Severe COVID-19 outcomes in pediatrics: an observational cohort analysis comparing Alpha, Delta, and Omicron variants

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Summary

Objective COVID-19 can rarely lead to severe illness in pediatric patients. The aim of this study was to determine if severe outcomes in pediatric COVID-19 have changed over the course of the pandemic.

Methods This was a multicenter, observational cohort analysis from a large regional healthcare system in metro Detroit using electronic health record data to evaluate emergency visits, hospitalization, and severe COVID-19 disease in pediatric patients. Consecutive pediatric patients presenting to the emergency department with a primary diagnosis of COVID-19 were included. Outcomes data was gathered from three distinct time intervals that coincided with Alpha, Delta, and Omicron variant predominance (Time interval 1 (T1) 1/1/2021–6/30/2021: Alpha, T2 7/1/2021–12/31/2021: Delta, T3 1/1/2022–6/16/2022): Omicron. The primary outcome was severe disease inclusive of composite intensive care unit admission, mechanical ventilation, multisystem inflammatory syndrome in children (MIS-C), myocarditis, or death. Secondary outcomes included severe outcomes considering viral coinfection and vaccination status.

Results Between 1/1/2021 and 6/16/2022, there were 4517 emergency COVID-19 visits, of which 12.5% (566) of children were hospitalized. 24.4% (138), 31.6% (179), and 44.0% (249) of admissions occurred during T1, T2 and T3 respectively. Most patients were male (55.1%) and 59.9% identified as Caucasian. The median age was 5.0 (interquartile range 1.0, 13.0) with infants comprising 22.8% (129), toddlers 25.1% (142), children 23.0% (130), and teenagers 29.2% (165). Over the course of the pandemic, the proportion of infants in hospitalization increased from 16.7% in T1 to 19.6% in T2 to 28.5% in T3 ($p < 0.01$) while the proportion of teenagers in hospitalization decreased from 39.1% in T1 to 31.3% in T2 to 22.1% in T3 ($p < 0.001$). Oxygen therapy was required in a minority (29.9%) of cases with supplemental oxygen utilized the least in T3 (16.5%) and most in T2 (30.2%). Composite severe disease decreased throughout the pandemic occurring in 36.2% in T1, 27.4% in T2, and 18.9% in T3. A multivariable logistic regression analysis revealed the odds of composite severe disease was significantly lower in T3 compared to T1 (adjusted odds ratio [aOR] 0.35, 95% Confidence Interval 0.21–0.60, $p < 0.001$). Fully vaccinated or fully vaccinated and boosted admission rates remained low throughout all periods with 4.4% in T1, 4.5% in T2 and 8.4% in T3. Viral coinfection was most common during T2 (16.8%) followed by T3 (12.5%) and least common in T1 (5.1%) ($p = 0.006$). Coinfection occurred more commonly in younger children with a median age of 1.2 (0.0, 4.5) compared to those with mono-infection with a median age of 6 (1.0, 14.0) ($p < 0.001$). Severe outcomes occurred in 45.6% of coinfection cases compared to 22.1% without coinfection ($p < 0.001$).

Conclusions While Omicron cases had the highest admission frequency, severe illness was lower than Delta and Alpha variants. Coinfection with respiratory viruses increased the risk of severe outcomes and impacted infants more than older children.

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Keywords: SARS-CoV-2; COVID-19; Omicron; Delta; Alpha; Viral co-infection; Pediatrics; Children

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Research in context

Evidence before this study

On June 16, 2022, we utilized PubMed to review data regarding severe outcomes in pediatric patients infected with COVID-19. Given the relatively low hospitalization rate in this population compared to the adult population, limited data were available, especially during the recent Omicron-predominant period. We utilized the search terms (COVID-19 OR novel coronavirus OR SARS-CoV-2) AND (emergency visit OR hospitalization) AND (pediatric OR children OR infants). No time or language restrictions were used. Several large trials from early in the COVID-19 pandemic evaluated pediatric outcomes, however, there was limited data available from more recent periods of increased hospitalization among the pediatric population. Furthermore, data regarding vaccination effectiveness and viral co-infection was limited.

Added value of this study

Our observational cohort analysis of a large, eight-hospital healthcare system in metro Detroit, Michigan, United States, evaluated the emergency visits and hospitalizations of pediatric patients infected with COVID-19 and assessed for severe outcomes, including intensive care unit admission at any time during hospitalization, need for mechanical ventilation, multisystem inflammatory syndrome in children (MIS-C), myocarditis, or in-hospital death. We found that the odds of composite severe disease were significantly lower during the Omicron-predominant time period compared to the alpha-predominant time period (adjusted odds ratio 0.35, 95% Confidence Interval 0.21–0.60, $p < 0.001$). Additionally, viral co-infection was associated with a higher frequency of severe outcomes ($p < 0.001$).

Implications of all the available evidence

As the COVID-19 pandemic continues and mutations lead to new variants, it is important to continuously assess severe outcomes among the pediatric population.

Introduction

Since the beginning of the pandemic, over 14 million children have been infected with SARS-CoV-2 infection representing 18.6% of all cases in the United States.[1] While hospitalization of children has been less frequent than their adult counterparts (21.37 admissions per 100,000 for adults age 70 and older),[2] the rate of hospitalization for children has peaked recently at 1.25 admissions per 100,000 during the Omicron predominant time period.[2] These hospitalization rates may be an overestimate, however, given the number of unconfirmed cases that occur.[3] When hospitalization is required, children commonly require supplemental oxygen therapy but, in some cases, can deteriorate and require vasopressors or mechanical ventilation. Several larger trials have evaluated pediatric outcomes from earlier phases of the pandemic.[4–7] However, as the virus has mutated over time, it is unclear if the risk of severe outcomes in pediatrics has shifted, particularly including the Omicron predominant time frame. Although vaccination efforts have had more time to filter through the pediatric population, the rates of transmission and hospitalization have peaked in the past 6 months.[8]

Given this trend, more real-world data is needed to examine hospitalization and severe outcomes in children. Therefore, we aimed to examine and compare pediatric COVID-19 outcomes in three-time intervals that correspond with a predominant variant strain. Further, we explored the impact of vaccination and viral co-infection on severe outcomes.

Methods

Study design, setting, and participants

This multicenter, observational cohort analysis utilized electronic health records (EHR; Epic Systems, Verona, WI, USA) to evaluate outcomes in pediatric patients over three distinct time periods during the pandemic.

The study was conducted at Beaumont Health, an eight-hospital acute care regional health system caring for 2.2 million people across the communities within the Metro Detroit area. The hospitals range from a large tertiary care academic center to intermediate-sized and smaller community hospitals. Beaumont Children's sees over 200,000 children annually with pediatric and neonatal units at three sites.

Consecutive patients less than 18 years old who presented to one of Beaumont Health's emergency departments (EDs) between January 1, 2021, and June 16, 2022, who had a principal diagnosis of COVID-19 (U07.1) were included. Patients were excluded if they had COVID-19 (U07.1) as a secondary diagnosis. Further, patients were excluded if transferred out of the health system and investigators did not have access to the transfer records. The Beaumont Institutional Review Board approved this investigation. Written informed consent was waived due to the retrospective nature of this study.

Severe disease was defined as a composite outcome of intensive care unit (ICU) admission at any time during hospitalization, need for mechanical ventilation, multisystem inflammatory syndrome in children (MIS-C), myocarditis, or in-hospital death.

Three distinct time segments, each approximating six months, were assessed during this study. Time interval 1 (T1) occurred 1/1/2021–6/30/2021 and coincided with Alpha variant predominance. T2 occurred 7/1/2021–12/31/2021 and coincided with Delta variant predominance. T3 occurred 1/1/2022–6/16/2022 and coincided with Omicron variant predominance.

Demographic, clinical, and outcomes data were obtained from the EHR. Demographics included age, race, and sex. Clinical data included body mass index (BMI), in hospital therapies such as supplemental oxygen, high flow oxygen, mechanical ventilation, and intensive care admission. Outcomes data included severe disease, MIS-C, myocarditis, viral co-infection, length of stay, disposition, and death.

Comorbid conditions were grouped via ICD-10-CM code classifications from the Pediatric Complex Chronic Conditions Classification System Version 2.[9] Patients were classified as immunocompromised if their clinical record contained any historical International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes consistent with the immunocompromised state as defined by the Agency of Healthcare Research and Quality (AHRQ) at the time of their ED presentation.[10]

EHR data was used to confirm SARS-CoV-2 vaccination status. This data was available through our EHR and linked to the Michigan Care Improvement Registry (MCIR) and therefore captured patients who had been vaccinated outside of the Beaumont Health System.[11] MCIR contains all SARS-CoV-2 immunization data for patients who received their vaccine within the state of Michigan. This data included vaccine type as well as the date of administration.

Viral co-infection was determined by query of commonly performed laboratory testing for pediatric patients with a presumed viral illness. The query consisted of a respiratory virus panel, obtained by nasopharyngeal swab and tested via multiplex nucleic acid amplification (NAA), which detects Influenza A (including subtypes H1, H3, and H1N1), Influenza B, respiratory syncytial virus (RSV) (A/B), Metapneumovirus, Rhinovirus/Enterovirus, Adenovirus, Parainfluenza virus 1–4, Coronavirus (SARS-CoV-2, 229E, NL63, HKU1, and OC43), and Bocavirus. The query also consisted of an Influenza A/B and RSV NAA panel obtained by nasopharyngeal swab and an ED-specific panel for COVID-19, Influenza A/B, RSV by NAA. All tests were performed at Beaumont Laboratories.

Outcomes and measurements

The primary outcome of this study was severe disease and included composite ICU admission during hospitalization, mechanical ventilation, MIS-C, myocarditis, or death. Secondary outcomes included severe disease in patients with viral co-infection and with vaccination.

Statistical analysis

Descriptive analysis was used to summarize patient characteristics. Numerical variables were reported as means with standard deviations or medians with interquartile ranges. Categorical variables were expressed as counts and frequencies (percentages). The Chi-square or Fisher's exact test was used for categorical variables and the Kruskal–Wallis (exact) test was used for numerical variables. Logistic regression was used to assess the effect of the predominant variant at the time of COVID-19 infection on the composite severe outcome for hospitalized patients. All tests performed in this analysis were two-sided tests. Analysis was performed using R-4.1.2 (R Foundation for Statistical Computing) and Excel (Microsoft).

Ethics committee approval

This study was approved by the Beaumont Health Institutional Review Board.

Role of the funding source

This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors.

Results

Between 1/1/2021 and 6/16/2022, there were 4517 pediatric emergency room encounters for COVID-19. 17.6% (795) of encounters occurred during T1 – Alpha, 38.0% (1714) of encounters during T2 – Delta, and 44.5% (2008) occurred during T3 – Omicron. In total, 3951 (87.5%) were discharged while 566 (12.5%) were admitted. Of the 53 transferred patients, 26 (49%) were included within the hospitalized cohort and 27 (50.9%) were excluded due to a lack of access to outside hospital records.

In our cohort, the median age was 5.2 (interquartile range (IQR) 1.0, 13.0) years old with infants (<1 year old) comprising 17.8% (806), toddlers (age 1–4) 28.2% (1274), children (age 5–11) 25.3% (1142), and teenagers (age 12–17) 28.7% (1295). Nearly half (48.4%) of the cohort was female, and a small minority were fully vaccinated or fully vaccinated and boosted (4.7%), with 95.3% being partially vaccinated or unvaccinated (Table 1).

Among the 566 hospitalized patients, 24.4% (138), 31.6% (179), and 44.0% (249) occurred during T1, T2, and T3, respectively. The median age was 5.0 (IQR 1.0, 13.0), with infants comprising 22.8% (129), toddlers 25.1% (142), children 23.0% (130), and teenagers 29.2% (165). Over the course of the pandemic, the proportion

Variables[a]		Time period			p value[d]
		T1 (Alpha)	T2 (Delta)	T3 (Omicron)	
n	4517	795 (17.60%)	1714 (37.95%)	2008 (44.45%)	
Demographics					
Age, years					
Mean	6.88 (5.97)	8.34 (6.25)	7.45 (6.03)	5.81 (5.61)	<0.001[b]
Median	5.20 (1.00, 13.00)	9.00 (2.00, 15.00)	6.15 (1.00, 13.00)	4.00 (1.00, 10.00)	
Age, category					
Infant (age 0)	806 (17.84%)	100 (12.58%)	276 (16.10%)	430 (21.41%)	<0.001[c]
Toddler (age 1–4)	1274 (28.20%)	200 (25.16%)	444 (25.90%)	630 (31.37%)	
Child (age 5–11)	1142 (25.28%)	174 (21.89%)	445 (25.96%)	523 (26.05%)	
Teen (age 12–17)	1295 (28.67%)	321 (40.38%)	549 (32.03%)	425 (21.17%)	
Sex					
Female	2187 (48.42%)	396 (49.81%)	854 (49.82%)	937 (46.66%)	0.108[c]
Male	2330 (51.58%)	399 (50.19%)	860 (50.18%)	1071 (53.34%)	
Race					
Black or African American	1974 (43.70%)	386 (48.55%)	817 (47.67%)	771 (38.40%)	<0.001[c]
White or Caucasian	2107 (46.65%)	332 (41.76%)	745 (43.47%)	1030 (51.29%)	
Other	436 (9.65%)	77 (9.69%)	152 (8.87%)	207 (10.31%)	
BMI, kg/m^2 (n = 2745/519/1013/1213)					
Mean	20.39 (7.47)	21.99 (7.88)	21.21 (8.03)	19.01 (6.51)	<0.001[b]
Median	18.31 (15.53, 22.86)	19.58 (16.55, 25.42)	18.75 (15.80, 24.33)	17.48 (15.09, 21.01)	
Vaccination status					
Boosted	17 (0.38%)	0 (0.00%)	0 (0.00%)	17 (0.85%)	<0.001[c]
Fully vaccinated	195 (4.32%)	6 (0.75%)	41 (2.39%)	148 (7.37%)	
Partially vaccinated	50 (1.11%)	7 (0.88%)	17 (0.99%)	26 (1.29%)	
Unvaccinated	4255 (94.20%)	782 (98.36%)	1656 (96.62%)	1817 (90.49%)	
Discharge location					
Home	3951 (87.47%)	657 (82.64%)	1535 (89.56%)	1759 (87.60%)	<0.001[c]
Admit	566 (12.53%)	138 (17.36%)	179 (10.44%)	249 (12.40%)	
Comorbidities (n = 4440)					
Neurologic and neuromuscular	37 (0.83%)	8 (1.05%)	8 (0.47%)	21 (1.06%)	0.118[c]
Cardiovascular	29 (0.65%)	9 (1.18%)	6 (0.36%)	14 (0.70%)	0.056[c]
Respiratory	9 (0.20%)	1 (0.13%)	3 (0.18%)	5 (0.25%)	0.909[c]
Renal and urologic	11 (0.25%)	2 (0.26%)	4 (0.24%)	5 (0.25%)	1.000[c]
Gastrointestinal	32 (0.72%)	5 (0.66%)	11 (0.65%)	16 (0.81%)	0.836[c]
Hematologic or immunologic	43 (0.97%)	8 (1.05%)	15 (0.89%)	20 (1.01%)	0.907[c]
Metabolic	60 (1.35%)	10 (1.31%)	18 (1.07%)	32 (1.61%)	0.359[c]
Other congenital or genetic defect	23 (0.52%)	6 (0.79%)	9 (0.53%)	8 (0.40%)	0.411[c]
Malignancy	5 (0.11%)	0 (0.00%)	0 (0.00%)	5 (0.25%)	0.081[c]
Premature and neonatal	13 (0.29%)	5 (0.66%)	1 (0.06%)	7 (0.35%)	0.021[c]
Immunocompromise	93 (2.09%)	19 (2.49%)	29 (1.72%)	45 (2.26%)	0.360[c]

Abbreviations: BMI = body mass index; T1 = time period 1 (1/1/21–6/30/21); T2 = time period 2 (7/1/21–12/31/21); T3 = time period 3 (1/1/22–6/16/22). [a]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented. [b]Kruskal–Wallis test. [c]Chi-squared or Fisher's exact test. [d]See Supplementary Table S1 for p-values from multiple comparisons test; post hoc Holm-Bonferroni procedure and the Tukey–Kramer method was used for categorical and numerical variables, respectively.

Table 1: **Demographics, in-hospital therapies, and outcomes among emergency room encounters with COVID-19 during Alpha, Delta, and Omicron predominant time periods.**

of infants in hospitalization increased from 16.7% in T1 to 19.6% in T2 and 28.5% in T3 ($p < 0.01$), while the proportion of teenagers in hospitalization decreased from 39.1% in T1 to 31.3% in T2 and 22.1% in T3 ($p < 0.001$). Most patients were male (55.1%) and 59.9% identified as White or Caucasian. Fully vaccinated or fully vaccinated and boosted admission rates remained low throughout all periods, with 4.4% in T1, 4.5% in T2 and 11.6% in T3. Oxygen therapy was required in a minority (29.9%) of cases, with supplemental oxygen utilized the least in T3 (24.5%) and the most in T2 (38.0%). Composite severe disease decreased

throughout the pandemic, occurring in 36.2% in T1, 27.4% in T2, and 18.8% in T3 (Table 2). A multivariable logistic regression analysis revealed the odds of composite disease was significantly lower in T3 compared to T1 (adjusted odds ratio [aOR] 0.35, 95% Confidence Interval 0.21–0.60, p < 0.001) (Table 3). There was a significant difference in the number of new MIS-C cases among hospitalized patients, with 17.4% in T1,

Variables[a]	All	Time Period			p value[d]
		T1 (Alpha)	T2 (Delta)	T3 (Omicron)	
n	566	138 (24.38%)	179 (31.63%)	249 (43.99%)	
Demographics					
Age, years					
Mean	6.68 (6.19)	8.05 (6.34)	7.16 (6.30)	5.57 (5.85)	<0.001[b]
Median	5.00 (1.00, 13.00)	7.55 (1.05, 14.35)	5.90 (1.00, 13.80)	3.00 (0.00, 10.00)	
Age, category					
Infant (age 0)	129 (22.79%)	23 (16.67%)	35 (19.55%)	71 (28.51%)	0.011[c]
Toddler (age 1–4)	142 (25.09%)	31 (22.46%)	45 (25.14%)	66 (26.51%)	
Child (age 5–11)	130 (22.97%)	30 (21.74%)	43 (24.02%)	57 (22.89%)	
Teen (age 12–17)	165 (29.15%)	54 (39.13%)	56 (31.28%)	55 (22.09%)	
Sex					
Female	254 (44.88%)	61 (44.20%)	78 (43.58%)	115 (46.18%)	0.852[c]
Male	312 (55.12%)	77 (55.80%)	101 (56.42%)	134 (53.82%)	
Race					
Black or African American	160 (28.27%)	49 (35.51%)	45 (25.14%)	66 (26.51%)	0.190[c]
White or Caucasian	339 (59.89%)	73 (52.90%)	109 (60.89%)	157 (63.05%)	
Other	67 (11.84%)	16 (11.59%)	25 (13.97%)	26 (10.44%)	
BMI, kg/m^2 (n = 547/133/171/243)					
Mean	20.13 (7.74)	21.07 (7.96)	21.10 (9.16)	18.93 (6.25)	0.018[b]
Median	17.94 (15.57, 21.73)	18.28 (15.77, 22.93)	17.94 (15.96, 22.31)	17.66 (15.27, 20.31)	
Vaccination status					
Boosted	8 (1.41%)	0 (0.00%)	0 (0.00%)	8 (3.21%)	0.005[c]
Fully vaccinated	35 (6.18%)	6 (4.35%)	8 (4.47%)	21 (8.43%)	
Partially vaccinated	15 (2.65%)	2 (1.45%)	3 (1.68%)	10 (4.02%)	
Unvaccinated	508 (89.75%)	130 (94.20%)	168 (93.85%)	210 (84.34%)	
In-hospital therapies					
O_2 therapy	169 (29.86%)	40 (28.99%)	68 (37.99%)	61 (24.50%)	0.010[c]
Nasal cannula/non-rebreather	125 (22.08%)	30 (21.74%)	54 (30.17%)	41 (16.47%)	0.003[c]
High flow O_2	39 (6.89%)	9 (6.52%)	19 (10.61%)	11 (4.42%)	0.043[c]
Primary outcomes					
Composite severe disease	146 (25.80%)	50 (36.23%)	49 (27.37%)	47 (18.88%)	<0.001[c]
ICU-level care	119 (21.02%)	40 (28.99%)	41 (22.91%)	38 (15.26%)	0.005[c]
Mechanical ventilation	12 (2.12%)	1 (0.72%)	3 (1.68%)	8 (3.21%)	0.249[c]
MIS-C	58 (10.25%)	24 (17.40%)	18 (10.06%)	16 (6.43%)	0.003[c]
Myocarditis	6 (1.06%)	5 (3.62%%)	0 (0.00%)	1 (0.40%)	0.005[c]
Death	3 (0.53%)	2 (1.45%)	0 (0.00%)	1 (0.40%)	–
Secondary outcomes					
Viral co-infection	68 (12.01%)	7 (5.07%)	30 (16.76%)	31 (12.45%)	0.006[c]
Length of stay, hours					
Mean	69.43 (165.55)	61.37 (57.46)	62.46 (64.89)	78.90 (239.65)	0.323[b]
Median	42.00 (24.00, 71.00)	41.11 (24.04, 72.60)	46.00 (25.00, 72.00)	38.00 (22.25, 68.00)	

Abbreviations: BMI = body mass index; ICU = intensive care unit; MIS-C = multisystem inflammatory syndrome in children; T1 = time period 1 (1/1/21–6/30/21); T2 = time period 2 (7/1/21–12/31/21); T3 = time period 3 (1/1/22–6/16/22). [a]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented. [b]Kruskal–Wallis test. [c]Chi-squared or Fisher's exact test. [d]See Supplementary Table S2A for p-values from multiple comparisons test; post hoc Holm-Bonferroni procedure and the Tukey–Kramer method was used for categorical and numerical variables, respectively.

Table 2: **Demographics, in-hospital therapies, and outcomes among hospitalized patients with COVID-19 during Alpha, Delta, and Omicron predominant time periods.**

Effect	Model 1[a]	Model 2[b]
	OR[a] (95% CI)	aOR[b] (95% CI)
Predominant variant at time		
T1 (Alpha)	Reference	Reference
T2 (Delta)	0.66 (0.41–1.07) p = 0.092	0.68 (0.41–1.12) p = 0.129
T3 (Omicron)	0.41 (0.26–0.66) p < 0.001	0.35 (0.21–0.60) p < 0.001

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; T1 = time period 1 (1/1/21–6/30/21); T2 = time period 2 (7/1/21–12/31/21); T3 = time period 3 (1/1/22–6/16/22). [a]Unadjusted multivariable logistic regression analysis in the hospitalized cohort. [b]Adjusted multivariable logistic regression analysis in the hospitalized cohort, adjusting for age group, gender, race, body mass index, and vaccination status.

Table 3: **Association between predominant variant at time of COVID-19 infection and the composite severe disease.**

10.1% in T2, and 6.4% in T3 (p < 0.001). There were three total deaths.

The presence of viral coinfection amongst hospitalized patients was most common during T2 (16.8%), followed by T3 (12.5%) and least common in T1 (5.1%) (p = 0.006). Coinfection occurred more commonly in younger children, with a median age of 1.2 (0.0, 4.5) years old compared to those without coinfection who had a median age of 6.0 (1.0, 14.0) years old (p < 0.001). Hospitalized patients with viral coinfection were more likely to require supplemental oxygen therapy (58.8% vs 25.9%; p < 0.001). High-flow oxygen therapy was utilized in 27.9% of coinfection cases compared to 4.0% of cases without coinfection (p < 0.001). Compared to those without coinfection, pediatric patients with viral coinfection were significantly more likely to have a severe outcome (45.6% vs 22.1%; p < 0.001) (Table 4).

There were 286 admitted patients who were eligible to receive the COVID-19 vaccine during the study period, of which 43 (15.0%) were fully vaccinated or fully vaccinated and boosted. The median age of vaccinated patients was 15.0 (IQR 13.0, 16.0) compared to 12.0 (IQR 8.0, 15.0) for unvaccinated (p < 0.001). Compared to 35.4% of unvaccinated encounters, only 11.6% of vaccinated patients required supplemental oxygen therapy (p = 0.004). There was no difference in composite severe outcomes comparing unvaccinated (25.6%) and vaccinated (25.9%) (p = 1.000). Likewise, the need for ICU-level care was similar among pediatric patients regardless of vaccination status (25.6% vs 25.9%; p = 1.000). MIS-C occurred in 9.3% of vaccinated patients and in 15.2% of unvaccinated patients (p = 0.432). Of the four immunized patients who developed MIS-C, three cases occurred during T3 while one occurred during T2. There was no difference in the occurrence of myocarditis among vaccinated patients (2.3%) compared to unvaccinated patients (2.1%) (p = 1.000) (Table 5).

Discussion

This study highlighted trends over the course of the pandemic regarding severe COVID-19 outcomes in pediatric patients. While the overwhelming majority of cases in the community are self-limited, this study focused on encounters requiring the most resources and medical attention.[12,13] It is notable that the three distinct time intervals represent roughly equal periods of Alpha, Delta, and Omicron variant dominance, therefore providing a balanced comparison. However, it is noteworthy that the variant data was not patient-specific and represents a good estimate rather than an exact comparison of variant type. Importantly, nearly half of all ED encounters and hospitalizations in the cohort were from the most recent Omicron period. There are several explanations for this observation. It has been well described that Omicron is more transmissible than other variants.[14] One study found that the Omicron variant replicates 70 times faster than the Delta variant in airways.[15] Further, as mask mandates and social distancing practices have diminished in various communities, the infectious potential of Omicron has likely increased.[16] Based on this study and other existing evidence, it is likely that the high Omicron hospitalization rate relative to other variants reflects a substantially higher incidence of COVID-19 in the general community rather than a more virulent variant. In fact, in this study, severe outcomes declined over time with a peak of 36.2% during the Alpha period and 18.9% during the Omicron period. Other relevant clinical outcomes such as the need for supplemental oxygen or the development of MIS-C were also the least in the Omicron period. This phenomenon of less severe outcomes in hospitalized COVID-19 with Omicron has been noted in other reports with one study highlighting that Omicron has difficulty multiplying in the lungs compared to the Delta variant which may explain reduced respiratory impairment with Omicron.[15]

This study also has implications for vaccination in pediatrics. In the United States, COVID-19 vaccinations first received emergency use authorization (EUA) by the U.S. Food and Drug Administration for ages 16 or greater on December 11, 2020, ages 12–15 on May 10, 2021, ages 5–11 on October 29, 2021.[17–19] Ages 6 months through 5 years old received EUA on June 17, 2022, which was outside of the study period.[20] Overall, the

Variables[a]	All	Viral coinfection		p value	Time period			p value[d]
		Yes	No		T1 (Alpha)	T2 (Delta)	T3 (Omicron)	
n	566	68 (12.01%)	498 (87.99%)		7 (10.29%)	30 (44.12%)	31 (45.59%)	
Demographics								
Age, years								
Mean	6.68 (6.19)	3.10 (4.17)	7.17 (6.26)	<0.001[b]	1.59 (2.39)	3.35 (5.00)	3.20 (3.61)	0.526[b]
Median	5.00 (1.00, 13.00)	1.20 (0.00, 4.47)	6.00 (1.00, 14.00)		1.00 (0.00, 1.70)	1.00 (0.00, 3.97)	2.00 (0.00, 6.00)	
Age, category								
Infant (age 0)	129 (22.79%)	22 (32.35%)	107 (21.49%)	<0.001[c]	3 (42.86%)	9 (30.00%)	10 (32.26%)	0.820[c]
Toddler (age 1–4)	142 (25.09%)	29 (42.65%)	113 (22.69%)		3 (42.86%)	14 (46.67%)	12 (38.71%)	
Child (age 5–11)	130 (22.97%)	13 (19.12%)	117 (23.49%)		1 (14.29%)	4 (13.33%)	8 (25.81%)	
Teen (age 12–17)	165 (29.15%)	4 (5.88%)	161 (32.33%)		0 (0.00%)	3 (10.00%)	1 (3.23%)	
Sex								
Female	254 (44.88%)	26 (38.24%)	228 (45.78%)	0.297[c]	1 (14.29%)	13 (43.33%)	12 (38.71%)	0.397[c]
Male	312 (55.12%)	42 (61.76%)	270 (54.22%)		6 (85.71%)	17 (56.67%)	19 (61.29%)	
Race								
Black or African American	160 (28.27%)	16 (23.53%)	144 (28.92%)	0.371[c]	2 (28.57%)	4 (13.33%)	10 (32.26%)	0.054[c]
White or Caucasian	339 (59.89%)	46 (67.65%)	293 (58.84%)		4 (57.14%)	21 (70.00%)	21 (67.74%)	
Other	67 (11.84%)	6 (8.82%)	61 (12.25%)		1 (14.29%)	5 (16.67%)	0 (0.00%)	
BMI, kg/m^2 (n = 547/66/481/7/29/30)								
Mean	20.13 (7.74)	16.93 (2.73)	20.57 (8.10)	<0.001[b]	18.02 (3.39)	17.18 (2.85)	16.44 (2.42)	0.558[b]
Median	17.94 (15.57, 21.73)	16.61 (15.09, 18.52)	18.23 (15.62, 22.33)		16.53 (15.26, 21.24)	16.64 (15.46, 18.55)	16.38 (14.98, 17.90)	
Vaccination status								
Boosted	8 (1.41%)	1 (1.47%)	7 (1.41%)	0.290[c]	0 (0.00%)	0 (0.00%)	1 (3.23%)	0.717[c]
Fully vaccinated	35 (6.18%)	1 (1.47%)	34 (6.83%)		0 (0.00%)	0 (0.00%)	0 (0.00%)	
Partially vaccinated	15 (2.65%)	1 (1.47%)	14 (2.81%)		0 (0.00%)	0 (0.00%)	1 (3.23%)	
Unvaccinated	508 (89.75%)	65 (95.59%)	443 (88.96%)		7 (100.00%)	30 (100.00%)	28 (90.32%)	
In-hospital therapies								
O_2 therapy	169 (29.86%)	40 (58.82%)	129 (25.90%)	<0.001[c]	5 (71.43%)	17 (56.67%)	18 (58.06%)	0.878[c]
NC/NRB	125 (22.08%)	22 (32.35%)	103 (20.68%)	0.043[c]	1 (14.29%)	13 (43.33%)	8 (25.81%)	0.232[c]
High flow O_2	39 (6.89%)	19 (27.94%)	20 (4.02%)	<0.001[c]	4 (57.14%)	6 (20.00%)	9 (29.03%)	0.128[c]
Primary outcomes								
Composite severe disease	141 (24.91%)	31 (45.59%)	110 (22.09%)	<0.001[c]	6 (85.71%)	12 (40.00%)	13 (41.94%)	0.090[c]
ICU-level care	119 (21.02%)	28 (41.18%)	91 (18.27%)	<0.001[c]	5 (71.43%)	11 (36.67%)	12 (38.71%)	0.273[c]
Mechanical ventilation	12 (2.12%)	2 (2.94%)	10 (2.01%)	0.645[c]	0 (0.00%)	1 (3.33%)	1 (3.23%)	1.000[c]
MIS-C	58 (10.25%)	9 (13.24%)	49 (9.84%)	0.514[c]	2 (28.57%)	5 (16.67%)	3 (9.68%)	0.315[c]
Myocarditis	6 (1.06%)	1 (1.47%)	5 (1.00%)	0.538[c]	0 (0.00%)	1 (3.33%)	0 (0.00%)	0.544[c]
Death	3 (0.53%)	0 (0.00%)	3 (0.60%)	–	0 (0.00%)	0 (0.00%)	0 (0.00%)	–
Secondary outcome								
Length of stay, hours								
Mean	69.43 (165.55)	57.64 (42.66)	71.04 (175.76)	0.228[b]	40.27 (16.42)	53.25 (44.50)	65.81 (44.02)	0.129[b]
Median	42.00 (24.00, 71.00)	45.50 (28.00, 73.05)	42.00 (23.00, 71.00)		40.00 (28.50, 50.11)	44.11 (25.25, 69.75)	49.00 (38.00, 82.00)	

Abbreviations: BMI = body mass index; ICU = intensive care unit; MIS-C = multisystem inflammatory syndrome in children; NC = nasal cannula; NRB = non-rebreather; T1 = time period 1 (1/1/21–6/30/21); T2 = time period 2 (7/1/21–12/31/21); T3 = time period 3 (1/1/22–6/16/22). [a]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented. [b]Kruskal–Wallis test. [c]Chi-squared or Fisher's exact test. [d]See Supplementary Table S2B for p-values from multiple comparisons test; post hoc Holm-Bonferroni procedure and the Tukey-Kramer method was used for categorical and numerical variables, respectively.

Table 4: **Demographics, in-hospital therapies, and outcomes among hospitalized COVID-19 patients with and without viral coinfection.**

Variables[a]	All	Vaccination status		p value	Time period			p value[d]
		≥2 immunizations	<2 immunizations		T1 (Alpha)	T2 (Delta)	T3 (Omicron)	
n	286	43 (15.03%)	243 (84.97%)		6 (13.95%)	8 (18.60%)	29 (67.44%)	
Demographics								
Age, years								
Mean	12.01 (3.94)	14.00 (3.01)	11.66 (3.99)	<0.001[b]	15.20 (1.19)	14.96 (1.54)	13.48 (3.45)	0.595[b]
Median	13.00 (8.22, 15.70)	15.00 (13.00, 16.00)	12.00 (8.00, 15.00)		15.25 (14.38, 15.60)	15.50 (13.47, 16.00)	14.60 (12.00, 16.00)	
Age, category								
Child (age 5–11)	123 (43.01%)	7 (16.28%)	116 (47.74%)	<0.001[c]	0 (0.00%)	0 (0.00%)	7 (24.14%)	0.246[c]
Teen (age 12–17)	163 (56.99%)	36 (83.72%)	127 (52.26%)		6 (100.00%)	8 (100.00%)	22 (75.86%)	
Sex								
Female	132 (46.15%)	22 (51.16%)	110 (45.27%)	0.583[c]	1 (16.67%)	4 (50.00%)	17 (58.62%)	0.182[c]
Male	154 (53.85%)	21 (48.84%)	133 (54.73%)		5 (83.33%)	4 (50.00%)	12 (41.38%)	
Race								
Black or African American	86 (30.07%)	9 (20.93%)	77 (31.69%)	0.287[c]	0 (0.00%)	2 (25.00%)	7 (24.14%)	0.579[c]
White or Caucasian	169 (59.09%)	30 (69.77%)	139 (57.20%)		5 (83.33%)	5 (62.50%)	20 (68.97%)	
Other	31 (10.84%)	4 (9.30%)	27 (11.11%)		1 (16.67%)	1 (12.50%)	2 (6.90%)	
BMI, kg/m^2 (n = 275/42/233/6/7/29)								
Mean	23.55 (9.25)	23.80 (7.51)	23.50 (9.54)	0.229[b]	26.09 (5.07)	25.54 (12.29)	22.91 (6.56)	0.200[b]
Median	20.79 (17.27, 25.60)	21.73 (19.57, 25.40)	20.76 (17.06, 25.65)		24.06 (22.09, 30.41)	22.29 (18.44, 26.28)	20.24 (19.25, 25.01)	
In-hospital therapies								
O_2 therapy	91 (31.82%)	5 (11.63%)	86 (35.39%)	0.004[c]	1 (16.67%)	1 (12.50%)	3 (10.34%)	0.803[c]
NC/NRB	71 (24.83%)	5 (11.63%)	66 (27.16%)	0.048[c]	1 (16.67%)	1 (12.50%)	3 (10.34%)	0.803[c]
High flow O_2	17 (5.94%)	1 (2.33%)	16 (6.58%)	0.484[c]	0 (0.00%)	1 (12.50%)	0 (0.00%)	0.326[c]
Primary outcomes								
Composite event	74 (25.87%)	11 (25.58%)	63 (25.93%)	1.000[c]	4 (66.67%)	3 (37.50%)	4 (13.79%)	0.013[c]
ICU-level care	73 (25.52%)	11 (25.58%)	62 (25.51%)	1.000[c]	4 (66.67%)	3 (37.50%)	4 (13.79%)	0.013[c]
Mechanical ventilation	7 (2.45%)	0 (0.00%)	7 (2.88%)	0.599[c]	0 (0.00%)	0 (0.00%)	0 (0.00%)	–
MIS-C	44 (15.38%)	4 (9.30%)	40 (16.46%)	0.007[c]	0 (0.00%)	1 (12.50%)	3 (10.34%)	1.000[c]
Myocarditis	6 (2.10%)	1 (2.33%)	5 (2.06%)	1.000[c]	0 (0.00%)	1 (12.50%)	0 (0.00%)	1.000[c]
Death	2 (0.70%)	0 (0.00%)	2 (0.82%)	–	0 (0.00%)	0 (0.00%)	0 (0.00%)	–
Secondary outcomes								
Viral co-infection	17 (5.94%)	2 (4.65%)	15 (6.17%)	1.000[c]	0 (0.00%)	0 (0.00%)	2 (6.90%)	1.000[c]
Length of stay, hours								
Mean	92.07 (228.14)	100.80 (164.62)	90.53 (237.86)	1.000[b]	60.50 (20.53)	102.96 (78.52)	108.55 (196.52)	0.540[b]
Median	48.00 (26.00, 92.59)	48.63 (25.09, 100.72)	48.00 (26.00, 92.39)		68.82 (53.42, 73.04)	86.50 (37.95, 169.33)	34.00 (24.00, 76.00)	

Abbreviations: BMI = body mass index; ICU = intensive care unit; MIS-C = multisystem inflammatory syndrome in children; NC = nasal cannula; NRB = non-rebreather; T1 = time period 1 (1/1/21–6/30/21); T2 = time period 2 (7/1/21–12/31/21); T3 = time period 3 (1/1/22–6/16/22). [a]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented. [b]Kruskal–Wallis test. [c]Chi-squared or Fisher's exact test. [d]See Supplementary Table S2C for p-values from multiple comparisons test; post hoc Holm-Bonferroni procedure and the Tukey–Kramer method was used for categorical and numerical variables, respectively.

Table 5: **Demographics, in-hospital therapies, and outcomes among hospitalized COVID-19 patients based on vaccination status.**

vaccinated cohort represented only 7.6% of all hospitalized pediatric patients. Interestingly the proportion of hospitalized cases in teens, the group with the earliest access to vaccination in pediatrics, has declined substantially over time and may reflect a benefit from vaccination. While vaccination efforts in children have been rolled out at different time intervals during the pandemic, with infants still ineligible, the percentage of vaccinated children now approaches 50%, and the implication of this data is that vaccination may be reducing hospitalization and severe outcomes compared to unvaccinated children. Importantly, even when hospitalized, severe outcomes trended lower in the vaccinated group from T1 to T3. However, it is unclear if the lower rates of severe disease are due to vaccination efforts, a less virulent Omicron strain, or a combination. As more children continue to become vaccinated and the youngest become eligible for vaccination, the precise impact of vaccination may be assessed better.

Previous literature on children has demonstrated mixed outcomes in viral coinfections, a subpopulation of interest. As one virus may synergistically or antagonistically alter the replication and proliferation of another pathogen, both positive and negative impacts on morbidity and mortality have been described.[21] There are several animal and human studies demonstrating severe outcomes in the setting of other respiratory viral coinfections.[22,23] In a study evaluating coinfections of RSV and Influenza in mice, researchers found increased airway resistance and reduced thoracic compliance in coinfected groups.[24] In the pediatric literature, children with coinfections demonstrated greater lower respiratory tract infections and moderate to severe illness.[25] In contrast, other evidence purports either neutral or opposite findings in viral coinfections. Scotta et al.[26] performed a systematic review including 17,000 children and found no increase in severe outcomes in children with viral coinfection. In another systematic review on children less than five years of age, Lim et al.[27] even identified a subgroup without comorbidities that had more severe outcomes with single virus infection.

In our study, children with respiratory coinfections experienced more severe outcomes. This finding is consistent with some existing COVID-19 evidence. In a study of adults, viral coinfection with SARS-CoV-2 occurred in 8.4% of cases and coinfection with influenza increased the odds of mechanical ventilation. Further, coinfection with influenza and adenoviruses also increased the odds of death, which reinforces the importance of annual influenza vaccination in the pediatric population as well.[28] While our findings highlight viral coinfection as a risk factor for more severe disease, the concept of viral coinfection in the setting of COVID-19 needs further exploration in children. Specifically, focusing on age, comorbidities, and precise viral–viral combinations may help identify children at the highest risk of severe outcomes.

Limitations

There were some limitations to this study. First, variant data was not patient-level data but rather represented the predominant variant strain during the time period. Thus, the precise impact of a particular variant strain upon severe outcomes cannot be extracted from this study. Second, this analysis does not account for infection in the community thus we cannot determine if increased encounters during a variant period was a function of severity of the disease or increased frequency of disease. Third, while a large number of pediatric patients that presented to emergency rooms across metro Detroit were included in this analysis, a relatively smaller cohort experienced hospitalization and even smaller additional severe outcomes. Further, the study included ages 0–17 and generalized findings for the entire cohort may not be evident for subgroups, specifically extremes of age. Fourth, outcomes data for some transferred patients were not available and these cases were excluded. It is possible that these patients had severe outcomes that were not included in our analysis. However, this group was small and included only 27 patients. Further, we performed a death instance query on 7/31/2022 on transferred patients and confirmed 18 were alive in this group with unknown status for only nine patients. Finally, data was retrieved from the EHR which may be incomplete or inaccurate at times. Specifically, while only patients with a principal diagnosis of COVID-19 based on EHR query were included in the analysis, it is possible that some patients with a secondary diagnosis of COVID-19 may have been inadvertently included. However, the number is likely small as this study used the same methodology that was employed in three previous large-scale (>40,000 encounters) COVID-19 investigations at the institution with <1% of cohort found to have secondary COVID-19.[29–31]

Conclusions

Over the course of the pandemic, children have required hospitalization for COVID-19 and some have experienced severe outcomes. While Omicron represents a high proportion of hospitalized cases, clinical outcomes are less severe for this variant. A small percentage of all inpatients were vaccinated with a trend of less severe outcomes. Further larger research investigations are needed to determine the impact of vaccination on pediatrics.

Contributors

A.B., N.M., S.J., A.D., and L.Q. designed the study, had full access to the data, and take responsibility for the integrity and accuracy of the data analysis. A.B. and N.M. contributed to data and statistical analysis. All authors contributed to the writing and editing of the manuscript. All authors contributed to data acquisition, analysis and interpretation, and all reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

The data that support the findings of this study are available via a data access agreement. Please contact the corresponding author (AB) for this request.

Declaration of interests

All authors declare no relevant conflicts of interest relevant to this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2022.100405.

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