Acute Upper Airway Disease in Children With the Omicron (B.1.1.529) Variant of SARS-CoV-2—A Report From the US National COVID Cohort Collaborative

SARS-CoV-2 can cause severe pediatric disease, including acute COVID-19 and multisystem inflammatory syndrome. Published reports associating SARS-CoV-2 with upper airway infection (UAI), such as laryngotracheobronchitis (croup), have been limited to small case series. Although noncoronaviruses, including parainfluenza and respiratory syncytial virus, most frequently cause UAI, coronaviruses (eg, type NL63) are also commonly implicated. Young children are especially vulnerable to UAI given their small and relatively collapsible airways.

Table. Characteristics and Outcomes of Hospitalized Children With Upper Airway Infection (UAI) and SARS-CoV-2 During the Pre-Omicron and Omicron Periods

| Variable                                      | Hospitalized UAI cases, No./Total No. (%); SE | Pre-Omicron | Omicron | P value |
|-----------------------------------------------|---------------------------------------------|-------------|---------|---------|
| % Children hospitalized with SARS-CoV-2 found to have UAI | 384/18 849 (2.0); 0.2 | 206/14 473 (1.4); 0.2 | 178/4376 (4.1); 0.6 | <.001 |
| Sex                                           |                                             |             |         |         |
| Female                                        | 132/384 (34.4); 4.9                          | 79/206 (38.3); 6.8 | 53/178 (29.8); 6.9 | .72    |
| Male                                          | 252/384 (65.6); 4.9                          | 127/206 (61.7); 6.8 | 125/178 (70.2); 6.9 |         |
| Age, mean (SD), y                             | 3.3 (3.8)                                    | 4.4 (4.5)    | 2.1 (2.1) | <.001 |
| Ethnicitya                                    |                                             |             |         |         |
| Hispanic or Latino                            | 102/384 (26.6); 4.5                          | 39/206 (18.9); 5.6 | 63/178 (35.4); 7.2 | <.001 |
| Not Hispanic or Latino                        | 255/384 (66.4); 4.8                          | 152/206 (73.8); 6.2 | 103/178 (57.9); 7.5 |         |
| Missing/unknown                               | 27/384 (7.0); 2.7                            | <20 (<9.7)   | <20 (<11) |         |
| Raceb                                         |                                             |             |         |         |
| Asian                                         | <20 (<5.2)                                   | <20 (<9.7)   | <20 (<11) |         |
| Black or African American                     | 50/384 (13.0); 3.5                           | 40/206 (19.4); 5.4  | <20 (<11) |         |
| Native Hawaiian or other Pacific Islander     | <20 (<5.2)                                   | <20 (<9.7)   | <20 (<11) | <.001 |
| White                                         | 222/384 (57.8); 5.0                          | 114/206 (55.3); 7.0 | 108/178 (60.7); 7.4 |         |
| Otherc                                        | 89/384 (23.2); 4.3                           | 46/206 (22.3); 5.9 | 43/178 (24.2); 6.5 |         |
| Missing/unknown                               | <20 (<5.2)                                   | <20 (<9.7)   | <20 (<11) |         |
| Comorbidities                                 |                                             |             |         |         |
| Known BMI                                      | 91/384 (23.7); 4.4                           | 71/206 (34.5); 6.7 | 201/178 (11.2); 4.9 | <.001 |
| Obese (BMI 95th percentile)                   | <20 (<5.2)                                   | <20 (<9.7)   | <20 (<11) | NA     |
| Diabetes (type 1 or 2)                        | <20 (<5.2)                                   | <20 (<9.7)   | <20 (<11) | NA     |
| Asthma                                        | 42/384 (10.9); 3.3                           | 40/206 (19.4); 5.4  | <20 (<11) | .41    |
| Medications received                          |                                             |             |         |         |
| Dexamethasone                                 | 114/384 (29.7); 4.7                          | 75/206 (36.4); 6.8 | 39/178 (21.9); 6.3 | <.001 |
| Systemic antibiotic                           | 100/384 (26.0); 4.5                          | 80/206 (38.8); 6.9  | <20 (<11) | <.001 |
| SARS-CoV-2 severitya                          |                                             |             |         |         |
| Moderate                                      | 303/384 (78.9); 4.2                          | 131/206 (63.6); 6.8 | 172/178 (96.6); 3.1 |         |
| Severe                                        | 81/384 (21.1); 4.2                           | 80/206 (38.8); 6.8  | <20 (<11) | <.001 |
| Mechanical ventilation                        | 76/384 (19.8); 4.1                           | 70/206 (34.0); 6.7  | <20 (<11) |         |
| Vasoactive inotropes                          | 34/384 (8.9); 3.0                            | 30/206 (14.6); 5.2  | <20 (<11) |         |

Abbreviations: BMI, body mass index; NA, not applicable; SE, standard error.

a The method by which each N3C site determines and stores race and ethnicity information is at the discretion of each participating health care site. Race and ethnicity variables were included in this analysis to help identify factors associated with development of UAI among children hospitalized with SARS-CoV-2.

b Result rounded to the nearest 10 to avoid exposure of cell values under 20 (as per N3C policy). Percentages are represented as if n = 20.

c Includes patients with a race value reported to the N3C by the health care site of other, other race, more than 1 race, or multiple race.

d BMI calculated as per the US Centers for Disease Control and Prevention guidelines with obesity defined as any child 2 years and older with a BMI ≥95th percentile for age and sex. Percentages reported in the obese row represent the percentage of patients with a known BMI who had a BMI greater than 95th percentile for age and sex.

e Severe disease includes children requiring invasive ventilation, vasoactive inotropes, or extracorporeal membrane oxygenation support or who died, whereas moderate disease includes hospitalized children without any of these. The number of patients who required extracorporeal membrane oxygenation support and the number of patients who died were both <20 and are not shown.

The Omicron (B.1.1.529) strain of SARS-CoV-2 became dominant in the US the week ending December 25, 2021. Omicron is known to cause lower severity disease than the Delta (B.1.617.2) variant. This may be because Omicron replicates less efficiently in lung parenchyma and more efficiently in the conducting airways. We conducted this retrospective cohort study to determine if cases of UAI among children increased when Omicron became the dominant SARS-CoV-2 variant in the US.

Methods | We leveraged the US National COVID Cohort Collaborative (N3C) and a pipeline we built for a National Institutes of Health–funded pediatric COVID-19 dashboard to conduct this study. Among children in N3C younger than 19 years with a positive SARS-CoV-2 test result (polymerase chain reaction, antigen, or antibody), we identified those with a UAI diagnosis (eTable in the Supplement). We included bacterial tracheitis because it can be difficult to distinguish from and can be a complication of viral croup. We compared demographic, comorbidity, and clinical outcome variables between patients from the pre-Omicron (March 1, 2020, to December 25, 2021)
and Omicron (December 26, 2021, to February 17, 2022) periods. We used χ² and Fisher exact tests for categorical variable comparisons and the Mood median and t tests for continuous variable comparisons. Race and ethnicity were identified from N3C site electronic health record data and included to aid with identification of variables associated with increased risk of UAI among children with SARS-CoV-2. Each N3C site determines race and ethnicity at its discretion. We used linear regression to determine the change over time in percentage of children with UAI among hospitalized cases (solid line) and 0.2% (standard error, 0.03%; \( P = .005 \)) among outpatient and emergency department cases (dotted line). Shaded regions indicate 95% CIs.

Results | The February 17, 2022, N3C data release contains 18 849 children hospitalized with SARS-CoV-2, 384 of whom (2.0%) had UAI (Table). Severe disease (defined as requiring invasive ventilation, vasopressors, or extracorporeal membrane oxygenation or death) occurred in 81 children (21%). SARS-CoV-2-positive UAI rates have increased with progression from the pre-Omicron to Omicron periods (206 of 14 473 [1.5%] vs 178 of 4376 [4.1%, respectively; \( P < .001 \)) (Figure), with 178 of 384 cases (46%) occurring during the Omicron period. Children with UAI during the Omicron period were more likely to be younger and Hispanic or Latino and less likely to receive dexamethasone or develop severe disease compared with those in the pre-Omicron period. Lastly, the proportion of children with a pediatric complex chronic condition was not significantly different in the pre-Omicron period compared with the Omicron period (74 of 206 [36%] vs 39 of 178 [22%], respectively; \( P = .54 \)).

Discussion | SARS-CoV-2-positive pediatric UAI rates increased during the Omicron surge. More than one-fifth of children hospitalized with SARS-CoV-2 and UAI developed severe disease. Given the high proportion of UAI cases during the Omicron period, these results appear to support recent mechanistic reports. A limitation of this analysis is that diagnosis codes will only be present for completed encounters; as such, children who are still hospitalized are not represented, and the frequency of severe disease observed in the Omicron period may be an underestimate.

Children with severe UAI are at risk of cardiac arrest from rapid-onset upper airway obstruction. They may require therapies typically provided in intensive care units, including frequent administration of nebulized racemic epinephrine, helium-oxygen mixtures, and intubation. While the rate of SARS-CoV-2 pediatric UAI is not overwhelmingly high, understanding this new clinical phenotype and the potential for acute upper airway obstruction may help guide therapeutic decision-making.
Risk and Phenotype of Multisystem Inflammatory Syndrome in Vaccinated and Unvaccinated Danish Children Before and During the Omicron Wave

Multisystem inflammatory syndrome in children (MIS-C) is a severe manifestation of SARS-CoV-2 in children and adolescents. We aimed to estimate the risk of MIS-C after SARS-CoV-2 infection in vaccinated and unvaccinated individuals during the Omicron wave. Further, we aimed to compare the risk and clinical characteristics of MIS-C with the pre-Omicron waves.

Methods | This population-based cohort study prospectively included patients aged 0 to 17 years with MIS-C from all 18 Danish pediatric departments. Patients were diagnosed from January 1, 2022, to March 15, 2022, after SARS-CoV-2 infection between January 1 and February 1, 2022, when Omicron constituted more than 95% of variants. We followed the STROBE reporting guidelines for cohort studies. We used previously reported data to compare MIS-C during Omicron with the pre-Omicron waves.1,2

We calculated the risk of MIS-C per 1 million estimated SARS-CoV-2 infections in children and adolescents. We estimated the number of infections by applying multipliers of 1.5 to 2.1 to laboratory-confirmed infections obtained from the Danish COVID-19 surveillance registries (Table 1). All 95% CIs were calculated using an exact method for binomial proportions. We compared risks of MIS-C in risk ratios (RRs) using Fisher exact test. Two-tailed Mann-Whitney U or χ² tests were used to compare patient characteristics. Permission to disclose patient data was obtained by oral and written parental consent or by a waiver of requirement.

Results | We identified 1 vaccinated and 11 unvaccinated patients with MIS-C among 583,618 estimated infected children and adolescents, including 267,086 vaccinated individuals (Table 1). No MIS-C cases occurred among 31,516 estimated individuals with reinfections.

During the Omicron wave, the risk of MIS-C after SARS-CoV-2 infection was significantly lower among vaccinated vs unvaccinated individuals (RR, 0.11; 95% CI, 0.01-0.83; P = .007) (Table 1). The risk of MIS-C among unvaccinated individuals during the Omicron wave was significantly lower than during the Delta wave (RR, 0.12; 95% CI, 0.06-0.23; P < .001) and wild-type wave (RR, 0.14; 95% CI, 0.07-0.29; P < .001). The phenotype of MIS-C was similar in Omicron and pre-Omicron waves (Table 2).

Discussion | We found the risk of MIS-C after SARS-CoV-2 infection during the Omicron wave substantially lower compared with previous SARS-CoV-2 variants. This could be explained by a reduced ability of Omicron to trigger hyperinflammation as it is phylogenetically different and associated with an increased immune escape.1 The lower risk could also partly be explained by a reduced risk after reinfection, although only 6% of our included infected individuals had confirmed reinfection, and such a reduced risk after reinfection has not yet been reported.

The risk of MIS-C during the Omicron wave was found to be significantly lower after breakthrough infection in vaccinated compared with unvaccinated children and adolescents. A high vaccine effectiveness against MIS-C has previously been found during the Delta wave, primarily explained by a high effectiveness against the Delta variant.1,4,5 The present study suggests a direct vaccine effectiveness against MIS-C after breakthrough infection. This may be caused by vaccine-induced modulation of the immune system rendering it less prone to cause hyperinflammation after SARS-CoV-2 infection.

The main limitation of this study was the small population size resulting in few MIS-C cases, making our estimates vulnerable to fluctuations. The multipliers of 1.5 to 2.1 used to estimate the true number of infected individuals were encumbered with uncertainty and lower than those previously used for the US population;6 our multipliers were low owing to thorough test capacity in Denmark with biweekly screening tests in schools. In this Danish population-based cohort study, we found a substantially decreased risk of MIS-C after infection with Omicron compared with pre-Omicron variants and a lower risk of MIS-C after breakthrough infections in vaccinated individuals.