)	20 (16–29)	23 (17–37)	19 (15–26)	.04
ALP, U per L, median (IQR)	147 (14.0)	229 (180–298)	232 (133–301)	226 (184–294)	.62
AST, U per L, median (IQR)	82 (7.8)	42 (32–54)	46 (37–69)	39 (31–53)	.02
GGT, U per L, median (IQR)	7 (0.7)	138 (84–237)	138 (116–266)	129 (90–168)	.86
Total bilirubin, mg per dL, median (IQR)	208 (19.9)	5.9 (2.6–8.5)	5.2 (1.6–9.0)	5.9 (2.8–8.4)	.63
Direct bilirubin, mg per dL, median (IQR)	53 (5.1)	0.3 (0.2–0.5)	0.3 (0.2-0.5)	0.3 (0.2–0.5)	.91
WBC, 10^3 per μL, median (IQR)	183 (19.9)	10 (7–14)	11 (7–20)	9 (7–13)	.137
Lymphocytes, 10^3 per μL, median (IQR)	144 (15.9)	5 (3–6)	5 (3–7)	4 (3–6)	.523
CRP, mg per L, median (IQR)	75 (8.2)	1 (0–5)	2 (1–8)	0 (0–5)	<.001

ALP, alkanine phosphatase; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; aPTT, activated partial thromboplastin time; GGT, γ-glutamyl transferase; PT, prothrombin time; WBC, white blood cell count. * Bonferroni-corrected P set significance at <.001.

Massachusetts, Maine, New Hampshire, New Jersey, Rhode Island, Vermont), with 77.1 per 100 000 encounters (95% CI 58.3–100.2) (Fig 2). This represented 8.1% of total cases. Region 1 (Delaware, New York, Pennsylvania) had the lowest rate at 22.5 per 100 000 (95% CI 14.6–33.3). The highest rate of severe neonatal COVID-19 cases occurred in region 3 (Alabama, Florida, Georgia, Mississippi, Tennessee), with 9.6 per 100 000 (95% CI 4.4–18.3) (Fig 3). Region 3 also has the lowest cumulative COVID-19 vaccination administration rates as per the

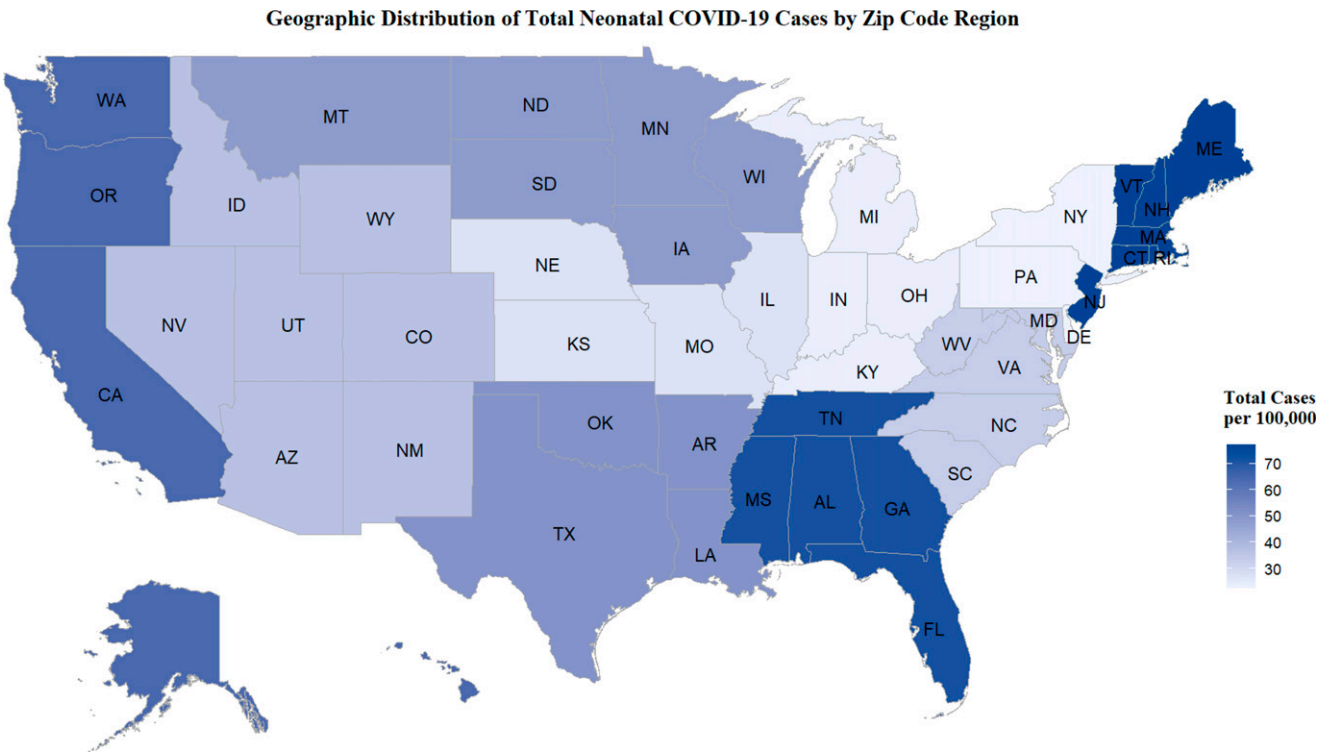

FIGURE 2
Geographical distribution of total neonatal COVID-19 cases in the CRWD per 100 000 encounters, by the 10 United States zip code regions (regions 0–9).

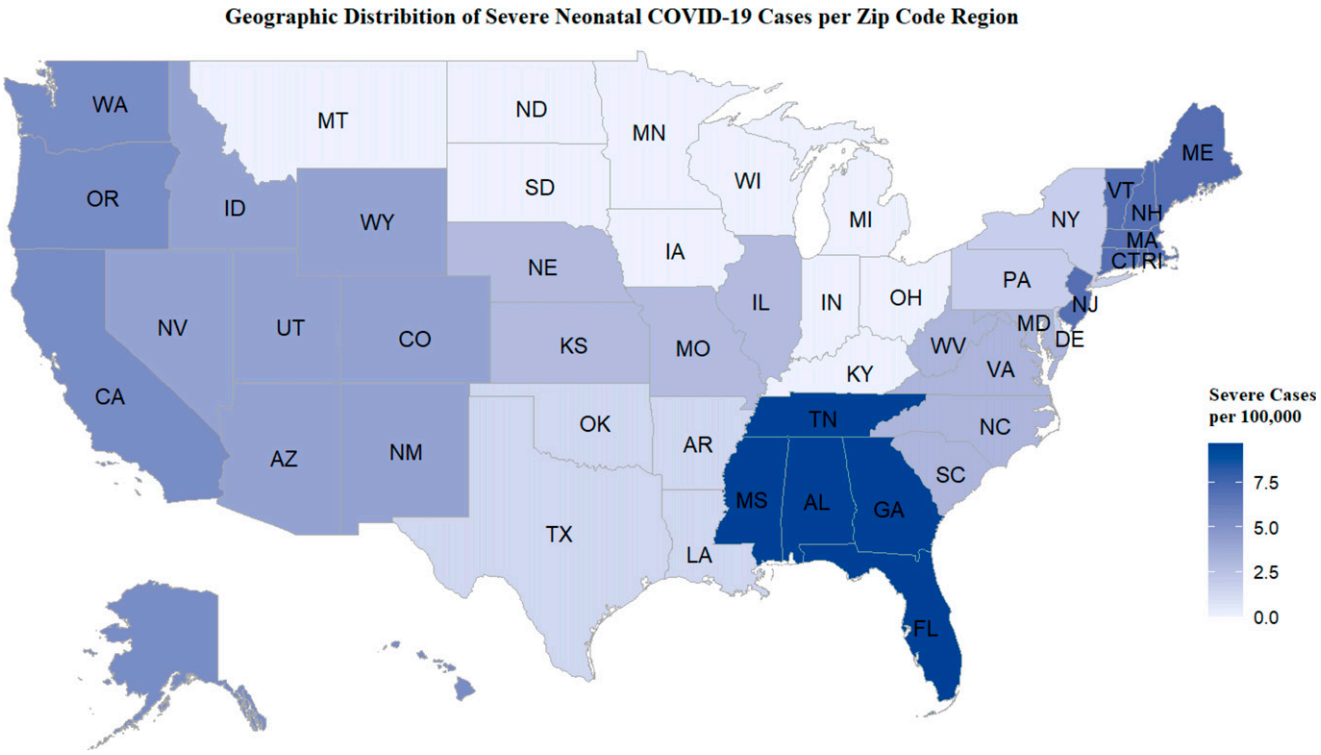

FIGURE 3
Geographical distribution of severe neonatal COVID-19 cases in the CRWD per 100 000 encounters, by the 10 United States zip code regions (regions 0–9).

Centers for Disease Control and Prevention (CDC), at <150 000 doses administered per 100 000 total population.[34]

DISCUSSION

In this study, we identified 918 cases of COVID-19 in neonates in the United States using a large, population-based data set. Most neonates presented with mild symptoms or were asymptomatic, in line with previous studies.[8,9,20] Neonates with severe COVID-19 were more likely to require respiratory support, receive a higher number of medications, and have a longer overall LOS. They were also likely to be premature neonates who may have required respiratory support for complications other than COVID-19. One neonate with suspected MIS-C died, resulting in a case fatality rate of 0.1%.

Neonates with severe COVID-19 had a higher incidence of comorbidities. Cardiac abnormalities may have an impact on disease progression. There have been documented cases of acute respiratory distress in COVID-19–positive neonates after congenital heart surgery or with medically-treated patent ductus arteriosus.[35–37] These findings indicate that the predisposition to severe COVID-19 due to cardiovascular conditions seen in adult and pediatric patients may extend to neonatal patients, as well.[38] Furthermore, it is unclear whether antiarrhythmics were administered for arrythmias in the presence of a cardiac condition, or if arrythmias were a complication of SARS-CoV-2 infection in some neonates. Investigations into the role of congenital abnormalities in COVID-19 in neonates may therefore be helpful.

Our findings agree with previous studies that found low or no vertical transmission in neonates born to SARS-CoV-2–positive mothers, on the basis of length of time from birth to COVID-19 diagnosis.[20,39,40] Neonates hospitalized since birth, such as premature babies, were potentially infected with SARS-CoV-2 via nosocomial transmission. Controlling nosocomial infections in hospital environments can be challenging, particularly in facilities that are at capacity.[41,42] Restricted parental visitation is associated with a lack of bonding time, inability to participate in care, and an adverse impact on breastfeeding.[43] Videoconferencing facilities can be helpful to parents, both for bonding with their baby and for communication with staff, without adversely impacting on infection prevention practices.[44]

MIS-C appeared to be a rare complication of COVID-19. Differential diagnoses, such as sepsis, may have initially been considered and coded.[30] Hypothermia or temperature instability, rather than prolonged fever,

TABLE 4 Treatment and Outcomes of Study Participants

	Total Neonates With COVID-19 (n = 918)	Neonates With Severe COVID-19 (n = 71)	Neonates With Nonsevere COVID-19 (n = 847)	Unadjusted P*
Encounter type, No. (%)				<.001
Inpatient	472 (51.4)	70 (98.6)	402 (47.5)	
Outpatient	270 (29.4)	0 (0)	270 (31.9)	
Emergency	124 (13.5)	1 (1.4)	123 (14.5)	
Unknown	52 (5.7)	0 (0)	52 (6.1)	
Location of care, No. (%)				<.001
NICU	61 (6.6)	17 (23.9)	44 (5.2)	
PICU	40 (4.4)	11 (15.5)	29 (3.4)	
Non-ICU care	742 (80.8)	43 (60.6)	699 (82.5)	
Unknown	75 (8.2)	0 (0)	75 (8.6)	
Highest level of respiratory support, total No. neonates (%)	80 (8.7)	36 (50.7)	44 (5.2)	<.001
Noninvasive ventilation, No. (%)	8 (0.9)	1 (1.4)	7 (0.8)	
IMV, No. (%)	18 (2.0)	8 (11.3)	10 (1.2)	
ECMO, No. (%)	1 (0.1)	1 (1.4)	0 (0)	
Respiratory support, unspecified, No. (%)	53 (5.8)	26 (36.6)	27 (3.2)	
Medication, total No. neonates treated (%)[a]	178 (19.4)	44 (62.0)	135 (16.0)	<.001
Analgesia, No. (%)	72 (7.8)	27 (38.0)	45 (5.3)	
Antiarrythmics, No. (%)	23 (2.5)	8 (11.3)	15 (1.8)	
Antibiotics, No. (%)	84 (8.8)	24 (33.8)	60 (7.1)	
Anticoagulants, No. (%)	37 (4.0)	23 (32.4)	14 (1.7)	
Antivirals, No. (%)	8 (0.9)	2 (2.8)	6 (0.7)	
Convalescent plasma, No. (%)	1 (0.1)	1 (1.4)	0 (0)	
Corticosteroids, No. (%)	29 (3.2)	19 (26.8)	10 (1.2)	
Immunoglobulins, No. (%)	4 (0.4)	4 (5.6)	0 (0)	
Inotropes/Vasopressors, No. (%)	12 (1.3)	10 (14.1)	2 (0.2)	
Vitamins, No. (%)	55 (6.0)	7 (9.9)	48 (5.7)	
Outcome, No. (%)				.003
Died	1 (0.1)	1 (1.4)	0 (0)	
Discharged	845 (93.6)	66 (93.0)	779 (93.6)	
Transfer to another facility	10 (1.1)	3 (4.2)	7 (0.8)	
Unknown	47 (5.2)	1 (1.4)	46 (5.5)	

Percentages may not add to 100 because of rounding. *Bonferroni-corrected P set significance at <.001.

[a] Twenty-two neonates were treated with >3 medications.

have been observed in cases of suspected neonatal MIS-C.[43,45] Abnormal laboratory findings, severely ill presentation, mild hypothermia, and ECMO requirement suggested an atypical MIS-C presentation in the term neonate who died in this study. This neonate also presented with features linked to poorer outcomes in pediatric and adult COVID-19 patients, including extremely elevated transaminases, hyperbilirubinemia, and severe thrombocytopenia.[46–48] ECMO itself may have contributed to the abnormal coagulation findings. It is unclear if there were other risk factors for hemolysis and liver damage outside of COVID-19. Further research in this area may identify neonates who are at increased risk for readmission with COVID-19 and development of MIS-C.

In the United Kingdom, Gale et al[20] reported a rate of 5.6 cases of COVID-19 per 10 000 births, 42% of whom had severe infection. Villar et al[17] found that 12.1% of neonates born to SARS-CoV-2 mothers in 18 countries had COVID-19. The incidence and case fatality rates observed in this study are reflective of both the larger number of encounters analyzed and the fact that the United States has had the highest number of COVID-19 cases globally. However, it is important to note that the neonates in this study were drawn from a data set of hospital encounters and were potentially a sicker population, which likely impacted upon the observed incidence rate.

Limitations

The study population was limited to neonatal data from 109 health systems. Although this is a large and representative data source, it does not include COVID-19 cases from facilities that do not contribute to the CRWD. It was not possible to link maternal and neonatal records for extraction of maternal SARS-CoV-2 status because of the use of deidentified data, and so potential vertical transmission cannot be confirmed. Variables contained in narrative clinical notes were not available, so variables were captured only for neonates with corresponding condition or procedure codes. We

included neonates who did not have a positive laboratory test for COVID-19 if their medical record had a diagnosis code for COVID-19. In some cases, the diagnosis code derived from testing at a different facility and before encounter. Recent research has shown that hospitals appear to provide reasonably accurate COVID-19 diagnosis codes in administrative data.[22]

One of the primary limitations of our study was difficulty in obtaining information about childbirth. Although we found records on mode of delivery for 209 neonates, other neonates may have had data on birth recorded in a database that was separate from the one that contained their EMR data. Others may have been transferred from a hospital other than the one with the record of childbirth. A further limitation was the high number of low birth weight or premature neonates in our data set. The physical manifestations of the criteria for severe or critical COVID-19, although previously used in studies of neonates, may be nonspecific in preterm infants. Our findings, particularly the number of neonates who received respiratory support or NICU care in the presence of severe COVID-19, could have been influenced by prematurity. A comparative exploration of outcomes between the COVID-19 era and the preceding year may therefore be helpful in identifying the impact of the pandemic on premature neonates.

Our finding that 33.8% of patients with severe COVID-19 also received antibiotics suggests either considerable overlap in presentation between concomitant bacterial infection and severe acute COVID-19 in neonates, or that these neonates received a short course of empirical antibiotics for suspected infection. However, it was not possible to determine how many days of antibiotic treatment that a neonate received in the data set, and so the proportion of true bacterial infection in the presence of COVID-19 is unclear. Furthermore, some neonates with nonsevere COVID-19 received antiviral treatment, indicating the possibility of cases where the definition of severe COVID-19 differed from the provider's judgment of illness severity or the need for treatment.

The geographic distribution of neonatal COVID-19 cases was made on the basis of the zip code regions used for data aggregation in the CWRD. National estimates from the CDC on neonatal COVID-19 cases would be a more accurate measure of distribution than sample estimates.

CONCLUSIONS

Using a large, deidentified, multicenter EHR database, we showed that neonatal COVID-19 rates are low, with severe presentation and death possible, although rare. Most neonates were asymptomatic or developed mild illness, with few requiring respiratory support or adjunct medication. Timing of diagnosis indicated community-acquired or nosocomial infection. An investigation into the role of congenital abnormalities in COVID-19 may be helpful. Discrete analysis of neonatal cases by reporting bodies is advised for a clearer picture of rates and impact of COVID-19 in this population.

ABBREVIATIONS

CCP: COVID-19 convalescent plasma
CDC: Centers for Disease Control and Prevention
CI: confidence interval
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
CRWD: Cerner Real World Database
ECMO: extracorporeal membrane oxygenation
EHR: electronic health record
IMV: invasive mechanical ventilation
IQR: interquartile range
LOS: length of stay
MIS-C: multisystem inflammatory syndrome in children
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FUNDING: Ms Devin is a recipient of a Fulbright-Enterprise Ireland Student Award 2021–2022. This study was supported by a hospital internal grant, the Chief Scientific Officer Award June 2021 to May 2022. The funders had no role in the conduct or design of this study.

CONFLICT OF INTEREST DISCLAIMER: The authors have indicated they have no conflicts of interest relevant to this article to disclose.

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