Family Medicine and Community Health

Association of COVID-19 with respiratory syncytial virus (RSV) infections in children aged 0–5 years in the USA in 2022: a multicentre retrospective cohort study

Lindsey Wang,[1] Pamela B Davis,[2] Nathan Berger,[1] David C Kaelber,[3] Nora Volkow,[4] Rong Xu [5]

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For numbered affiliations see end of article.

Correspondence to
Dr Rong Xu; rxx@case.edu

ABSTRACT

Objective To investigate whether COVID-19 infection was associated with increased risk for incident respiratory syncytial virus (RSV) infections and associated diseases among young children that might have contributed to the 2022 surge of severe paediatric RSV cases in the USA.

Design This is a retrospective population-based cohort study. Five outcomes were examined, including overall RSV infection, positive lab test-confirmed RSV infection, clinically diagnosed RSV diseases, RSV-associated bronchiolitis and unspecified bronchiolitis. Risk ratio (RR) and 95% CI of the outcomes that occurred during the 2022 and 2021 RSV seasons were calculated by comparing propensity-score matched cohorts.

Setting Nationwide multicentre database of electronic health records (EHRs) of 61.4 million patients in the USA including 1.7 million children 0–5 years of age, which was accessed through TriNetX Analytics that provides web-based and secure access to patient EHR data from hospitals, primary care and specialty treatment providers.

Participants The study population consisted of 228 940 children of 0–5 years with no prior RSV infection who had medical encounters in October 2022. Findings were replicated in a separate study population of 370 919 children of 0–5 years with no prior RSV infection who had medical encounters in July 2021–August 2021 during a non-overlapping time period.

Results For the 2022 study population (average age 2.4 years, 46.8% girls, 61% white, 16% black), the risk for incident RSV infection during October 2022–December 2022 was 6.40% for children with prior COVID-19 infection, higher than 4.30% for the matched children without COVID-19 (RR 1.40, 95% CI 1.27 to 1.55); and among children aged 0–1 year, the overall risk was 7.90% for those with prior COVID-19 infection, higher than 5.64% for matched children without (RR 1.40, 95% CI 1.21 to 1.62). For the 2021 study population (average age 2.2 years, 46% girls, 57% white, 20% black), the risk for incident RSV infection during July 2021–December 2021 was 4.85% for children with prior COVID-19 infection, higher than 3.68% for the matched children without COVID-19 (RR 1.32, 95% CI 1.12 to 1.56); and 7.30% for children aged 0–1 year with prior COVID-19 infection, higher than 4.98% for matched children without (RR 1.47, 95% CI 1.18 to 1.82).

Conclusion COVID-19 was associated with a significantly increased risk for RSV infections among children aged 0–5 years in 2022. Similar findings were replicated for a study population of children aged 0–5 years in 2021. Our findings suggest that COVID-19 contributed to the 2022 surge of RSV cases in young children through the large buildup of COVID-19-infected children and the potential long-term adverse effects of COVID-19 on the immune and respiratory system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Is COVID-19 infection a contributing factor to the 2022 surge in respiratory syncytial virus (RSV) infections among young children in the USA?

WHAT THIS STUDY ADDS

⇒ This cohort study of 228 940 children aged 0–5 years found that prior COVID-19 infection was associated with a significantly increased risk for RSV infection among young children in 2022. Similar findings were replicated for a study population of children aged 0–5 years in 2021.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that COVID-19 contributed to the 2022 surge of RSV cases in young children through the large buildup of COVID-19-infected children and the potential long-term adverse effects of COVID-19 on the immune and respiratory systems.

INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection in young children.[1] The COVID-19 pandemic disrupted RSV and other respiratory viral infection patterns in the USA for 2020–2021.[2] Unusually early and high rates of hospitalisations with RSV infections

were reported in 2022, particularly among the youngest children.[3 4] However, the underlying reasons remain unknown. A recent study sequenced 105 RSV-positive specimens from symptomatic patients diagnosed with RSV during the autumn 2022 surge and showed that viral characteristics did not contribute to the extent or severity of the surge,[5] suggesting that non-viral influences on RSV transmission and severity may have contributed to that surge.[3] Non-pharmaceutical interventions such as masking and social distancing earlier in the pandemic prevented RSV from spreading and built a susceptible population with diminished immunity ('immunity debt'),[6–8] which may have led to the large outbreaks in the 2022 winter in the USA[9] and in other countries.[10] On the other hand, a quasi-experimental interrupted time-series analysis based on a multicentre international study in 14 European countries showed that non-pharmaceutical interventions were associated with a reduction of bronchiolitis outbreaks.[11] However, the unusual surge of severe RSV cases in the winter of 2022 suggests that additional factors contributed. COVID-19 has long-lasting adverse effects in children[12 13] and on multiple organ systems, including immune, respiratory, endocrine, cardiovascular and neurological among others.[14–17] We hypothesise that COVID-19 contributed to the 2022 surge of severe paediatric RSV diseases, likely through its damage to the immune and respiratory systems of young children. Leveraging a nationwide, real-time database of electronic health records (EHRs) of 61.4 million patients in the USA, including 1.7 million children 0–5 years of age, we performed retrospective cohort studies to investigate whether prior COVID-19 infection was associated with increased risk for medically attended RSV infections while accounting for other risk factors.

METHODS

Database description

We used the TriNetX platform ('Research USA No Date Shift') to access aggregated and deidentified EHRs of 61.4 million patients in the USA including 1.7 million children 0–5 years of age from 34 healthcare organisations, covering diverse geographical regions, age, race/ethnic, income and insurance groups and clinical setting.[18]

TriNetX is a platform that deidentifies and aggregates EHR data from contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations, across all 50 states in the USA. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care and specialty treatment providers. Any data displayed on the TriNetX Platform in aggregate form. TriNetX built-in analytical functions (eg, outcomes analysis, survival analysis, propensity score matching) allow for patient-level analyses, while only reporting population-level data. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX Platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX Platform only contains deidentified data as per the deidentification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The MetroHealth System, Cleveland OH, IRB determined research using TriNetX, in the way described here, is not Human Subject Research and therefore IRB exempt. We previously used the TriNetX platform to perform retrospective cohort studies in various populations[19–35] including young children.[19 27]

Self-reported sex (female, male), race and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: (1) race: Asian, American Indian or Alaskan Native, black or African American, Native Hawaiian or other, white, unknown race and (2) ethnicity: Hispanic or Latino, not Hispanic or Latino, unknown ethnicity.

TriNetX completes an intensive data preprocessing stage to minimise missing values. All covariates are either binary, categorical (which expands to a set of binary columns), or continuous but essentially guaranteed to exist. Age is guaranteed to exist. Missing sex values are represented using 'unknown sex'. The missing data for race and ethnicity are presented as 'unknown race' or 'unknown ethnicity'. For other variables including medical conditions, procedures, lab tests and socioeconomic determinant health, the value is either present or absent so 'missing' is not pertinent.

Study population

We examined whether prior COVID-19 infection was associated with an increased risk of medically attended RSV infection among young children who had no prior RSV infection. The status of RSV infection was based on 12 lab test codes and 3 disease clinical diagnosis codes (details in online supplemental file 1).

For examining the association of prior COVID-19 infection with RSV infection in the 2022 RSV season (October 2022–December 2022) among children aged 0–5 years, the study population comprised 228 940 children of 0–5 years (age as of October 2022) who had medical encounters with healthcare organisations in October 2022 and had no prior medically attended RSV infection. The study population was then divided into two cohorts: (1) COVID-19 (+) cohort—14 493 children who contracted COVID-19 any time prior to August 2022 as documented in their EHR, and (2) COVID-19 (−) cohort—214 447 children who had no documented COVID-19 (figure 1). A separate analysis was performed for children aged 0–1 year, for which the study population comprised 99 105 children of 0–1 year (as of October 2022) who had medical encounters with healthcare organisations in October 2022 and had no prior medically attended RSV infection. The study population was then divided into two cohorts: (1) COVID-19 (+) cohort—5193 children who contracted COVID-19 prior to August 2022 as documented in their

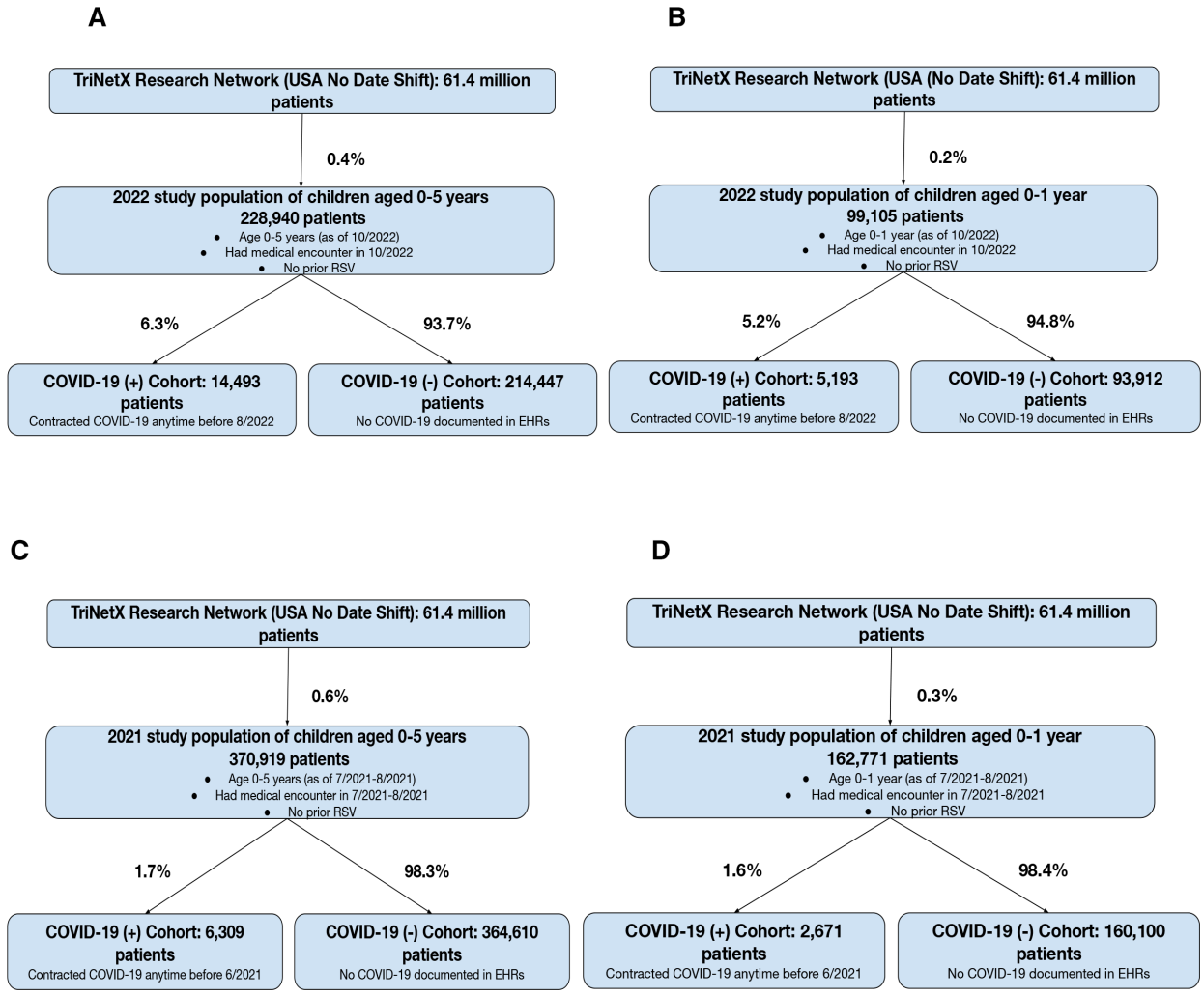

Figure 1 Flow chart of patient selection from TriNetX. (A) 2022 cohorts of children aged 0–5 years (age as of October 2022), (B) 2022 cohorts of children aged 0–1 year (age as of October 2022), (C) 2021 cohorts of children aged 0–5 year (age as of July 2021–August 2021), and (D) 2021 cohorts of children aged 0–1 year (age as of July 2021–August 2021). EHRs, electronic health records; RSV, respiratory syncytial virus.

EHR, and (2) COVID-19 (–) cohort—93 912 children who had no documented COVID-19.

We replicated the findings in a separate cohort of children from 2021. For examining the association of prior COVID-19 infection with first-time RSV infection in the 2021 RSV season (July 2021–December 2021) among children aged 0–5 years, the study population comprised 370 919 children of 0–5 years (as of July 2021–August 2021) who had medical encounters with healthcare organisations in July 2021–August 2021 and had no prior medically attended RSV infection. The study population was then divided into two cohorts: (1) COVID-19 (+) cohort—6309 children who contracted COVID-19 prior to June 2022 as documented in their EHR, and (2) COVID-19 (–) cohort—364 610 children who had no documented COVID-19. For examining the association of prior COVID-19 infection with first-time RSV infection in the 2021 RSV season (July 2021–December 2021) among children aged 0–1 year, the study population comprised 162 771 children of 0–1 year (as of July 2021–August 2021) who had medical encounters with healthcare organisations in July 2021–August 2021 and had no prior medically attended RSV infection. The study population was then divided into two cohorts: (1) COVID-19 (+) cohort—2671 children who contracted COVID-19 prior to June 2022 as documented in their EHR, and (2) COVID-19 (–) cohort—160 100 children who had no documented COVID-19.

Statistical analysis

COVID (+) and COVID (–) cohorts were propensity-score matched (1:1 using a nearest neighbour greedy matching with a calliper of 0.25 times the SD) for demographics (age, gender, race/ethnicity) that were based on the underlying clinical EHR systems of the contributing healthcare systems; adverse socioeconomic determinants of health (SDOHs) that were based on ICD-10 codes (Z55–Z65), which includes problems related to housing and economic circumstance, upbringing, education, physical environment, social environment, family circumstances, among others; comorbidities and medical treatments that are risk factors for RSV infection[36] and are

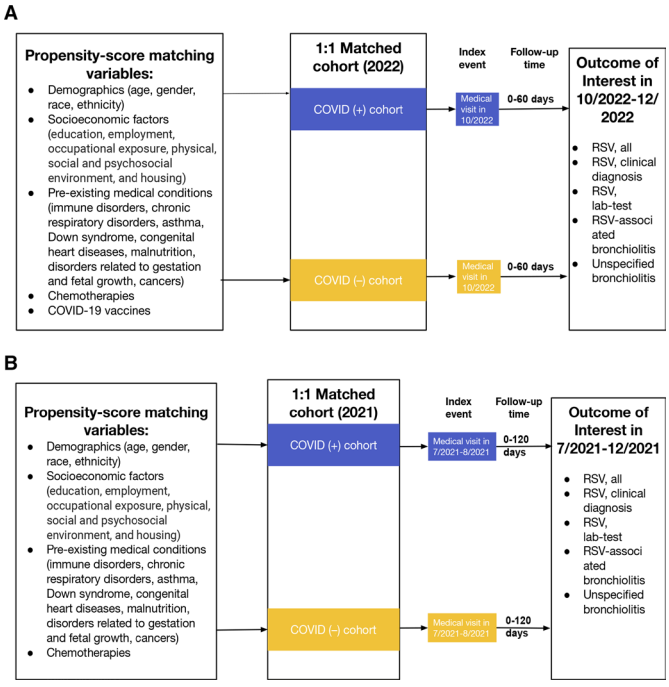

Figure 2 Retrospective cohort study design in TriNetX for (A) comparing risk for first-time medically attended RSV infections occurred during 1 October 2022–31 December 2022 between propensity-score matched COVID-19 (+) and COVID-19 (–) cohorts and (B) comparing risk for first-time medically attended RSV infections occurred during 1 July 2021–31 December 2021 between propensity-score matched COVID-19 (+) and COVID-19 (–) cohorts. RSV, respiratory syncytial virus.

also potential risk factors for COVID-19,[37] and COVID-19 vaccination (for 2022 cohorts). However, EHRs captured limited information on day-care attendance and the presence of older siblings in school or daycare, which are risk factors for both RSV and COVID-19 infection. Five outcomes were examined, including overall RSV infection, positive lab test-confirmed RSV infection (based on 12 lab test codes), clinically diagnosed RSV diseases (ICD-10 code J12.1, J21.0, B97.4), RSV-associated bronchiolitis (J21.0) and unspecified bronchiolitis (J21.9). The outcomes were followed for 60 days starting from the index event (a medical visit in October /2022) and occurred from 1 October 2022–31 December 2022 (figure 2A). The index event of a medical visit in October 2022 and a 60-day follow-up time were chosen since the 2022 RSV season peaked from October to December 2022 according to data from the National Respiratory and Enteric Virus Surveillance System (NREVSS).[38] Risk ratios (RRs) and 95% CIs were used to describe the relative risk of the outcomes between the matched COVID-19 (+) and COVID-19 (–) cohorts. Separate analyses were performed for children aged 0–5 years and children 0–1 year.

The similar cohort study was performed to examine the association of prior COVID-19 infection with first-time medically attended RSV infections occurring in the 2021 RSV peak season (July 2021–December 2021) in young children by comparing the COVID-19 (+) and COVID-19 (–) cohorts. Cohorts were propensity-score matched (1:1) for variables that are risk factors for RSV infection[36] and are also potential risk factors for COVID-19.[37] The index event was a medical visit in July 2021–August 2021. Five outcomes were examined including first-time medically attended overall RSV infection, positive lab test-confirmed RSV, clinical diagnosis code-based RSV diseases, RSV-associated bronchiolitis and unspecified bronchiolitis. The outcomes were followed for 120 days starting from the index event (medical visit in July 2021–August 2021), which were outcomes that occurred in 1 July 2021–31 December 2021 (figure 2B). The index event of a medical visit in July 2021–August /2021 and a 120-day follow-up time were chosen since the 2021 RSV season peaked earlier and lasted longer from July 2021 to February 2022 according to data from NREVSS.[38] RRs and 95% CIs were used to calculate the relative risk of the outcomes. Separate analyses were performed for children aged 0–5 years and children 0–1 year.

The data used in this study were collected from the TriNetX 'Research USA No Date Shift' Network and analysed within the TriNetX Analytics Platform during 22 February 2023–5 March 2023. The TriNetX platform calculates RRs and associated CIs using R V.4.0.2.

Patient and public involvement

As the data were derived from patient records, there was no patient involvement.

RESULTS

COVID-19 is associated with a significantly increased risk for first-time medically attended RSV infection among young children during the peak season in 2022

To examine the association between prior COVID-19 infection and first-time RSV infection in the 2022 peak season (October–December) among young children, the study population comprised 228 940 children aged 0–5 years (age as of October 2022) who had medical encounters with healthcare organisations in October 2022 and had no prior medically attended RSV infection. The study population included 14 493 children who contracted COVID-19 prior to August 2022 ('COVID-19 (+) cohort') and 214 447 children who had no EHR-documented COVID-19 infection ('COVID-19 (–) cohort'). Compared with the COVID-19 (–) cohort, the COVID-19 (+) cohort was older and had a significantly higher prevalence of adverse SDOHs, pre-existing medical conditions, procedures and COVID-19 vaccination (table 1). After propensity-score matching, the two cohorts (14 488 children in each) were balanced (table 1).

Both cohorts were followed for 60 days starting from a medical visit in October 2022. The overall risk for first-time medically attended RSV infection during October 2022–December 2022 was 6.04% for the COVID-19 (+) cohort, higher than the 4.30% for the propensity-score

Table 1 Characteristics of the 2022 study cohorts of children aged 0–5 years (age as of October 2022) who had a medical encounter with healthcare organisations in October 2022 and had no prior medically attended RSV infection before and after propensity-score matching for the listed variables

	Before propensity-score matching			After propensity-score matching		
	COVID-19 (+) cohort	COVID-19 (–) cohort	SMD	COVID-19 (+) cohort	COVID-19 (–) cohort	SMD
Total no	14 493	214 447		14 488	14 488	
Age at index event (years, mean±SD)	2.4±1.6	2.1±1.8	0.15*	2.4±1.6	2.4±1.6	0.008
Sex (%)						
Female	46.8	46.9	0.003	46.8	46.8	0.001
Male	53.2	53.1	0.003	53.2	53.2	0.001
Ethnicity (%)						
Hispanic/Latinx	22.0	20.6	0.03	22.0	21.8	0.005
Not Hispanic/Latinx	62.5	59.5	0.06	62.4	62.7	0.005
Unknown	15.6	19.9	0.11*	15.6	15.5	0.001
Race (%)						
Asian	3.2	3.5	0.01	3.2	3.1	0.005
Black	15.5	15.6	0.002	15.5	15.5	<0.001
White	60.7	57.9	0.06	60.7	61.2	0.01
Unknown	20.1	22.4	0.06	20.1	19.7	0.01
Adverse SDOHs (%)	7.5	3.8	0.16*	7.4	7.6	0.006
Pre-existing medical conditions and treatments (%)						
Diseases related to blood and immune mechanisms	13.6	6.4	0.24*	13.5	13.7	0.005
Diseases related to immune mechanisms	2.3	0.6	0.14*	2.3	2.2	0.007
Chronic lower respiratory diseases	8.6	4.1	0.19*	8.5	8.6	0.002
Chronic lower respiratory diseases originating in the prenatal period	1.4	0.8	0.06	1.4	1.2	0.02
Asthma	7.6	3.7	0.17*	7.6	7.7	0.004
Down syndrome	0.6	0.4	0.04	0.6	0.4	0.02
Malnutrition	2.0	0.8	0.11*	1.9	1.6	0.03
Disorders of newborn related to length of gestation and fetal growth	8.4	4.7	0.15*	8.4	8.5	0.005
Neoplasms	7.5	3.8	0.16*	7.5	7.4	0.002
Congenital malformations of the circulatory system	6.4	4.0	0.11*	6.4	6.1	0.01
Heart diseases	5.1	2.3	0.15*	5.1	4.9	0.01
Neuromuscular disorders	0.2	0.0	0.04	0.2	0.2	0.02
Chemotherapy	2.1	0.8	0.10*	2.1	1.9	0.02
COVID-19 vaccines	9.3	4.6	0.21*	9.3	9.3	0.002

COVID-19 (+) cohort—children who contracted COVID-19 prior to August 2022 as documented in their EHRs. COVID-19 (–) cohort—children who had no documented COVID-19 in their EHRs. Index event was a medical visit in October 2022. Cohorts were propensity-score matched for the list variables with variable status based on anytime to 1 day before the index event. The status of adverse SDOHs was based on the ICD-10 code 'persons with potential health hazards related to socioeconomic and psychosocial circumstances' (Z55–Z65), which includes codes 'problems related to housing and economic circumstances' (Z59), 'problems related to upbringing' (Z62), among others.
*SMD>0.1, a threshold recommended for declaring imbalance.
EHRs, electronic health records; SDOHs, socioeconomic determinants of health; SMD, standardised mean differences.

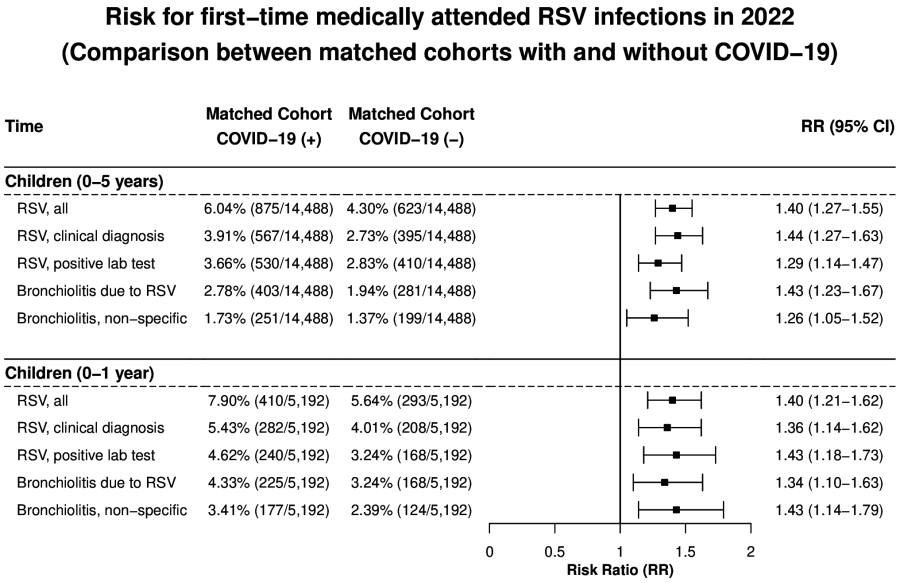

Figure 3 Comparison of risk for first-time medically attended RSV infection that occurred during the 2022 RSV peak season (October–December 2022) among young children who had medical encounters with healthcare organisations in October 10/2022 and had no prior medically attended RSV infection. COVID-19 (+) cohort—children who contracted COVID-19 prior to August 2022 as documented in their EHRs. COVID-19 (–) cohort—children who had no documented COVID-19 in their EHRs. Index event was a medical visit in October 2022. Outcomes (RSV infections) were followed 0–60 days starting from the index event and occurred during 1 October 2022–31 December 2022. Cohorts were propensity-score matched for demographics (actual age at index event, gender, race, ethnicity), adverse socioeconomic determinants of health, pre-existing medical conditions and procedures and COVID-19 vaccination. EHRs, electronic health records; RSV, respiratory syncytial virus.

matched COVID-19 (–) cohort (RR 1.40, 95% CI 1.27 to 1.55), with highest association for clinically diagnosed RSV diseases (RR 1.44, 95% CI 1.27 to 1.63) including RSV-associated bronchiolitis (RR 1.43, 95% CI 1.23 to 1.67) (figure 3). Prior COVID-19 infection was associated with a significantly increased risk for unspecified bronchiolitis (RR 1.26, 95% CI 1.05 to 1.53).

Among the population of 228 940 children aged 0–5 years, 99 105 children were aged 0–1 year (as of October 2022), including 5193 with prior COVID-19 infection (COVID (+) cohort) and 93 912 without (COVID-19 (–) cohort). Compared with the COVID-19 (–) cohort, the COVID-19 (+) cohort was older and had a higher prevalence of adverse SDOHs, pre-existing medical conditions, and COVID-19 vaccinations. After propensity-score matching, both cohorts comprised 5192 children and were balanced (online supplemental file 1). The overall risk for RSV among children aged 0–1 year during October 2022–December 2022 was 7.90% for the COVID-19 (+) cohort, higher than 5.64% for the matched COVID-19 (–) cohort (RR 1.40, 95% CI 1.21 to 1.62). Increased risks were observed for clinically diagnosed RSV diseases, positive lab test-confirmed RSV infection and unspecified bronchiolitis (figure 3).

COVID-19 is associated with a significantly increased risk for first-time medically attended RSV infection among young children during the peak season in 2021

The 2021 study population comprised 370 919 children aged 0–5 years (age as of July 2021–August 2021), among whom 6309 contracted COVID-19 prior to June 2021 ('COVID-19 (+) cohort') and 364 610 children who had no EHR-documented COVID-19 infection ('COVID-19 (–) cohort'). Compared with the COVID-19 (–) cohort, the COVID-19 (+) cohort was similar in age, comprised more Hispanics, and had a significantly higher prevalence of adverse SDOHs and pre-existing medical conditions (table 2). After propensity-score matching, the two cohorts (14 488 children in each) were balanced (table 2). By comparing propensity-score matched COVID-19 (+) and COVID-19 (–) cohorts, we showed that prior COVID-19 infection was associated with increased risk for first-time medically attended RSV infection during the 2021 RSV season (July 2021–December 2021) among children aged 0–5 years (RR 1.32, 95% CI 1.12 to 1.56) and children 0–1 year (RR 1.47, 95% CI 1.18 to 1.82). Prior COVID-19 infection was associated with a significantly increased risk for clinically diagnosed RSV diseases, positive lab test-confirmed RSV and unspecified bronchiolitis in 2021 (figure 4).

DISCUSSION

In this study, we focused on medically attended RSV infections, which was based on the presence of clinical diagnosis codes for RSV infections and RSV-associated diseases including pneumonia and bronchiolitis or positive lab test results for RSV infections in a patient's EHR that required medical care or hospitalisation.

The findings comparing the propensity-matched cohorts showed that prior COVID-19 infection was associated with a significantly increased risk for RSV

Table 2 Characteristics of the 2021 study cohorts of children aged 0–5 years (age as of July 2021–August 2021) who had medical encounters with healthcare organisations during July 2021–August 2021and had no prior medically attended RSV infection, before and after propensity-score matching the listed variables

	Before propensity-score matching			After propensity-score matching		
	COVID-19 (+) cohort	COVID-19 (–) cohort	SMD	COVID-19 (+) cohort	COVID-19 (–) cohort	SMD
Total no	6309	364 610		6308	6308	
Age at index event (years, mean±SD)	2.2±1.6	2.1±1.7	0.07	2.2±1.6	2.2±1.6	0.002
Sex (%)						
Female	45.8	46.5	0.01	45.8	46.1	0.005
Male	54.2	53.5	0.01	54.2	54.9	0.005
Ethnicity (%)						
Hispanic/Latinx	30.8	20.1	0.25*	30.8	30.7	0.002
Not Hispanic/Latinx	54.6	59.1	0.09	54.6	55.0	0.008
Unknown	14.6	20.8	0.16*	14.6	14.3	0.009
Race (%)						
Asian	2.2	3.1	0.06	2.2	2.0	0.008
Black	20.3	20.0	0.007	20.3	20.1	0.005
White	57.0	56.8	0.003	57.0	57.4	0.008
Unknown	20.2	19.6	0.02	20.2	20.0	0.006
Adverse SDOHs (%)	9.0	3.9	0.21*	9.0	9.3	0.01
Pre-existing medical conditions and treatments (%)						
Diseases related to blood and immune mechanisms	15.2	6.6	0.28*	15.2	15.1	0.002
Diseases related to immune mechanisms	2.2	0.7	0.13*	2.2	1.8	0.03
Chronic lower respiratory diseases	10.0	4.5	0.21*	10.0	10.0	<0.001
Chronic lower respiratory diseases originating in the prenatal period	1.8	0.8	0.09	1.8	1.5	0.02
Asthma	9.3	4.2	0.21*	9.3	9.2	0.001
Down syndrome	0.9	0.4	0.06	0.9	0.9	<0.001
Malnutrition	2.0	0.7	0.11*	2.0	1.6	0.03
Disorders of newborn related to length of gestation and fetal growth	8.1	4.3	0.16*	8.1	8.3	0.008
Neoplasms	7.4	3.7	0.17*	7.4	7.5	0.004
Congenital malformations of the circulatory system	7.5	3.9	0.16*	7.5	8.1	0.02
Heart disease	5.9	2.2	0.18*	5.8	5.9	0.003
Neuromuscular disorders	0.2	0.1	0.05	0.2	0.2	0.02
Chemotherapy	2.2	0.8	0.05	2.2	2.1	0.008

COVID-19 (+) cohort—children who contracted COVID-19 prior to 1 June 2022 as documented in their EHRs. COVID-19 (–) cohort—children who had no documented COVID-19 in their EHRs. Index event was a medical encounter in July 2021–August 2021. Cohorts were propensity-score matched for the list variables with status based on anytime to 1 day before the index event. The status of adverse SDOHs was based on the ICD-10 code 'persons with potential health hazards related to socioeconomic and psychosocial circumstances' (Z55–Z65), which includes codes 'problems related to housing and economic circumstances' (Z59), 'problems related to upbringing' (Z62), among others.
*SMD>0.1, a threshold being recommended for declaring imbalance.
SDOHs, socioeconomic determinants of health; SMD, standardised mean differences.

infection during both 2022 and 2021 RSV peak seasons. This finding is consistent with our hypothesis that COVID-19 is an important contributing factor to the 2022 surge of severe paediatric RSV diseases, possibly through its lasting damage to the immune and respiratory systems of young children. Although the strength

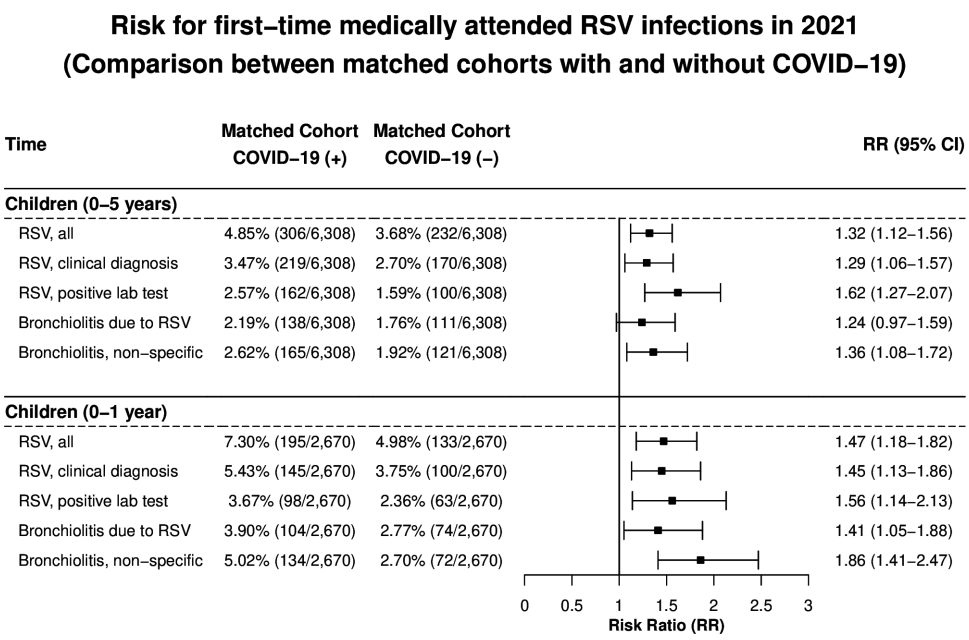

Figure 4 Comparison of risk for medically attended RSV infection that occurred during the 2021 RSV peak season (July–December 2021) among young children who had medical encounters with healthcare organisations from July 2021–August 2021and had no prior medically attended RSV infection. COVID-19 (+) cohort—children who contracted COVID-19 prior to 1 June 2022 as documented in their EHRs. COVID-19 (–) cohort—children who had no documented COVID-19 in their EHRs. Index event was a medical encounter during July 2021–August 2021. Outcomes (RSV infections) were followed 0–120 days starting with the index event and occurred from July 2021 to December 2021. COVID-19 (+) and COVID-19 (–) cohorts were propensity-score matched for demographics (actual age at index event, gender, race, ethnicity), adverse socioeconomic determinants of health, pre-existing medical conditions and procedures. EHRs, electronic health records; RSV, respiratory syncytial virus.

of the associations in 2022 was similar to that in 2021, we observed a historically high surge of paediatric RSV cases only in 2022 but not in 2021. Although there was a buildup of susceptible children in 2021, certain COVID-19 preventative measures remained in place in 2021 that limited the spread of RSV infections. In April 2022, the CDC lifted the mask mandate but still recommended that people wear masks at public transportation settings.[39] Interestingly, very young children aged 0–1 year (as of 2021), many of whom were born after 2020, also showed increased RSV infection in 2021. Waning maternal immunity due to low RSV exposure during the COVID-19 pandemic and the consequent decrease in transplacental RSV antibody transfer may have contributed to increased RSV infections in 2021 compared with 2020. Our cohort studies comparing the matched COVID-19 (+) and COVID-19 (–) cohorts for children aged 0–5 years and children aged 0–1 year showed that prior COVID-19 infection was associated with an increased risk for RSV infection including both clinically diagnosed RSV diseases and positive lab test-confirmed RSV infection in 2021. However, RSV infections in 2021 did not reach the levels in 2022, largely because of the preventive measures and fewer COVID-19-infected children.

In 2022, RSV infections and hospitalisations surged among young children. These data suggest that the 2022 RSV surge was disproportionately driven by more severe cases of RSV diseases, which could not be fully explained by increased testing practices, awareness or transmission through day-care or siblings alone. While immunity debt due to nonpharmaceutical interventions in 2020–2021 might have contributed to the surge, this factor alone could not fully explain the huge surge in November 2022. For children aged 0–1 year (as of 2022), if the immune debt due to waning maternal immunity was the main contributor, we would expect that the level of RSV infection in 2022 to be similar to that in 2021. In 2022, significantly more children contracted COVID-19[40] due to the relaxation of preventive measures and the dominance of the highly transmissible Omicron variant.[19] Studies show that SARS-CoV-2 virus fragments can persist in the body and have the ability to stimulate tissue-specific immunity in children[41 42] and children affected by long COVID may have a compromised cellular immune response.[43] Together with the effects of RSV-specific immunity debt and other factors, the large buildup of COVID-19-infected children and the potential long-term adverse effects of COVID-19 on the immune and respiratory systems[14–17] may have contributed to the 2022 winter surge of severe RSV diseases that was not seen in 2021.

The cohort studies showed that prior COVID-19 infection was associated with increased risk for unspecified bronchiolitis in both 2021 and 2022. Individuals infected with COVID-19 can have long-lasting changes in both innate and lymphocyte-based immune functions,[14 15 43] precisely the systems most engaged in

defence against respiratory viruses.[44 45] Recent studies showed that the overall bronchiolitis severity is similar in 2021 and 2022[46 47] and there was no emergence of new RSV viral lineages.[5] Taken together, these findings further support our hypothesis that COVID-19 had an adverse impact on the immune and respiratory systems of children, making them susceptible to severe respiratory viral infections from RSV and other viruses. Since COVID-19 has long-term effects on multiple organ systems in diverse populations we expect that it will also be associated with increased risk for other severe respiratory viral infections or other bacterial or viral infections in other populations including adults, older adults, immunocompromised patients (ie, cancer, HIV, receiving immunosuppressive treatments) and people with underlying medical conditions. While COVID-19 infection was associated with an increased risk for unspecified bronchiolitis, we did not observe a historically high surge of bronchiolitis in 2022, likely because unspecified bronchiolitis was not as common as RSV infection. Findings from our study could offer a unique opportunity to further understand the mechanisms of SARS-CoV-2 viral infection, RSV infection, other respiratory viruses and their potential positive interactions.[48]

Our study has several limitations: First, it focused on medically attended RSV infection. Although we stratified RSV infection based on positive lab-test and clinical diagnoses, due to restrictions from TriNetX we were unable to assess the severity of RSV infections and its outcomes (eg, hospitalisation) in different clinical settings (eg, inpatient, outpatient, emergency). Second, the patients from the TriNetX network are those who had medical encounters with healthcare systems contributing to TriNetX. Therefore, they do not necessarily represent the entire US population. Results from this study need to be validated in other populations. Third, many children have contracted COVID-19 though the actual prevalence is unknown.[40] The status of prior COVID-19 in our study was based on the clinical diagnosis code or positive lab test results captured in EHRs, which very likely was an underestimate of the actual rate because many COVID-19 tests were performed at home. This means that the COVID-19 (–) cohorts in our study might have included children with mild COVID-19 that were not documented in their EHRs. This could have underestimated the associations of COVID-19 with RSV infection reported in our study. Fourth, there may be overdiagnosis/misdiagnosis/underdiagnosis of RSV infection and other diseases in patient EHRs. However, we compared the relative risk for RSV infection between cohorts drawn from the same TriNetX dataset, therefore, these issues should not substantially affect the comparative risk analyses. Fifth, the COVID-19 (+) and COVID-19 (–) cohorts were matched for age, gender, ethnicity, race, adverse socioeconomic determinants of health (including physical, social and psychosocial environment and housing), pre-existing medical conditions, procedures and COVID-19 vaccinations. Among risk factors for RSV infection among young children,[36] day-care attendance and presence of older siblings in school or day-care may also be risk factors for SARS-CoV-2 viral transmission.[49] To mitigate potential confounding effects, we put an extra restriction on the relative timing of prior COVID-19 infection and RSV infection for the COVID-19 (+) cohort: COVID-19 occurred at least 2 months prior to RSV infection. However, patient EHRs did not capture such information and these uncaptured risk factors could represent unmeasured confounders. Nonetheless, these factors alone could not explain the 2022 surge that was disproportionately driven by more severe cases of RSV diseases. Future studies are needed to examine the associations between COVID-19 and RSV in adults, which are not as often confounded by factors such as the presence of siblings or schooling. Finally, the EHR data that we used captured substantial information of SDOHs of the study population. As shown in table 1, the percentage of the study population with the ICD-10 codes Z55–Z65 ('persons with potential health hazards related to socioeconomic and psychosocial circumstances') was 7.5% for the COVID-19 (+) cohort, significantly higher than the 3.8% for the COVID-19 (–) cohort for children aged 0–5 years in 2022, which is consistent with the previous finding that the most economically disadvantaged particularly vulnerable to COVID-19.[50] While our cohort studies may have captured the proportions of SDOHs between cohorts, it remains unknown how complete and accurate these EHR-derived structured data elements capture SDOHs. In addition, although we have controlled for COVID-19 vaccination for the 2022 cohorts, we were unable to assess how vaccination further modified the associations of COVID-19 with RSV due to small sample sizes as only 4.9% of our 2022 study population were vaccinated.

In conclusion, our study supports that prior COVID-19 infection was associated with a significantly increased risk for RSV infection and may have been a driving force for the 2022 surge of severe paediatric RSV cases in the USA and this should be further investigated. Prevention measures such as vaccines would be beneficial in preventing both COVID-19 infection and COVID-19-associated diseases including RSV infection.

Author affiliations
[1]Center for Science, Health, and Society, Case Western Reserve University, Cleveland, Ohio, USA
[2]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA
[3]The Center for Clinical Informatics Research and Education and the Departments ofInternal Medicine, Pediatrics, and Population and Quantitative Health Sciences, MetroHealth Medical Center, Cleveland, Ohio, USA
[4]National Institute on Drug Abuse, National Institute of Health, Bethesda, Maryland, USA
[5]Center for AI in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

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Please add the following statement to the Contributors section RX is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had acess to the data, and controlled the decision to publish.

ORCID iD

Rong Xu http://orcid.org/0000-0003-3127-4795

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Supplemental File

Supplemental Table 1: Clinical diagnosis, lab-test and other codes used to determine the status of variables in the TriNetX database.

Variables	Name, code	Data type
RSV infection (all)	• Respiratory syncytial virus RNA [Presence] in Specimen by NAA with probe detection (Logical Observation Identifiers Names and Codes (LOINC) code: 40988-8) • Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with probe detection (LOINC code 76089-2) • Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with non-probe detection (LOINC code 82176-9) • Respiratory syncytial virus RNA [Presence] in Respiratory specimen by NAA with probe detection (LOINC code 92131-2) • Respiratory syncytial virus RNA [Presence] in Isolate by NAA with probe detection (LOINC code 60271-4) • Respiratory syncytial virus RNA [Presence] in Upper respiratory specimen by NAA with probe detection (LOINC code 85479-4) • Respiratory syncytial virus Ag [Presence] in Specimen (LOINC code 31950-9) • Respiratory syncytial virus Ag [Presence] in Nasopharynx by Rapid immunoassay (LOINC code 72885-7) • Respiratory syncytial virus Ag [Presence] in Nose (LOINC code 33045-6) • Respiratory syncytial virus Ab [Presence]	positive/negative (LOINC lab result code)

	in Serum (LOINC code 33390-6) • Respiratory syncytial virus Ag [Presence] in Specimen by Immunoassay (LOINC code 5876-8 • Respiratory syncytial virus Ag [Presence] in Specimen by Immunofluorescence (LOINC code 5877-6) • Respiratory syncytial virus as the cause of diseases classified elsewhere (The International Classification of Diseases, Tenth Revision (ICD-10) code: B97.4) • Respiratory syncytial virus pneumonia (ICD-10 code: J12.1) • Acute bronchiolitis due to respiratory syncytial virus (ICD-10 code: J21.0)	present/absent (ICD-10 diagnosis code)
RSV infection (clinical diagnosis)	• Respiratory syncytial virus as the cause of diseases classified elsewhere (The International Classification of Diseases, Tenth Revision (ICD-10) code: B97.4) • Respiratory syncytial virus pneumonia (ICD-10 code: J12.1) • Acute bronchiolitis due to respiratory syncytial virus (ICD-10 code: J21.0)	present/absent
RSV infection (positive lab test)	• Respiratory syncytial virus RNA [Presence] in Specimen by NAA with probe detection (Logical Observation Identifiers Names and Codes (LOINC) code: 40988-8)	

	• Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with probe detection (LOINC code 76089-2) • Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with non-probe detection (LOINC code 82176-9) • Respiratory syncytial virus RNA [Presence] in Respiratory specimen by NAA with probe detection (LOINC code 92131-2) • Respiratory syncytial virus RNA [Presence] in Isolate by NAA with probe detection (LOINC code 60271-4) • Respiratory syncytial virus RNA [Presence] in Upper respiratory specimen by NAA with probe detection (LOINC code 85479-4) • Respiratory syncytial virus Ag [Presence] in Specimen (LOINC code 31950-9) • Respiratory syncytial virus Ag [Presence] in Nasopharynx by Rapid immunoassay (LOINC code 72885-7) • Respiratory syncytial virus Ag [Presence] in Nose (LOINC code 33045-6) • Respiratory syncytial virus Ab [Presence] in Serum (LOINC code 33390-6) • Respiratory syncytial virus Ag [Presence] in Specimen by Immunoassay (LOINC code 5876-8 • Respiratory syncytial virus Ag [Presence] in Specimen by Immunofluorescence (LOINC code 5877-6)	positive/negative

	• Respiratory syncytial virus as the cause of diseases classified elsewhere (The International Classification of Diseases, Tenth Revision (ICD-10) code: B97.4) • Respiratory syncytial virus pneumonia (ICD-10 code: J12.1) • Acute bronchiolitis due to respiratory syncytial virus (ICD-10 code: J21.0)	
Bronchiolitis, non-specific	• Acute bronchiolitis, unspecified (ICD-10 code J21.9)	present/absent
Visit	• TNX:Visit	present/absent
Age	Age	continuous
Female	F	present/absent
Male	M	present/absent
Asian	Asian (Demographics: 2028-9)	present/absent
Black or African American	Black or African American (Demographics: 2054-5)	present/absent
White	White (Demographics: 2106-3)	present/absent
Hispanic/Latino	Hispanic or Latino (Demographics: 2135-2)	present/absent
Not Hispanic or Latino	Not Hispanic or Latino (Demographics: 2186-5)	present/absent
Adverse socioeconomic and psychosocial circumstances	Persons with potential health hazards related to socioeconomic and psychosocial circumstances (ICD-10 code: Z55-Z65), including: • Problems related to education and literacy (Z55) • Problems related to employment and unemployment (Z56) • Occupational exposure to risk factors (Z57) • Problems related to physical environment (Z58) • Problems related to housing and economic circumstances (Z59) • Problems related to social environment (Z60) • Problems related to upbringing (Z62)	present/absent

	• Other problems related to primary support group, including family circumstances (Z63) • Problems related to certain psychosocial circumstances (Z64) • Problems related to other psychosocial circumstances (Z65)	
COVID-19	• COVID-19 (ICD-10 code: U07.1) • SARS coronavirus 2 and related RNA [Presence] (LOINC code: 9088)	present/absent (ICD-10 code) Positive/negative (lab results)
Diseases related to blood and immune mechanisms	• Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 code: D50-D89)	present/absent
Diseases related to immune mechanisms	• Certain disorders involving the immune mechanism (ICD-10 code: D80-D89)	present/absent
Chronic lower respiratory diseases	• Chronic lower respiratory diseases (ICD-10 code: J40-J47)	present/absent
Chronic lower respiratory diseases originating in the prenatal period	• Chronic respiratory disease originating in the perinatal period (ICD-10 code: P27)	present/absent
Asthma	• Asthma (ICD-10 code: J45)	present/absent
Down syndrome	• Down Syndrome (ICD-10 code: Q90)	present/absent
Malnutrition	• Malnutrition (ICD-10 code: E40-E46)	present/absent
Disorders of newborn related to length of gestation and fetal growth	• Disorders of newborn related to length of gestation and fetal growth (ICD-10 code: P05-P08)	present/absent
Neoplasms	• Neoplasms (ICD-10 code: C00-D49)	present/absent
Congenital malformations of the circulatory system	• Congenital malformations of the circulatory system (ICD-10 code: Q20-Q28)	present/absent
Heart disease	• Ischemic heart diseases (ICD-10 code: I20-I25) • Other forms of heart disease	present/absent

	(ICD-10 code: I30-I5A)	
Neuromuscular Disorders	• Myasthenia gravis and other myoneural disorders (ICD-10 code: G70)	present/absent
Chemotherapy	• Chemotherapy (TNX procedure code: 1002)	present/absent
COVID-19 vaccination	• SARS-CoV-2 (COVID-19) Vaccine (CDC CVX (vaccine administered) code: 213) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted, for intramuscular use (CPT code 91300) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use (CPT code 91300) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5 mL dosage, for intramuscular use (CPT code 91303) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation, for intramuscular use (CPT code 91305) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 50 mcg/0.25 mL dosage, for intramuscular use (CPT code 91306) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-	present/absent

	LNP, spike protein, preservative free, 10 mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation, for intramuscular use (CPT code 91307) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 3 mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation, for intramuscular use (CPT code 91308) • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 25 mcg/0.25 mL dosage, for intramuscular use (CPT code 91311)	

Supplemental Table 2. Characteristics of the 2022 study cohorts of children aged 0–1 year (age as of 10/2022) who had medical encounters with healthcare organizations in 10/2022 and had no prior medically attended RSV infection before and after propensity-score matching for the listed variables.

	Before Propensity-Score Matching			**After Propensity-Score Matching**		
	COVID-19 (+) cohort	**COVID-19 (–) cohort**	**SMD**	**COVID-19 (+) cohort**	**COVID-19 (–) cohort**	**SMD**
Total number	5,193	93,912		5,192	5,192	
Age at index event (years, mean±SD)	0.7± 0.4	0.4± 0.5	0.68*	0.7± 0.4	0.7± 0.4	<.001
Sex (%)						
Female	47.0	47.0	<.001	47.0	47.1	0.003
Male	53.0	53.0	<.001	53.0	52.9	0.003
Ethnicity (%)						
Hispanic/Latinx	24.9	21.0	0.09	24.9	24.5	0.009
Not Hispanic/Latinx	58.6	56.4	0.04	58.6	59.2	0.01
Unknown	16.5	22.6	0.15*	16.5	16.4	0.005
Race (%)						
Asian	2.6	3.2	0.04	2.6	2.7	0.007
Black	15.2	15.3	0.002	15.2	14.9	0.008
White	59.1	56.5	0.05	59.1	59.6	0.01

Unknown	22.7	24.5	0.04	22.7	22.4	0.008
Adverse socioeconomic determinants of health (%)	5.2	2.5	0.14*	5.1	5.4	0.01
Pre-existing medical conditions and treatments (%)						
Diseases related to blood and immune mechanisms	8.5	3.5	0.21*	8.4	8.3	0.003
Diseases related to immune mechanisms	1.2	0.3	0.10*	1.2	1.2	<.001
Chronic lower respiratory diseases	2.9	0.9	0.15*	2.9	2.7	0.01
Chronic lower respiratory diseases originating in the prenatal period	1.5	1.0	0.04	1.5	1.5	0.006
Asthma	2.4	0.8	0.13*	2.4	2.1	0.02
Down syndrome	0.6	0.3	0.04	0.6	0.6	0.005
Malnutrition	1.4	0.5	0.09	1.4	1.1	0.02
Disorders of newborn related to length of gestation and fetal growth	8.7	5.3	0.13*	8.7	9.0	0.01
Neoplasms	5.7	3.0	0.13*	5.6	5.9	0.01
Congenital malformations of the circulatory system	6.4	4.1	0.10*	6.3	6.3	0.001
Heart diseases	4.0	1.8	0.13*	4.0	4.0	0.004
Neuromuscular Disorders	0.2	0.0	<.001	0.2	0.2	<.001
Chemotherapy	0.6	0.2	0.06	0.6	0.5	0.01
COVID-19 vaccines	7.7	3.3	0.17*	7.7	7.7	0.003

COVID-19 (+) cohort – children who contracted COVID-19 prior to 8/2022 as documented in their EHRs. COVID-19 (–) cohort – children who had no documented COVID-19 in their EHRs. Index event was a medical visit in 10/2022. Cohorts were propensity-score matched for the list variables with variable status based on anytime to 1 day before the index event. The status of adverse socioeconomic determinants of health (SDOHs) was based on the ICD-10 code "Persons with potential health hazards related to socioeconomic and psychosocial circumstances" (Z55-

Z65), which includes codes "Problems related to housing and economic circumstances" (Z59), "Problems related to upbringing" (Z62), among others. SMD – standardized mean differences. *SMD greater than 0.1, a threshold recommended for declaring imbalance.

Supplemental Table 3. Characteristics of the 2021 study cohorts of children aged 0-1 year (age as of 7/2021-8/2021) who had medical encounters with healthcare organizations during 7/2021-8/2021and had no prior medically attended RSV infection, before and after propensity-score matching the listed variables.

	Before Propensity-Score Matching			**After Propensity-Score Matching**		
	COVID-19 (+) cohort	**COVID-19 (-) cohort**	**SMD**	**COVID-19 (+) cohort**	**COVID-19 (-) cohort**	**SMD**
Total number	2,671	160,100		2,670	2,670	
Age at index event (years, mean±SD)	0.7± 0.4	0.5± 0.5	0.61*	0.7± 0.4	0.7± 0.4	0.005
Sex (%)						
Female	45.4	46.9	0.03	45.4	46.0	0.01
Male	54.6	53.1	0.03	54.6	54.0	0.01
Ethnicity (%)						
Hispanic/Latinx	33.9	20.9	0.29*	33.9	33.7	0.002
Not Hispanic/Latinx	53.4	57.0	0.07	53.4	53.0	0.01
Unknown	12.7	22.1	0.25*	12.7	12.3	0.01
Race (%)						
Asian	2.4	3.0	0.04	2.4	2.2	0.01
Black	20.3	19.8	0.01	20.3	20.8	0.01
White	56.3	55.8	0.01	56.3	56.0	0.005
Unknown	20.7	20.9	0.004	20.7	20.6	0.004
Adverse socioeconomic determinants of health (%)	6.4	2.5	0.19*	6.4	6.9	0.02
Pre-existing medical conditions and treatments (%)						
Diseases related to blood and immune mechanisms	10.7	3.6	0.28*	10.7	10.7	<.001
Diseases related to immune mechanisms	1.2	0.4	0.08	1.2	1.1	0.007
Chronic lower	3.1	0.9	0.16*	3.1	2.9	0.009

respiratory diseases						
Chronic lower respiratory diseases originating in the prenatal period	1.5	0.8	0.07	1.5	1.3	0.02
Asthma	2.8	0.8	0.15*	2.7	2.7	0.005
Down syndrome	0.8	0.3	0.06	0.8	0.7	0.004
Malnutrition	1.3	0.5	0.10*	1.3	1.0	0.03
Disorders of newborn related to length of gestation and fetal growth	7.7	4.4	0.14*	7.7	7.6	0.004
Neoplasms	5.4	3.0	0.12*	5.4	5.7	0.01
Congenital malformations of the circulatory system	7.6	3.7	0.17*	7.6	7.5	0.006
Heart disease	5.1	1.7	0.19*	5.0	5.0	0.002
Neuromuscular Disorders	0.4	0.0	0.08	0.4	0.4	<.001
Chemotherapy	0.4	0.2	0.04	0.4	0.4	0.006

COVID-19 (+) cohort – children who contracted COVID-19 prior to 6/1/2022 as documented in their EHRs. COVID-19 (-) cohort – children who had no documented COVID-19 in their EHRs. Index event was a medical encounter during 7/2021-8/2021. Cohorts were propensity-score matched for the list variables with status based on anytime to 1 day before the index event. The status of adverse socioeconomic determinants of health (SDOHs) was based on the ICD-10 code "Persons with potential health hazards related to socioeconomic and psychosocial circumstances" (Z55-Z65), which includes codes "Problems related to housing and economic circumstances" (Z59), "Problems related to upbringing" (Z62), among others. SMD – standardized mean differences. *SMD greater than 0.1, a threshold being recommended for declaring imbalance.