Infants Born to Mothers Who Were SARS-CoV-2 Positive during Pregnancy and Admitted to Neonatal Intensive Care Unit

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Abstract

Introduction: Our objective was to compare neonatal outcomes and resource use of neonates born to mothers with SARS-CoV-2 positivity during pregnancy with neonates born to mothers without SARS-CoV-2 positivity. ***Methods:*** We conducted a two-country cohort study of neonates admitted between January 1, 2020, and September 15, 2021, to tertiary neonatal intensive care unit (NICU) in Canada and Sweden. Neonates from mothers who were SARS-CoV-2 positive during pregnancy were compared with three randomly selected NICU neonates of mothers who were not test-positive, matched on gestational age, sex, and birth weight (±0.25 SD). Subgroup analyses were conducted for neonates born <33 weeks' gestation and mothers who were SARS-CoV-2 positive ≤10 days prior to birth. Primary outcome was duration of respiratory support. Secondary outcomes were in-hospital mortality, neonatal morbidity, late-onset sepsis, receipt of breast milk at discharge, and length of stay. ***Results:*** There were 163 exposed and 468 matched neonates in Canada, and 303 exposed and 903 matched neonates in Sweden. There was no statistically significant difference in invasive or noninvasive respiratory support durations, mortality, respiratory and other neonatal morbidities, or resource utilizations between two groups in both countries in entire cohort and in subgroup analyses. Receipt of breast milk at discharge was lower in the Canadian neonates of mothers who were SARS-CoV-2 positive ≤10 days before birth (risk ratio 0.68, 95% CI: 0.57–0.82). ***Conclusion:*** Maternal SARS-CoV-2 positivity was not associated with increased durations of respiratory support, morbidities, mortality, or length of hospital stay in Canada and Sweden among neonates admitted to tertiary NICU.

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Introduction

Pregnancy and neonatal outcomes during the COVID-19 pandemic have been an area of interest. Overall, there is a reported increase in preterm birth among women with COVID-19, especially iatrogenic preterm birth [1, 2] and an increase in neonatal intensive care unit (NICU) admission [1–3]. Norman et al. [4] reported higher rates of respiratory distress syndrome and need for continuous positive airway pressure among neonates born to mothers testing positive for SARS-CoV-2 compared to those who were not positive. However, mediation analysis indicated that the increased respiratory problems were attributed to preterm birth and not to neonatal COVID-19. Hudak [5] reported that respiratory distress was the commonest clinical sign in neonates.

With an approximate NICU admission rate of 10–13% among all neonates born during the pandemic, there is a need to identify outcomes and resource usage of neonates born to pregnant women who tested positive for SARS-CoV-2 during pregnancy to help resource planning, understanding health effects, and family counseling. The aim of this study was to compare outcomes and resource usage of neonates admitted to tertiary NICUs after maternal SARS-CoV-2 positivity during pregnancy with matched neonates born to mothers without a positive SARS-CoV-2-test in two countries with different mitigation strategies and rates of COVID-19.

Material and Methods

Design and Setting

A two-country, multicenter, cohort study of infants admitted to NICUs using data from the Canadian Neonatal Network (CNN) and three Swedish registers was conducted. For the most part of the study period, apart from a few hospitals implementing policy of screening all admitted women for labor, there was no universal screening implemented.

The CNN maintains a national database of admissions to tertiary-level NICUs in Canada. Trained research assistants at each NICU abstracted data following a manual of standardized definitions. Data collection and transmission from each participating NICU were approved by each hospital's local Research Ethics Board or Quality Improvement Committee [6, 7].

The Swedish Pregnancy Register (SPR), the Swedish Neonatal Quality Register (SNQ), and the Swedish Register for Communicable Diseases (SmiNet) prospectively extracted standardized and pre-defined data daily including specific variables added to SmiNet databases in the first quarter of 2020. The SPR provided information on each pregnancy and birth for 92% of all pregnant women (18 of 21 regions) in Sweden [8]. The SNQ provided information on procedures and diagnoses for all infants admitted for neonatal care [9]. SmiNet included dates of the first positive result on a PCR test for SARS-CoV-2 in all Swedish inhabitants. Using the unique identity numbers, data were linked between the three registers. The study was approved by the Swedish Ethical Review Authority, which also waived patient informed consent. Approval from the Mount Sinai Hospital Research Ethics Board, Toronto, and from the Executive Committee of the CNN was also obtained.

Study Population

Neonates admitted from January 1, 2020, to September 15, 2021, were included. All 32 tertiary-level NICUs in Canada participated, and data from the initial admission were included. Data from 83 nontertiary neonatal units in Canada were not part of the CNN database. Data from all 8 tertiary NICUs in Sweden were included, and if neonates were transferred to any of the 29 nontertiary units in the country after initial admission to tertiary units, these data were also included. Neonates who had major congenital anomalies [10], or those who had planned palliative care, were excluded.

Exposed Cohort

Neonates born to mothers who were SARS-CoV-2 positive via PCR test at any point during pregnancy were used to identify exposed cohort.

Matched Cohort

Infants born to mothers who did not have a SARS-CoV-2-positive test or were not tested during pregnancy and admitted to NICUs were used to identify matched cohort. Three neonates were randomly selected from with the closest birth date to that of index child in the corresponding network. Infants were matched on gestational age (GA) in weeks, sex, and birth weight of ±0.25 SD of the index child. When three matched cases were not available, we included infants with at least one match. Index infants with no match were excluded.

Outcomes and Study Variables

Both networks have harmonized data variables as part of international collaboration [11]. Primary outcomes were duration of respiratory support during the NICU stay in any form as maternal SARS-CoV-2 test positivity has been associated with admission for neonatal respiratory disorder [12]. Secondary outcomes were mortality prior to discharge, late-onset sepsis, and length of NICU stay. Other outcomes were delivery room resuscitation, and resource utilization outcomes were durations of noninvasive and invasive respiratory support, oxygen support, antimicrobials use, parenteral nutrition, type of nutritional support received including breast milk/breastfeeding at discharge.

Two subgroup analyses were preplanned: (a) neonates <33 weeks' GA and (b) mothers who were SARS-CoV-2 positive within the 10 days prior to birth. For the subgroup of neonates <33 weeks' GA, following neonatal outcomes were compared. Bronchopulmonary dysplasia was defined as supplemental oxygen use at 36 weeks of postmenstrual age or at discharge to a level I or II center [13]. Treated patent ductus arteriosus (PDA) was defined as pharmacological or surgical treatment of PDA. Severe IVH was defined as grade 3 or 4 IVH according to the criteria of Papile [14]. NEC was defined according to the criteria of Bell and included infants with ≥ stage 2 [15]. Retinopathy of prematurity was defined according to the international classification of retinopathy and included infants with ≥stage 3 in either eye [16]. Late-onset sepsis

was defined as the presence of a pathogenic organism in either blood or cerebrospinal fluid culture after 2 days of age.

Data on maternal and neonatal characteristics were collected. GA was based on an algorithm using date of embryo transfer, early ultrasound estimation, obstetric history, obstetric examination, and newborn examination. We defined small for GA as birth weight less than the 10th percentile for the given GA and sex [17].

Sample Size

No formal sample size calculation was made. We estimated there would be 200 Swedish and 100 Canadian NICU admissions in which mothers tested positive for SARS-CoV-2 during pregnancy, resulting in an expected sample size of ~300 index neonates and 900 matched neonates for a total of 1,200 neonates.

Statistical Analysis

The country-specific coordinating centers conducted analyses using the same analytical code, and country-specific results were reported separately without any data transferred between the countries. A priori decision was made not to pool the country-specific data and results because of possible heterogeneity in population due to different testing protocols, and different public health measures adopted to mitigate COVID-19. Descriptive statistics was applied to maternal and infant characteristics. Standardized differences were used to identify imbalances between groups for baseline characteristics [18]. Risk ratios (RRs) were estimated using a generalized estimated equation model assuming a binomial distribution clustering on the identity of the mother (to account for correlations among infants born to the same mother). The duration variables (respiratory support, length of stay, etc.) were not normally distributed and were reported as median, interquartile range, and range. Differences in medians were calculated using "arithmetic mean" and reported with difference in medians and 95% confidence interval using quantile regression. Because of the potential for type 1 error due to multiple comparisons, findings for the analyses should be interpreted as exploratory. Statistical analyses were performed using Statistical Analysis System v9.4 (SAS Institute; Cary, NC, USA). A two-sided p value of <0.05 and adjusted standardized difference of |0.1| were considered for statistical significance. Since Sweden also had data from all nontertiary neonatal units, characteristics and outcomes of entire country cohort as a corroborative exercise were also compared.

Results

During the study period, 163 neonates were in exposed cohort in Canada and 306 in Sweden. A match could not be identified for 3 neonates in Sweden. The final study population comprised 163 exposed and 468 matched neonates in Canada and 303 exposed and 903 matched neonates in Sweden (shown in Fig. 1). In Canada, data on neonatal test results were available for 73 neonates, and of these, 3 (4.1%) tested positive (recommendations in Canada were to test neonates born to mothers with active COVID-19 during birth within 24–48 h). All Swedish neonates were tested in the first 6 days, and 7 (2.3%) tested

positive for SARS-CoV-2 (recommendations were to test all neonates within 6 days irrespective of GA when mother was positive, and to test all NICU admissions three times). The baseline characteristics are compared in Table 1 separately for each country. Most characteristics were comparable within each country. The proportion of infants born after a multifetal pregnancy was higher in the matched compared to the exposed cohort in both countries. In Canada, more infants had an umbilical arterial pH <7.1, need for resuscitation, and Apgar score <7 at 5 min in the exposed compared to the matched cohort.

There was no statistically significant difference in respiratory support or durations of parenteral nutrition, antimicrobial therapy, length of stay or outcomes of mortality, and late-onset sepsis between the two groups in both countries. The proportion of infants who had parenteral nutrition initiated was higher in Canada among exposed group compared to matched group; however, the median duration of parenteral nutrition was not significantly different as shown in Table 2.

The results of resource utilization, outcomes, and therapies for infants born at <33 weeks' GA are compared in Table 3. There was no statistically significant difference in any of the parameters between exposed and matched cohorts in both countries.

Subgroup analysis of those born to the mothers who tested positive ≤10 days of birth identified no differences in outcomes or therapies between groups shown in Table 4 except that the receipt of breast milk at discharge was significantly lower in the Canadian cohort. Population-based data from all infants born to mothers who tested positive ($n = 972$) and admitted to any neonatal unit in Sweden were compared with matched cohort of infants born to nonpositive women ($n = 2,912$) and identified no significant differences (shown in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526313).

Discussion

This two-nation, matched cohort study adds knowledge on outcomes of neonates admitted to NICU after exposure to maternal SARS-CoV-2 positivity. Irrespective of being born and cared for in a Canada or Sweden, maternal positivity for SARS-CoV-2 during pregnancy was not associated with differences in any outcomes studied as compared to infants delivered by nontest-positive women. In a subgroup analysis, there was lower rate of breast milk receipt at discharge among neonates whose
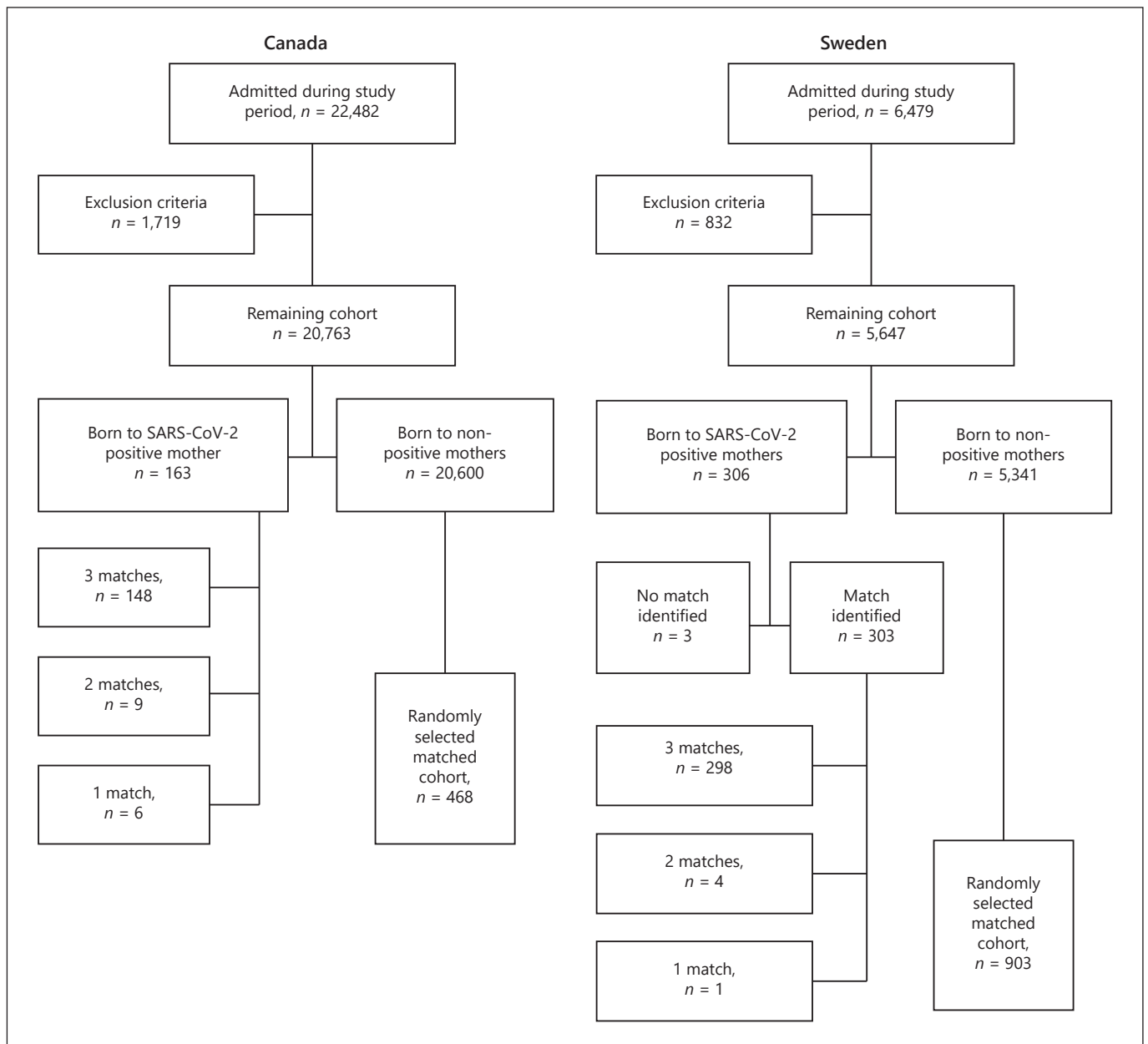
Fig. 1. Study flow diagram of admissions to neonatal intensive care units ($n = 32$ in Canada and $n = 8$ in Sweden).

mothers tested positive within 10 days of birth in Canada. There was no difference in outcomes known to be triggered and aggravated by inflammation. The lack of any detectable difference between exposed and unexposed can be interpreted as either there are no fetal/neonatal effects from maternal COVID infection during pregnancy, or if there is an effect, it is small and the contamination of the matched cohort group with mothers who had unrec-

ognized infection may have obscured any difference between the groups.

In the USA, 86% of infants born to mothers who tested positive for SARS-CoV-2 in pregnancy or during delivery did not show any signs of illness [5], and in Sweden, 88% of prenatally exposed infants were never admitted for neonatal care [4]. This confirms the previous reports that vertical transmission rates are low and that direct effects

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Table 1. Characteristics of neonates admitted to neonatal intensive care in tertiary hospitals, stratified by cohort and study location

Characteristics	Canada			Sweden		
	infants admitted for neonatal intensive care stratified by maternal test status for SARS-CoV-2			infants admitted for neonatal intensive care stratified by maternal test status for SARS-CoV-2		
	infants to positive women (n = 163)	infants to nonpositive women (n = 468)	standardized difference	infants to positive women (n = 303)	infants to nonpositive women (n = 903)	standardized difference
GA when mother was positive for SARS-CoV-2, median (IQR, range), weeks	28 (21–33, 3–41)	NA	NA	24.3 (14.6–32.4, 0.4–41.9)	NA	NA
Time from date of positive test status to birth, median (IQR, range), days	28 (4–85, 0–232)	NA	NA	63 (12–152, 0–287)	NA	NA
Maternal age, mean (SD)	32.8 (5.7)	31.6 (5.7)	0.212	31.9 (5.1)	32.0 (4.8)	-0.026
Nulliparity, n (%)	46 (28.2)	169 (36.1)	-0.170	147 (48.5)	461 (51.1)	-0.051
Maternal hypertension, n (%)	29 (19.0)	99 (23.6)	-0.114	48 (15.8)	138 (15.3)	0.015
Maternal diabetes, n (%)	46 (30.1)	86 (20.4)	0.223	14 (4.6)	25 (2.8)	0.098
Multiple pregnancy, n (%)	17 (10.4)	81 (17.4)	-0.202	22 (7.3)	126 (14.0)	-0.219
Cesarean section	103 (63.2)	266 (58.1)	0.105	153 (50.5)	394 (43.6)	0.138
Antenatal steroids in neonates <33 weeks GA, n (%)	45 (84.9)	128 (90.1)	-0.158	63 (82.9)	186 (81.9)	0.025
Boy, n (%)	79 (48.5)	229 (48.9)	-0.009	161 (53.1)	483 (53.5)	-0.007
GA at birth, median (IQR, range), weeks	34 (31–37, 23–41)	34 (31–37, 23–41)	NA	37 (32–40, 22–42)	37 (32–40, 22–42)	NA
22–<28^0 weeks, n (%)	17 (10.4)	45 (9.6)	0.027	31 (10.2)	93 (10.3)	-0.002
28–<33^0 weeks, n (%)	36 (22.1)	105 (22.4)	-0.008	45 (14.9)	134 (14.8)	0.000
33–<37^0 weeks, n (%)	57 (35.0)	162 (34.6)	0.007	66 (21.8)	196 (21.7)	0.002
37–<42^0 weeks, n (%)	53 (32.5)	156 (33.3)	-0.017	156 (51.5)	467 (51.7)	-0.005
≥42^0 weeks, n (%)	0	0	NA	5 (1.7)	13 (1.4)	0.017
Birth weight, mean (SD), grams	2,320 (993)	2,320 (977)	0.001	2,774 (1,137)	2,773 (1,125)	0.001
LGA 90th percentile, n (%)	21 (12.9)	55 (11.8)	0.034	28 (9.2)	85 (9.4)	-0.006
SGA 10th percentile, n (%)	26 (16.0)	73 (15.6)	0.010	58 (19.1)	152 (16.8)	0.060
UA pH <7.1, n (%)	18 (15.8)	32 (10.6)	0.153	25 (8.3)	59 (6.5)	0.066
Receipt of any resuscitation, n (%)	111 (68.1)	270 (59.0)	0.191	149 (49.2)	441 (48.8)	0.007
Receipt of extensive resuscitation, n (%)	2 (1.2)	14 (3.0)	-0.123	6 (2.0)	14 (1.6)	0.033
Apgar score <7 at 5 min, n (%)	42 (26.3)	92 (20.3)	0.141	46 (15.2)	140 (15.5)	-0.009

NA, not applicable; SGA, small for gestational age; LGA, large for gestational age; UA, umbilical artery.

of SARS-CoV-2, i.e., severe neonatal infection, are rare [19, 20]. The number of confirmed cases with COVID-19 per million people is twice as high in Sweden as in Canada which was reflected in total number of positive women included in this study.

Significantly lower receipt of breast milk at discharge in Canada probably reflects initial uncertainty at the start of the pandemic regarding transmission of virus due to proximity with baby or via breast milk from women who tested positive for SARS-CoV-2, unit policies, parental preference, or a combination of these factors. However, as knowledge and experience increased over time, most international policies aligned with support of breast milk or breastfeeding as the best source of infant nutrition [21].

The clinical outcomes presented herein were limited to the neonatal period. Shuffrey et al. [22] reported no statistically significant difference in neurodevelopmental outcomes at 6 months of age using Ages and Stage Questionnaire-3 between neonates born to mothers who had infection compared to infants born to mothers who did not have infection. However, compared to historical controls from pre-pandemic period, infants born during the pandemic period had lower scores in gross motor, fine motor, and personal-social domains. Further data from longitudinal studies are needed as maternal infection with SARS-CoV-2 is associated with thromboembolism, placental perfusion abnormalities, and heightened inflammatory response, all of which may have effects on overall health, development, and aging [23, 24].

This study has several strengths. This is so far the largest cohort of infants admitted for tertiary NICU exposed to maternal SARS-CoV-2 positivity during pregnancy. Infants during the first, second, and third waves of the COVID-19 pandemic were included. Comparing outcomes for infants to test-positive mothers with those of a matched cohort minimized bias and confounding. The matched cohort design allows for variations in SARS-CoV-2 exposure and vaccination, and accounts for important covariates associated with outcomes. Maternal SARS-CoV-2 test positivity relied on at least one positive PCR test, and equivalent definitions of end points were used in both countries. The study included clinically important subgroup analyses. Moreover, both countries have reliable databases for capturing this information at a national level increasing confidence in the information. The two countries included in this analysis followed slightly different public health approaches to the pandemic which could have resulted in significant differences in outcomes; however, no such difference was ob-

Table 2. Resource utilization and outcomes of neonates admitted to neonatal intensive care in tertiary hospitals, comparing those born to mother with SARS-CoV-2 positivity during pregnancy (exposed cohort) with infants born to nonpositivity mothers (matched cohort), Canada and Sweden

Outcomes and resource utilization	Canada			Sweden		
	infants to positive women (n = 163)	infants to nonpositive women (n = 462)	RR (95% CI) or median difference (95% CI)	infants to positive women (n = 303)	infants to nonpositive women (n = 903)	RR (95% CI) or median difference (95% CI)
Number of infants who received invasive respiratory support, n (%)	35 (21.5)	108 (23.1)	0.93 (0.66–1.30)	63 (20.8)	158 (17.5)	1.18 (0.90–1.54)
Duration of invasive respiratory support, median (IQR, range), days	0 (0–0, 0–78)	0 (0–0, 0–78)	0	0 (0–0, 0–60)	0 (0–0, 0–70)	1 (–infinity, 8)
Duration of noninvasive respiratory support, median (IQR, range), days	0 (0–5, 0–55)	2 (0–3, 0–56)	0 (–6, 10)	0 (0–3, 0–96)	0 (0–2, 0–215)	0
Duration of any respiratory support, median (IQR, range), days	2 (0–8, 0–127)	2 (0–7, 0–200)	0 (0, 2)	0 (0–5, 0–120)	0 (0–3, 0–271)	0
Number of infants who received oxygen, n (%)	86 (52.8)	214 (45.7)	1.15 (0.97–1.38)	158 (52.1)	452 (50.1)	1.04 (0.91–1.18)
Duration of oxygen support, median (IQR, range), days	1 (0–3, 0–127)	0 (0–3, 0–200)	1 (–Infinity, 1)	1 (0–4, 0–125)	1 (0–3, 0–160)	0
Number of infants who received antimicrobials, n (%)	88 (54.0)	228 (48.7)	1.11 (0.94, 1.31)	140 (46.2)	360 (39.9)	1.15 (0.99–1.33)
Duration of antimicrobial treatment, median (IQR, range), days	2 (0–3, 0–41)	0 (0–3, 0–105)	2 (–Infinity, 2)	0 (0–6, 0–175)	0 (0–5, 0–107)	0
Number of infants who received parenteral nutrition, n (%)	94 (57.7)	223 (47.7)	1.21 (1.03–1.42)	83 (27.4)	226 (25.0)	1.08 (0.87–1.35)
Duration of parenteral nutrition, median (IQR, range), days	3 (0–6, 0–63)	0 (0–6, 0–230)	3 (–9, 5)	0 (0–2, 0–107)	0 (0–1, 0–115)	0
Breast milk at discharge, n (%)	91 (55.8)	291 (63.5)	0.88 (0.75–1.02)	207 (68.3)	647 (71.7)	0.95 (0.87–1.04)
Length of stay[a], median (IQR, range), days	11 (5–21, 1–131)	9 (4–24, 1–230)	2 (–6, 14)	10 (4–33, 1–167)	9 (4–35, 1–239)	–1 (–1, 24)
Mortality, n (%)	3 (1.8)	16 (3.4)	0.54 (0.16–1.82)	13 (4.3)	29 (3.2)	1.34 (0.71–2.54)
Late-onset sepsis, n (%)	9 (5.5)	15 (3.2)	1.72 (0.77–3.86)	14 (4.6)	33 (3.7)	1.27 (0.69–2.33)

[a] Length of stay in Canada included admission to death/discharge from tertiary units whereas for Sweden included admission to discharge home or death.

Table 3. Resource utilization and outcomes of neonates born at <33 weeks' GA admitted to neonatal intensive care in tertiary hospitals, comparing those born to mother with SARS-CoV-2 positivity during pregnancy (exposed cohort) with infants born to nonpositive mothers (matched cohort), Canada and Sweden

Characteristics	Canada			Sweden		
	infants to positive women (n = 53)	infants to nonpositive women (n = 150)	Median difference (95% CI)	infants to positive women (n = 76)	infants to nonpositive women (n = 227)	Median difference (95% CI)
Resource utilization						
Duration of invasive respiratory support, median (IQR, range), days	0 (0–1, 0–24)	0 (0–3, 0–78)	0	0 (0–2, 0–60)	0 (0–3, 0–70)	0
Duration of noninvasive respiratory support, median (IQR, range), days	9 (3–24, 0–55)	6 (1–17, 0–56)	3 (–3, 17)	15 (4–41, 0–96)	14 (2–51, 0–215)	1 (–12, 14)
Duration of any respiratory support, median (IQR, range), days	15 (6–50, 0–127)	14 (4–44, 0–200)	1 (–12, 20)	15 (4–44, 0–120)	17 (3–53, 0–271)	–2 (–15, 12)
Duration of oxygen support, median (IQR, range), days	2 (1–40, 0–127)	3 (0–21, 0–200)	–1 (–7, Infinity)	7 (2–40, 0–125)	9 (1–47, 0–160)	–2 (–9, 5)
Duration of antimicrobial treatment, median (IQR, range), days	3 (2–10, 0–41)	3 (0–7, 0–105)	0 (0, 5)	6 (2–11, 0–175)	6 (0–15, 0–107)	0
Duration of parenteral nutrition, median (IQR, range), days	7 (4–13, 0–63)	7 (4–13, 0–230)	0 (–4, 7)	8 (3–12, 0–107)	7 (2–11, 0–115)	1 (–3, 6)
Length of stay[a], median (IQR, range), days	45 (17–83, 1–131)	39 (16–61, 0–230)	6 (–14, 28)	59 (38–83, 2–167)	63 (42–94, 1–139)	–4 (–23, 20)
			RR (95% CI)			RR (95% CI)
Outcomes						
Mortality, n (%)	2 (3.8)	11 (7.3)	0.51 (0.12–2.25)	6 (7.9)	21 (9.3)	0.87 (0.37–2.04)
Late-onset sepsis, n (%)	9 (17.0)	12 (8.0)	2.12 (0.95–4.75)	10 (13.2)	30 (13.2)	1.00 (0.51–1.94)
Severe neurological injury, n (%)	3/25 (12.0)	4/92 (4.4)	2.76 (0.66–11.5)	7/55 (12.7)	13/163 (8.0)	1.61 (0.66–3.89)
Severe/treated ROP, n (%)	1/51 (2.0)	8/141 (5.7)	0.35 (0.04–2.70)	4/32 (12.5)	11/96 (11.5)	1.08 (0.36–3.31)
Treated PDA, n (%)	5 (9.4)	21 (14.0)	0.67 (0.27–1.70)	11/76 (14.5)	32/227 (14.1)	1.03 (0.54–1.96)
BPD, n (%)	19/51 (37.3)	37/139 (26.6)	1.40 (0.89–2.20)	11/76 (14.5)	38/227 (16.7)	0.82 (0.43–1.56)
			Standardized difference			Standardized difference
Therapies						
Receipt of surfactant, n (%)	27 (50.9)	67 (44.7)	0.125	40 (52.6)	111 (48.9)	0.075
Pneumothorax drained, n (%)	1 (1.9)	4 (2.7)	–0.052	1 (1.3)	8 (3.5)	–0.14

ROP, retinopathy of prematurity; PDA, patent ductus arteriosus. [a] Length of stay in Canada included admission to death/discharge from tertiary units whereas for Sweden included admission to discharge home or death.

Table 4. Subgroup analyses limited to infants born to mothers who tested positive for SARS-CoV-2 within 10 days of giving birth and their matched counterparts

Characteristics	Canada			Sweden		
	infants to positive women (n = 61)	infants to nonpositive women (n = 174)	Standardized difference	Infants to positive women (n = 73)	infants to nonpositive women (n = 219)	Standardized difference
Demographic characteristics						
GA at birth, median (IQR, range), weeks	33 (31–37, 23–41)	33 (31–37, 23–41)	NA	33 (30–37, 22–42)	33 (30–37, 22–42)	NA
Birth weight, mean (SD), grams	2,290 (960)	2,250 (946)	0.042	2,286 (1,103)	2,280 (1,103)	0.005
SGa 10th percentile, n (%)	5 (8.2)	11 (6.3)	0.072	19 (26.0)	58 (26.5)	−0.010
Apgar score <7 at 5 min, n (%)	24 (40.7)	44 (25.9)	0.318	13 (17.8)	34 (15.5)	0.061
			RR (95% CI) or median difference (95% CI)			RR (95% CI) or median difference (95% CI)
Resource utilization and outcomes						
Number of infants who received any respiratory support, n (%)	43 (70.5)	108 (62.1)	1.14 (0.93–1.39)	53 (72.6)	149 (68.0)	1.07 (0.90–1.27)
Duration of any respiratory support, median (IQR, range), days	3 (0–10, 0–127)	2 (0–10, 0–200)	1 (−5, 6)	1 (0–8, 0–110)	1 (0–7, 0–271)	0 (−1, 1)
Length of stay, median (IQR, range), days	16 (7–41, 1–131)	9 (5–33, 0–230)	7 (−2, 14)	19 (5–42, 1–115)	26 (6–51, 1–239)	−7 (−20, 15)
Breast milk at discharge, n (%)	18 (29.5)	109 (64.1)	0.46 (0.31–0.69)	40 (54.8)	145 (66.2)	0.80 (0.63–1.01)
Mortality, n (%)	1 (1.6)	10 (5.8)	0.29 (0.04–2.18)	3 (4.1)	12 (5.5)	0.78 (0.23–2.65)
Late-onset sepsis, n (%)	4 (6.6)	8 (4.6)	1.43 (0.45–4.57)	8 (11.0)	14 (6.4)	1.71 (0.76–3.89)

served. This may reflect "universal" health care pregnant women and infants receive or no difference in care provision for infants irrespective of their mother's test positive or negative status. Whether these findings apply to different settings of health care provision remains to be studied.

This study has limitations. First, variations in test capacity over time, in test policy between countries, health care regions, and hospitals, and in mitigation strategies are likely to have affected the proportion of test-positive women. Women with pregnancy complications may have been tested more often than women without complications [25]. On the other hand, some mothers among matched cohort could have had asymptomatic COVID-19 which would dilute any group differences in outcome [26]. Second, this study does not reflect outcomes related to the latest variant of SARS-CoV-2 (Omicron). As such, we did not have information on strains of virus during the study period, and thus, we cannot comment on differential effect s of various strains. Third, despite obtaining information from two countries at a national level, the numbers of included infants, rates of some outcome variables, and number of neonates with positivity were small. Fourth, only infants admitted for neonatal care were included, excluding stillbirths and delivery room deaths. This may restrict us from making inferences on association of maternal positivity on pregnancy outcomes. Fifth, we do not have data on maternal severity of illness or condition at the time of birth.

Conclusion

Irrespective of being born and cared for in tertiary neonatal units in Canada or Sweden, maternal positivity for SARS-CoV-2 at any time during pregnancy when compared matched infants from the remaining cohort was not associated with increased neonatal respiratory support, neonatal morbidities, mortality, or length of hospital stay. Receipt of breast milk at discharge was lower in the subgroup of neonates whose mothers were SARS-CoV-2 positive within the 10 days prior to birth which may need attention in practice.

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Statement of Ethics

This study protocol was reviewed and approved by Research Ethics Board at Mount Sinai Hospital, approval number 21-0168C. The study also received approval from Swedish Ethical Review Authority application number 2020-01499. Consent from individual patients was waived due to retrospective nature of this database study.

Conflict of Interest Statement

The authors have no conflicts of interest or potential conflicts of interest relevant to this article to disclose.

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Author Contributions

Drs. Prakesh S. Shah and Mikael Norman were involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and revising it critically for important intellectual content. Mr. Junmin Yang and Dr. Jonas Söderling contributed to conception and design of the study, analysis of data, and revising article critically for important intellectual content. All other authors (Chloe Joynt, Stellan Hakansson, Michael Narvey, Lars Naver, Marc Beltempo, Olof Stephansson, Deshayne B. Fell, Deborah Money, and Joseph Y. Ting) were involved in the conception and design of the study, interpretation of results, and revising the article critically for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Prakesh S. Shah, Mount Sinai Hospital, Toronto, ON, Canada, has full access to the data in the study for Canada and Jonas Söderling has full access to the data in the study for Sweden. Both take responsibility for the integrity of the data and the accuracy of the data analysis. The data analyses were conducted by Junmin Yang (Canada) and Jonas Söderling (Sweden). Data are confidential and not available for public access. Further inquiries can be directed to the corresponding author.

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