Younger and Rural Children are More Likely to be Hospitalized for SARS-CoV-2 Infections.

Rebecca M. Cantu, MD, MPH[1,2,*]; Sara C. Sanders, MD[1,2,*]; Grace A. Turner, BA[3]; Jessica N. Snowden, MD[1,2,3,4]; Ashton Ingold, BS[3]; Susanna Hartzell, BA[3]; Suzanne House, BS[1,2]; Dana Frederick, MS[1,3]; Uday K. Chalwadi, MBBS, MD[1]; Eric R. Siegel, MS[4]; Joshua L. Kennedy, MD[1,2,3,5]

1 University of Arkansas for Medical Sciences, Department of Pediatrics, Little Rock, AR.

2 Arkansas Children's Hospital, Little Rock, AR.

3 Arkansas Children's Research Institute, Little Rock, AR.

4 University of Arkansas for Medical Sciences, Department of Biostatistics, Little Rock, AR.

5 University of Arkansas for Medical Sciences Department of Internal Medicine, Little Rock, AR.

*Authors contributed equally to writing of this manuscript

Corresponding Author:

Rebecca M. Cantu, Department of Pediatrics, University of Arkansas for Medical Sciences, 1 Children's Way, Slot 512-8, Little Rock, AR 72202, USA (e-mail: rmcantu@uams.edu)

Funding Source: This work was supported by the Center for Translational Pediatric Research (NIH/NIGMS P20GM121293) at Arkansas Childrens Hospital, and by the Translational Research Institute (NIH/NCATS UL1TR003107) at the University of Arkansas for Medical Sciences.

Financial Disclosure Statement: Dr. Joshua Kennedy, Mr. Eric Siegel, and Ms. Grace Turner, Ashton Ingold, Susanna Hartzell, Suzanne House, and Dana Frederick are supported by the Center for Translational Pediatric Research (NIH/NIGMS P20GM121293). Drs. Joshua Kennedy and Uday Chalwadi as well as Mr. Eric Siegel are supported by the Translational Research Institute (NIH/NCATS UL1TR003107).

Conflict of Interest Statement: Dr. Kennedy has been a consultant for Genentech for asthma. Funding organizations were not involved in the design or conduct of the study, nor were they involved in the collection, analysis, or interpretation of the data, nor were they involved in the preparation, editing, or censuring of the manuscript.

Abstract

Purpose: To identify characteristics of SARS-CoV-2 infection that are associated with hospitalization in children initially evaluated in a Pediatric Emergency Department (ED).

Methods: We identified cases of SARS-CoV-2 positive patients seen in the Arkansas Children's Hospital (ACH) ED or hospitalized between May 27, 2020, and April 28, 2022 using ICD-10 codes within the Pediatric Hospital Information System (PHIS) Database. We compared infection waves for differences in patient characteristics, and used logistic regressions to examine which characteristics led to a higher chance of hospitalization.

Findings: We included 681 pre-Delta cases, 673 Delta cases, and 970 Omicron cases. Almost 17% of patients were admitted to the hospital. Compared to Omicron infected children, pre-Delta and Delta infected children were twice as likely to be hospitalized (OR=2.2 and 2.0, respectively; $p<0.0001$). Infants less than 1 year of age were >3 times as likely to be hospitalized than children ages 5-14 years regardless of wave (OR=3.42; 95%CI=2.36–4.94). Rural children were almost 3 times as likely than urban children to be hospitalized across all waves (OR=2.73; 95%CI=1.97–3.78). Finally, those with a complex condition had nearly a 15-fold increase in odds of admission (OR=14.6; 95%CI=10.6–20.0).

Conclusions: Children diagnosed during the pre-Delta or Delta waves were more likely to be hospitalized than those diagnosed during the Omicron wave. Younger and rural patients were more likely to be hospitalized regardless of wave. We suspect lower vaccination rates and larger distances from medical care influenced higher hospitalization rates.

Key Words: Rural Children, Pediatric SARS-CoV-2, Infants, Hospitalization Risk

Background

COVID-19 was first reported in late December of 2019 in Wuhan China, with the first case in the United States reported on January 18, 2020 in Washington state.[1] As of August 2022, SARS-CoV-2 has infected over 600 million individuals worldwide and caused over 6 million deaths. Over the course of two years, SARS-CoV-2 has undergone numerous genetic mutations, resulting in multiple variant strains, each capable of different transmission rates, risks for severe disease, and even risk for mortality.[2] The Delta variant, also known as B.1.617.2, was shown to be 40%-60% more transmissible than the prior Alpha variant.[3] Studies have determined that Delta also increased hospitalization risk by 108%, increased intensive care unit (ICU) admission by 235%, and caused a 133% higher mortality in adults as compared to Alpha.[4] The Omicron variant, also known as B.1.1.529, became the predominant strain in the United States by December 2021. Soon after, scientists discovered that though symptoms due to this variant were seemingly less severe, Omicron was more transmissible than Delta and had increased resistance to antiviral immunity.[5-7]

Much of the research on SARS-CoV-2 and its variants has focused on adults; yet, the effect of variants in children has been largely ignored. This is likely because, early in the pandemic, pediatric COVID-19 infections presented with milder symptoms than adult infections. However, recent data have shown that, since December 2021, hospitalization rates increased more rapidly in children < 5 years than in any other age group.[8] The rise of the Omicron variant greatly increased the number of pediatric cases, which grew from <2% of total reported cases in the early pandemic to 25% of U.S. cases by early February 2022.[9]

Many of the studies that focused on hospitalized children with SARS-CoV-2 infection were either done early in the pandemic (pre-Omicron) when the greatest risk was older age and co-morbidities[10, 11] or focused upon larger, more populous regions, where there were more children with SARS-CoV-2 to study.[8, 12, 13] We previously reported on demographic and clinical factors

associated with pediatric hospitalizations in Arkansas from March 2020-December 2020.[14] In this study, rural children were more likely to be hospitalized during SARS-CoV-2 infection. Given the increased complexity of patients seen during the time when the Delta variant was rampant and the explosion of infections during when the Omicron variant predominated, we wished to extend this study and determine the effect of the newer variants. With this in mind, we aimed to identify characteristics of SARS-CoV-2 infection that are associated with hospitalization in children initially evaluated in a Pediatric Emergency Department from a largely rural state. We hypothesized that certain demographic and clinical factors would be associated with hospitalization in a pediatric population infected with SARS-CoV-2. We also evaluated whether these differences were variant-specific within our population.

Methods

This was a cross-sectional study utilizing the Pediatric Hospital Information System (PHIS) Database. PHIS is a pediatric database that includes clinical and resource utilization data for more than 50 children's hospitals, including Arkansas Children's Hospital (ACH). This study was approved by the University of Arkansas for Medical Sciences Institutional Review Board (IRB #23497) with waiver of consent and HIPAA authorization.

This study included children $\leq$18 years of age who presented to ACH between March 1, 2020 and April 28, 2022. Inclusion criteria for this study were emergency department (ED) visit or hospital admission during the study visit and COVID or related diagnoses as defined by ICD-10 codes, including U07.1 (COVID), M35.81 (Multisystem Inflammatory Syndrome in Children, MIS-C), and J12.82 (Pneumonia due to coronavirus disease 2019). Those with diagnoses of other systematic connective tissue involvement (either "other specified' or "unspecified", ICD-10 codes M35.8 or M35.9, respectively), two codes utilized for MIS-C prior to the release of the final ICD-10 code,[15] were combined with MIS-C.

For this study, we focused on children seen in the Emergency Department (ED) at ACH so that we could validate information received via the PHIS database in our home institution's electronic health record. To confirm and validate the ICD-10 diagnosis codes, we randomly selected 241 (10%) charts for review. All 241 charts had these diagnosis codes associated with an ED and/or hospital visit and ~85% had a positive viral test in the medical record at the time of the visit. PHIS reports were also cross-referenced for accuracy with data from the ACH Infection Prevention Department, which maintains a list of patients identified as having COVID-19, and a list from the University of Arkansas for Medical Sciences Department of Pediatrics Section of Infectious Diseases of patients with MIS-C.

Data elements collected from the PHIS Database included age, sex, race/ethnicity based on the Equity Race Category (ERC) classifications provided by PHIS, rurality based on rural-urban commuting-area (RUCA) code, visit type (ED visit, inpatient, or observation), intensive care unit (ICU) admission, length of stay (LOS), presence of a complex chronic-condition flag in PHIS,[16] disposition, mortality, and diagnosis of MIS-C. A chart review was conducted to validate the ERC-based race/ethnicity groups for subjects obtained through the PHIS database. We found that many of those assigned to Race=Other by PHIS data were actually Hispanic and/or Latino after review of the ACH medical record. Reviewed subjects whose ACH information indicated they were Hispanic and/or Latino were deemed to have been misclassified by the PHIS algorithm, and were accordingly reclassified as Hispanic.

Cases were assigned to the then-predominant SARS-CoV-2 variant based on sequencing that was performed at similar times in pediatric samples from Arkansas. No sequencing was available prior to March 2021 in the state, during what was likely the alpha wave. Therefore, we assigned cases by admission date into the pre-Delta (May 27, 2020-May 1 2021), Delta (June 1, 2021-November 15, 2021), and Omicron groups (December 16, 2021- March 31, 2022). The month-long transition periods between waves and after Omicron were defined in order to ensure

that a variant of concern would be present in higher numbers and include less overlap between each variant (**Figure 1**). The n=86 cases that had admission dates falling into one of these transition periods were not included in the statistical analyses, but data for them can be found in **supplemental Table 1.**

Data preprocessing

To combine multiple records from the same case, we defined an admission to be a unique combination of medical record number (MRN), admission date, and discharge date. Two or more records from the same admission were combined in a manner that preserved the "Yes" value of any Yes/No "flag" variable that changed between records. If the same MRN had a second admission ≤30 days after the discharge date from their first admission, then this was considered a readmission of the same case. Records from two or more admissions of the same case were combined as described above while setting admission date, discharge date, and age at admission to be the first admission date, last discharge date, and age at first admission. Conversely, if the same MRN had a second admission ≥31 days after the last discharge date from their first admission, then this was considered a new case that accordingly was labelled a second infection.

Statistical analysis

Age in years and LOS in days (d) were summarized by group as means and standard deviations [SDs] as well as medians and quartiles, and assessed for the presence of differences among the three COVID groups with the Kruskal-Wallis test. Age Groups, other categorical variables, and flag variables were compared for differences between pre-Delta, Delta, and Omicron groups with the Pearson chi-square test. To analyze Race/Ethnicity, we retained as-is the three ERC classifications of Hispanic, Non-Hispanic Black, and Non-Hispanic White that occurred frequently in our data extract, but condensed the four infrequent ERC classifications of Asian, Multiracial, Other, and Unknown into a single group named Other. To examine the

independent associations of patient characteristics with hospital admission, we employed logistic regression in both univariable and multivariable mode after excluding 22 cases that had missing RUCA codes. The seven predictors used in both modes were Infection Wave, Gender, Age Group, ERC-based Race/Ethnicity, RUCA-based Urban status, Payor Type, and Complex Chronic Condition. All seven predictors were entered without variable selection in the multivariable logistic-regression model, which did not contain any interaction terms. For subgroup analyses of hospital admission within each infection wave, we repeated this multivariable logistic-regression procedure for the six remaining predictors. All statistical-hypothesis tests employed a 2-sided $\alpha=0.05$ significance level, and all analyses were performed using SAS v9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Cohort Characteristics. We identified 2410 individual cases of SARS-COV-2-positive patients seen in the ED or admitted to observation or inpatient at ACH between May 28, 2020, and April 28, 2022. Their mean age in years was 5.91 (standard deviation [SD] 6.04), and 27.5% (n=662) were less than one year of age. Forty-seven percent (n=1141) were female, and 83.8% (n=2019) lived in an urban area code. The proportion of subjects admitted to hospital was 16.6% (n=400). Thirteen percent (n=303) had complex chronic conditions. The 2410 cases included 681 during pre-Delta, 673 during Delta, and 970 during Omicron. Table 1 provides patient demographics.

Primary Comparisons of Demographic and Clinical Characteristics. With regards to admission, we found differences between the variant waves. During the pre-Delta wave, 142 pediatric patients (20.9%) were admitted to the hospital. One hundred and thirty patients (19.3%) were admitted during the Delta wave, and 116 (12%) were admitted during the Omicron wave. **Table 1** shows that race varied significantly between waves ($p<0.001$) in a complex manner. The proportion of non-Hispanic Black patients fell slightly with each successive wave, from 34.7% pre-Delta to 30.8% during Delta and 26.6% during Omicron. In contrast, the proportion of Hispanic

patients fell noticeably from 27.8% pre-Delta to 16.5% during Delta, but rebounded to 25% (n=242) of the total population during Omicron. In partial compensation, the proportion of White subjects increased noticeably from 32.9% pre-Delta to 43.2% during Delta before falling to 39.6% during Omicron, while the proportion of Other rose from 4.7% pre-Delta to 9.5% during Delta and 8.9% during Omicron (**Table 1**). Between each variant wave, there were differences in the ages of infected subjects. In subjects 4 years of age and less, the proportion of patients infected with SARS-COV-2 stayed nearly equal from pre-Delta (46.6%) to Delta (47.5%), but then jumped more than 15 percentage points (to 62.9%) during Omicron (**Table 1**), while those who were 5-18 years old decreased in mirror fashion each time period. Rates of MIS-C reached 4.7% (n=32/681) in the pre-Delta wave, compared to 1.9% (n=13/673) in the Delta wave, and 0.6% (n=6/970) for the Omicron wave. LOS in days was significantly different ($p<0.001$) between children hospitalized for SARS-CoV-2 infections between variant waves. Those hospitalized during the pre-Delta wave had a mean LOS of 0.86d (standard deviation [SD], 2.30d), while those hospitalized during Omicron had a mean LOS of 0.46d (SD 1.79d), and those hospitalized during the Delta wave had a mean LOS of 1.36d (SD 6.91d). None of the other demographic factors showed a statistically significant change between COVID variants **(Table 1**).

Univariate and Multivariate Logistic Regression for All Waves. Univariate and multivariate logistic regressions were employed to assess risk factors for hospitalization across the entire study; **Table 2** shows the results. Both the unadjusted and adjusted odds ratios (ORs) show that the odds of hospitalization were highest during the pre-Delta wave, and declined only slightly during the Delta wave, in comparison to the Omicron wave as reference (**Table 2**). Age group was not a significant risk factor in univariate analysis, but became a highly significant risk factor in multivariate analysis. In particular, the OR of admission (95% confidence interval) for infants <1 year old increased from 1.23 (0.92–1.62) before multivariate adjustment to 2.35 (1.67–3.29) after multivariate adjustment, whereas the ORs of admission for the other age groups changed

only modestly (**Table 2**). In contrast, gender, race/ethnicity, and payor type were univariately significant risk factors that lost their significance after multivariate adjustment (**Table 2**). If the patient was considered to be rural based on their home zip code, their odds of admission was roughly 3-fold (3x) higher than patients from urban zip codes in both univariate and multivariate analysis (**Table 2**). Finally, patients with a complex chronic condition had >10x higher odds of admission when compared to those without in both univariate and multivariate analysis (**Table 2**).

Univariate and Multivariate Logistic Regression Between Waves. Next, we performed multivariate logistic regressions subgrouped by the variant wave into which the patient was classified; **Figure 2** shows the resulting adjusted ORs for hospitalization. In the pre-Delta wave, infants less than one year of age were 75% more likely to be admitted than the 5-to-14-year-old age group, patients with rural zip codes were more than twice as likely as those with urban zip codes to be admitted, and patients with a complex medical condition were 10x as likely to be admitted as those without one (**Figure 2A**). During the Delta wave, the pattern of admission risks was similar, but the adjusted ORs were slightly larger. This time, children less than one year of age were >3x as likely to be admitted as children from the 5–14-year-old age group. Children from rural zip codes were >3x as likely to be admitted as to those from urban zip codes, while children with a complex care code were 14x as likely to be admitted (**Figure 2B**). During the Omicron wave, children less than 1 year old were >2x as likely to be admitted as 5-to-14-year olds, whereas children from rural zip codes were almost 2.9x as likely to be admitted as those from urban zip codes. Finally, those with a complex medical condition had nearly a twenty-fold increase in odds for admission when compared to those without (**Figure 2C).**

Discussion

This study compared demographic and clinical characteristics of children presenting with SARS-CoV-2 infections to a large, freestanding pediatric hospital in the Southeastern United States during three variant waves of SARS-COV-2. When comparing those seen in the ED versus

174 those admitted to the hospital, we found subpopulations that were more likely to be admitted.
175 Throughout all waves, we noted that infants less than one year of age, patients from rural zip
176 codes, and patients with a complex medical condition had significantly increased likelihoods of
177 hospital admission. These findings suggest a propensity for admissions in those who were
178 younger, rural, and more complex. While this propensity seems obvious for the more complex
179 patients, it warrants closer investigation for the younger and the rural patients. The study hospital
180 is the primary location for inpatient pediatric care in the state, with nearly 95% of the pediatric-
181 specific acute-care beds and the only pediatric intensive-care unit in the state. Furthermore, it is
182 located in the central portion of the state. It is certainly possible that decreased access to care
183 and barriers such as lack of transportation may have influenced clinicians' decisions to admit to
184 the hospital versus discharge home. It is also possible that vaccine uptake within the rural
185 populations in Arkansas was lower. McElfish, et al., used a cross-sectional design to study the
186 intentions of Arkansan parents/guardians to vaccinate their children to COVID-19 in July of 2020
187 to July of 2021. Her team showed that only 26-28% of the population intended to vaccinate their
188 child when it became available. A full third of those surveyed who intended to get their child
189 vaccinated for COVID-19 right away still had not vaccinated their child 2 months after approval.[17]
190 While we were unable to collect vaccination rates, we suspect that vaccine hesitancy in Arkansas'
191 rural counties may have played a role in overall lower vaccine uptake with increased frequency
192 of infections in these areas.

193 Infants were more likely than other age groups to be admitted to the hospital during all
194 waves. Although more recent evidence [14] has shown that many neonates with COVID have
195 asymptomatic or mild illness, infants less than 60 days have an increased risk for serious bacterial
196 infection and are likely to be admitted due to institutional practices and policies because of age
197 regardless of symptoms or viral testing results. This study did not further delineate ages below 1
198 year, so we could not determine if younger infants were hospitalized at different rates than older

199 infants. More work is needed to determine the severity of infections in these neonates leading to
200 hospitalization.

201 A recent study also utilizing PHIS data showed that total hospital admissions in children
202 with chronic conditions decreased nearly 20% in the first 15 months of the pandemic, compared
203 to the same timeframe 3 years earlier.[18] A 2021 study using another large database showed that
204 children with both complex and noncomplex chronic disease were more likely than children
205 without chronic diseases to be hospitalized or have severe illness with COVID.[19] Similarly, in our
206 study population, children with chronic complex conditions had statistically significant increases
207 in hospital admission compared to those without in all waves.

208 A large study performed in Europe showed a 2.50-fold increase in adjusted risk for
209 hospitalization during the Alpha wave, along with a more modest 1.32-fold increase in this
210 adjusted risk during Delta wave, when compared to Omicron.[20] The authors of the European study
211 postulate that the lower risk of hospitalization with the later waves may have been secondary to
212 increased vaccination rates in the pediatric population. Here, we also show that pediatric patients
213 were more likely to be admitted to the hospital during the pre-Delta and Delta waves (Adjusted
214 ORs of 2.51 and 2.07, respectively) as compared to Omicron. As mentioned previously, we did
215 not collect vaccination information on our subjects.

216 Our previous work showed that most demographic characteristics did not significantly
217 differ in the first six months of SARS-CoV-2 infections.[14] In the current study, we do see an
218 increase in White Non-Hispanic patients and a decrease in the proportion of Hispanic patients
219 along with no appreciable change among Black patients presenting during the Delta wave. This
220 could be explained secondary to higher numbers of Hispanics contracting COVID-19 in earlier
221 waves in Arkansas[21] and, therefore, developing antibodies to future infections. There was a
222 subsequent increase of Hispanic subjects in our study that were infected during the Omicron

wave. We suspect that those with previous antibodies to other variants were less protected to the Omicron variant given the mutations in this COVID-19 strain.[22-24]

This study has several limitations, including its use of retrospective data from an administrative database. This data relies on billing and coding information and is subject to data reliability problems including misclassification of exposure and outcomes.[25] Further, our data from a single state may not be generalizable to other states. Our study did not include vaccination status, which may have impacted those patients that were ill enough to present to the emergency department or be admitted to the hospital. While it was widely anticipated that vaccination would significantly mitigate COVID-19 infection, >60% of children remain unvaccinated,[26] and among those vaccinated, protection wanes quickly, becoming negligible in 3 months.[27] Because race and ethnicity are social constructs, the authors are careful not to draw biological conclusions regarding these data. More prospective studies are needed to evaluate the differences in those hospitalized in our study against those who were evaluated in the emergency department and sent home.

A major strength of this study is clear definitions of variant waves based on molecular sequencing data, allowing visualization of the impact of each variant on resource utilization and outcomes. This study was conducted at the main children's hospital in the state, with a large catchment area, so most pediatric COVID patients were likely included in the study, especially if they were admitted to the hospital. Use of a large pediatric-specific administrative database offered a large sample size with institutional and geographical representation.

Conclusions

Children diagnosed with SARS-CoV-2 during the pre-Delta or Delta variants were more likely to be hospitalized than those diagnosed during the Omicron wave. Younger children were more likely to be hospitalized regardless of wave, and the average age of hospitalized patients was lower for the Omicron variant than for Delta and pre-Delta variants. Patients with acute

247 SARS-CoV-2 infection who lived in rural areas were more likely hospitalized than urban
248 patients. While more studies are required to evaluate the reason for these findings, we suspect
249 a lower vaccination status and the larger distance from medical care could have influenced
250 higher hospitalization rates.

251

252 **Acknowledgments**

253 This work was supported by the Center for Translational Pediatric Research (NIH/NIGMS
254 P20GM121293) at Arkansas Childrens Hospital, and by the Translational Research Institute
255 (NIH/NCATS UL1TR003107) at the University of Arkansas for Medical Sciences.

Figure Legend

Figure 1. Total visits (ED and Hospitalizations) and Hospitalization Data for ACH. Spikes (labelled "actual" in the legend) show the actual numbers of total visits (lighter blue) and hospital admissions (ligher orange) seen at ACH on each calendar day of the study period. Heavier curves (labelled "smoothed" in the legend) were generated by loess regressions on the actual numbers, and show the locally weighted average numbers of total visits (darker blue) and hospital admissions (reddish orange) over the course of the study. The uncolored regions represent the three infection waves attributed to the pre-Delta, Delta, and Omicron SARS-CoV-2 variants. The two yellow regions between waves plus the 3rd yellow region after the Omicron wave denote the 1-month-long transition periods.

Figure 2. Forest Plots Comparing Demographic Factors within SARS-CoV-2 Variant Waves. (A) Children less than 1 year of age and rural children were more likely to be admitted during the pre-Delta (A), Delta (B), or Omicron (C) waves.

Table 1. Demographics.					
Demographic Factor (Whole study)	**Whole Study (N=2,410)**	**Pre-Delta Wave (N=681)**	**Delta Wave (N=673)**	**Omicron Wave (N=970)**	***P* value†**
Age in years					**<0.001§**
Mean [SD[1]]	5.91 [6.04]	6.99 [6.39]	6.60 [6.0]	4.72 [5.56]	
Median (1st – 3rd Quartiles)	3 (0 – 11)	6 (1 – 13)	5 (1 – 12)	2 (0 – 9)	
CDC Age Group, % (N)					
Under 1 year of age	27.5% (662)	24.4% (166)	23.6% (159)	32.2% (312)	**<0.001**
1–4 years of age	26.2% (632)	22.0% (150)	23.9% (161)	30.7% (298)	
5–14 years of age	32.0% (771)	34.4% (234)	36.4% (245)	27.0% (262)	
15–18 years of age	14.3% (345)	19.2% (131)	16.0% (108)	10.1% (98)	
Gender, % (N)					0.498
Female	47.3% (1,141)	46.3% (315)	49.2% (331)	46.7% (453)	
Male	52.7% (1,269)	53.7% (366)	50.8% (342)	53.3% (517)	
Race[2], % (N)					**<0.001**
Hispanic	23.3% (561)	27.8% (189)	16.5% (111)	25.0% (242)	
Non-Hispanic Black	29.8% (717)	34.7% (236)	30.8% (207)	26.6% (258)	
Non-Hispanic White	39.1% (942)	32.9% (224)	43.2% (291)	39.6% (384)	
Other	7.9% (190)	4.7% (32)	9.5% (64)	8.9% (86)	
Urban[3], % (N)					0.095
Urban	83.8% (2,019)	84.0% (572)	83.1% (559)	83.8% (813)	
Non-Urban	13.6% (328)	13.1% (89)	15.5% (104)	12.8% (124)	
Unknown	2.6% (63)	2.9% (20)	1.5% (10)	3.4% (33)	
Admitted, % (N)	16.6% (400)	20.9% (142)	19.3% (130)	12.0% (116)	**<0.001**
Any Complex Care Code[4], % (N)	12.6% (303)	12.6% (86)	13.4% (90)	12.1% (117)	0.733
Principal Diagnosis, % (N)					**<.001**
COVID-19 Only	97.6% (2,352)	95.0% (647)	97.5% (656)	99.4% (964)	
More Serious	2.4% (58)	5.0% (34)	2.5% (17)	0.6% (6)	
• *MIS-C*	*2.1% (51)*	*4.7% (32)*	*1.9% (13)*	*0.6% (6)*	
• *COVID-19 Pneumonia*	*0.3% (7)*	*0.3% (2)*	*0.6% (4)*	*0% (0)*	
ICU Use?, % (N)	3.0% (73)	4.3% (29)	3.7% (25)	1.6% (16)	**0.004**
Length of Stay, days (mean [SD[1]])	0.83 [4.04]	0.86 [2.30]	1.36 [6.91]	0.46 [1.79]	**<0.001§**

†: *P* values are from either Pearson chi-square or §Kruskal-Wallis tests. **Bold** denotes significance at α=0.05 (2-sided).
1: Standard Deviation.
2: Based on Equity Race Category classifications.
3: Based on Rural-Urban Commuting-Area (RUCA) Code.
4: Any Complex Chronic Condition.

Table 2. Risk of hospitalization in SARS-COV-2-infected pediatric patients.

Outcome: Any Hospitalization	Univariate Analyses				Multivariate Analysis			
	Unadjusted Odds Ratio	95% Conf. Limits Lower	Upper	p-value	Adjusted Odds Ratio	95% Conf. Limits Lower	Upper	p-value
Infection Wave				**<.0001**				**<.0001**
Pre-Delta	1.940	1.484	2.536		2.511	1.831	3.444	
Delta	1.763	1.342	2.315		2.069	1.508	2.840	
Omicron†	1.00	---	---		1.00	---	---	
Gender				0.0398				0.3008
Male	1.260	1.011	1.570		1.143	0.887	1.473	
Female†	1.00	---	---		1.00	---	---	
Age Group				0.1320				**<.0001**
<1 year old	1.225	0.924	1.623		2.345	1.673	3.287	
1-4 years old	0.922	0.683	1.244		1.379	0.968	1.964	
5-14 years old†	1.00	---	---		1.00	---	---	
15-18 years old	1.288	0.921	1.801		1.228	0.821	1.836	
Race/Ethnicity				**.0005**				0.4008
Hispanic	0.533	0.393	0.724		0.742	0.515	1.069	
Non-Hispanic Black	0.760	0.587	0.984		0.893	0.652	1.224	
Other	0.652	0.418	1.018		0.782	0.469	1.305	
Non-Hispanic White†	1.00	---	---		1.00	---	---	
Payor Type				**0.0001**				0.1712
Commercial	1.769	1.356	2.306		1.352	0.977	1.871	
Other/Self/Unknown	1.033	0.644	1.658		0.951	0.550	1.646	
Medicaid†	1.00	---	---		1.00	---	---	
Urban				**<.0001**				**<.0001**
No	3.589	2.758	4.672		2.757	2.016	3.770	
unknown	1.352	0.697	2.625		1.135	0.531	2.428	
Yes†	1.00	---	---		1.00	---	---	
Complex Chronic Condition				**<.0001**				**<.0001**
Yes	12.415	9.451	16.309		14.075	10.404	19.043	
No†	1.00	---	---		1.00	---	---	

†Reference category. ‡MIS-C or Pneumonia Due To COVID-19.

Supplemental Table 1. Demographic factors associated with the transition zones left out of the study.

Demographic Factor (Whole study)	Transition #1 (N=18)	**Transition #2 (N=58)**	**Transition #3 (N=10)**
Age in years			
Mean ±Standard Deviation	4.94 ±6.07	5.78 ±5.78	5.00 ±5.56
Median (1st – 3rdQuartiles)	2.5 (0 – 11)	3.5 (0 – 10)	3 (0 – 11)
CDC Age Group, % (N)			
Under 1 year of age	44% (8)	22% (13)	40% (4)
1–4 years of age	17% (3)	33% (19)	10% (1)
5–14 years of age	28% (5)	34% (20)	50% (5)
15–18 years of age	11% (2)	10% (6)	0% (0)
Gender, % (N)			
Female	50% (9)	47% (27)	60% (6)
Male	50% (9)	53% (31)	40% (4)
Race, % (N)			
Hispanic	11% (2)	24% (14)	30% (3)
Non-Hispanic Black	28% (5)	16% (9)	20% (2)
Non-Hispanic White	56% (10)	50% (29)	40% (4)
Other	6% (1)	10% (6)	10% (1)
Urban[1], % (N)			
Urban	89% (16)	86% (50)	90% (9)
Non-Urban	11% (2)	14% (8)	10% (1)
Unknown	0% (0)	0% (0)	0% (0)
Insurance Payor Category, % (N)			
Commercial	11% (2)	16% (9)	20% (2)
Medicaid	89% (16)	78% (45)	80% (8)
Other/Self/Unknown	0%(0)	7% (4)	0%

Supplemental Table 2. Disease Characteristics associated with the transition zones left out of the study.

Disease Characteristic (Whole study)	Transition #1 (N=18)	**Transition #2 (N=58)**	**Transition #3 (N=10)**
Admitted, % (N)			
No	89% (16)	84% (49)	90% (9)
Yes	11% (2)	16% (9)	10% (1)
Observation Unit	*6% (1)*	*5% (3)*	*0% (0)*
Inpatient	*6% (1)*	*9% (5)*	*10% (1)*
Both	*0% (0)*	*2% (1)*	*0% (0)*
Principal Diagnosis, % (N)			
COVID-19 Only	94% (17)	100% (58)	100% (10)
More Serious	6% (1)	0% (0)	0% (0)
MIS-C	*0% (0)*	*0% (0)*	*0% (0)*
Systemic C-T Involvement	*0% (0)*	*0% (0)*	*0%(0)*
COVID-19 Pneumonia	*6% (1)*	*0% (0)*	*0% (0)*
Any Complex C.C.[1], % (N)			
No	94% (17)	86% (50)	90% (9)
Yes	6% (1)	14% (8)	10% (1)
ICU Use?, % (N)			
No	100% (18)	95% (55)	100% (10)
Yes	0% (0)	5% (3)	0% (0)
Length of Stay, days			
Mean ±Standard Deviation	0.33 ±0.84	0.57 ±1.57	0.30 ±0.48
Median (1st – 3rd Quartiles)	0 (0 – 0)	0 (0 – 0)	0 (0 – 1)
Return visit ≤7 days?, % (N)			
No	89% (16)	90% (52)	90% (9)
Yes	11% (2)	10% (6)	10% (1)
Return visit ≤30 days?, % (N)			
No	89% (16)	90% (52)	80% (8)
Yes	11% (2)	10% (6)	20% (2)
Second Infection?, % (N)			
No	100% (18)	97% (56)	90% (9)
Yes	0% (0)	3% (2)	10% (1)

Figure 1

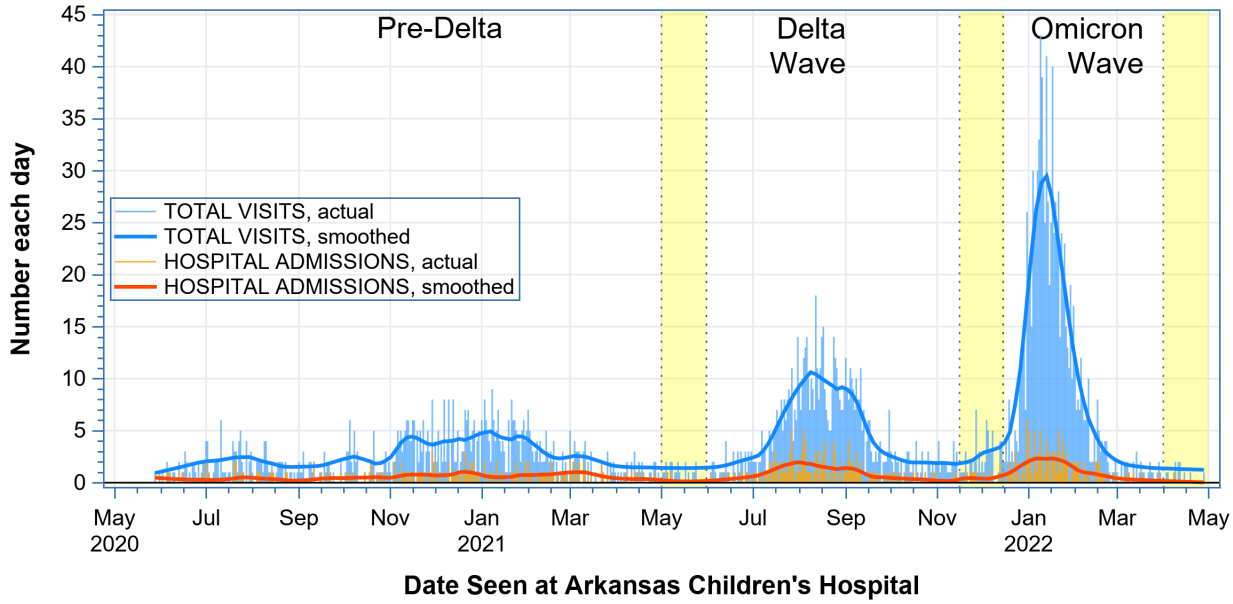


Figure 2A

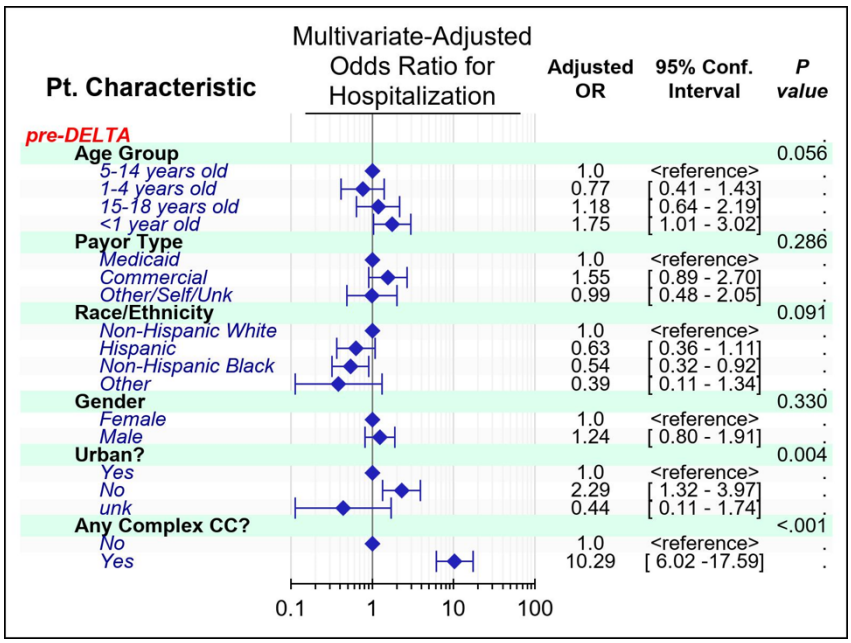


Figure 2B

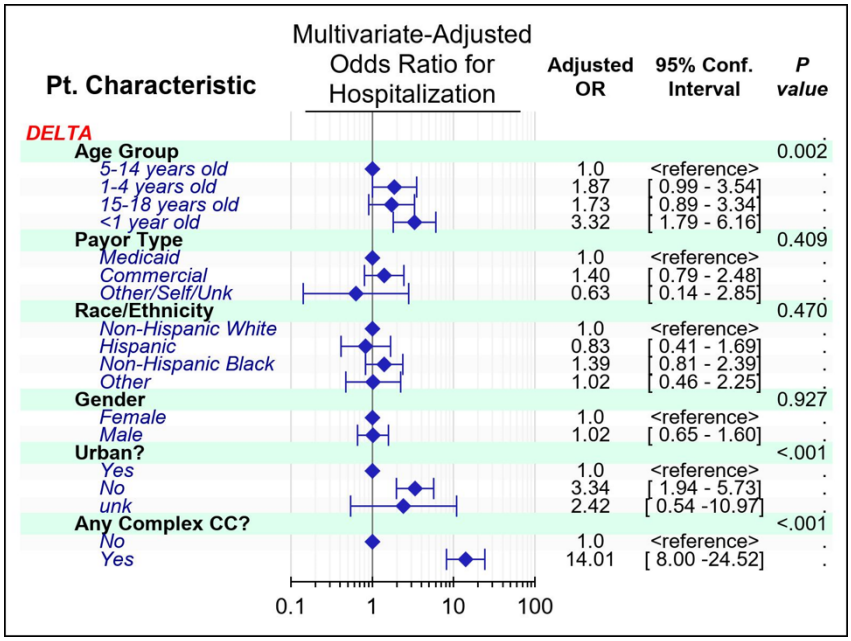
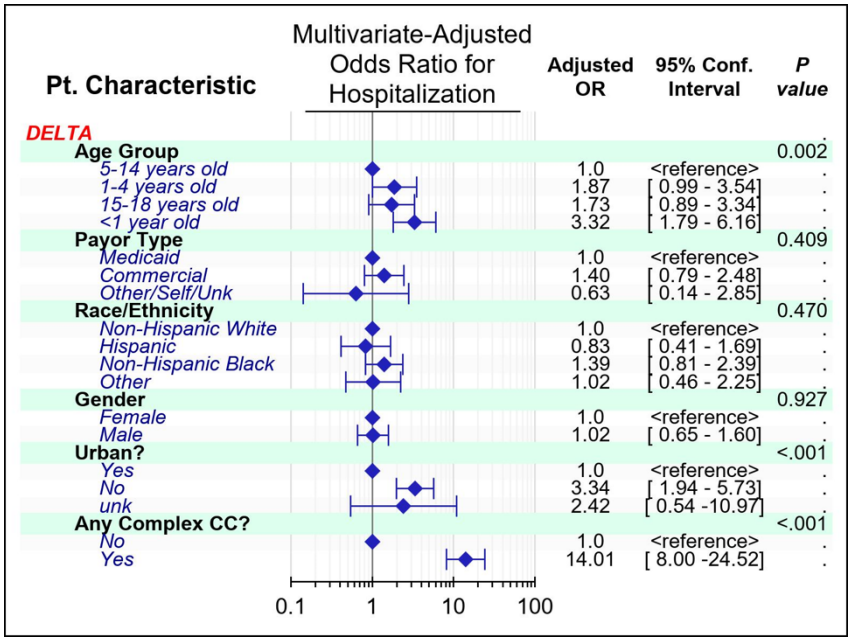


Figure 2C



References

1. Worldometer. Reported Cases and Deaths by Country or Territory. https://www.worldometers.info/coronavirus/#countries. Accessed August 2022.
2. Abdul AS, ABA; Slenker, AK. *Emerging Variants of SARS-CoV-2 and Novel Therapeutics Against Coronavirus (COVID-19)*. Treasure Island, FL: StatPearls Publishing; 2022.
3. Shiehzadegan S, Alaghemand N, Fox M, Venketaraman V. Analysis of the Delta Variant B.1.617.2 COVID-19. *Clin Pract.* Oct 21 2021;11(4):778-784.
4. Kannan S, Shaik Syed Ali P, Sheeza A. Omicron (B.1.1.529) - variant of concern - molecular profile and epidemiology: a mini review. *Eur Rev Med Pharmacol Sci.* Dec 2021;25(24):8019-8022.
5. Ren SY, Wang WB, Gao RD, Zhou AM. Omicron variant (B.1.1.529) of SARS-CoV-2: Mutation, infectivity, transmission, and vaccine resistance. *World J Clin Cases.* Jan 7 2022;10(1):1-11.
6. Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods - United States, December 2020-January 2022. *MMWR Morb Mortal Wkly Rep.* Jan 28 2022;71(4):146-152.
7. Balint G, Voros-Horvath B, Szechenyi A. Omicron: increased transmissibility and decreased pathogenicity. *Signal Transduct Target Ther.* May 7 2022;7(1):151.
8. Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of Infants and Children Aged 0-4 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. *MMWR Morb Mortal Wkly Rep.* Mar 18 2022;71(11):429-436.
9. Zhu F, Ang JY. COVID-19 Infection in Children: Diagnosis and Management. *Curr Infect Dis Rep.* 2022;24(4):51-62.
10. Garazzino S, Lo Vecchio A, Pierantoni L, et al. Epidemiology, Clinical Features and Prognostic Factors of Pediatric SARS-CoV-2 Infection: Results From an Italian Multicenter Study. *Front Pediatr.* 2021;9:649358.
11. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations Associated with COVID-19 Among Children and Adolescents - COVID-NET, 14 States, March 1, 2020-August 14, 2021. *MMWR Morb Mortal Wkly Rep.* Sep 10 2021;70(36):1255-1260.
12. Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of Children Aged 5-11 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. *MMWR Morb Mortal Wkly Rep.* Apr 22 2022;71(16):574-581.
13. Marks KJ, Whitaker M, Anglin O, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, July 2021-January 2022. *MMWR Morb Mortal Wkly Rep.* Feb 18 2022;71(7):271-278.
14. Sanders SC, Taylor MD, Filipek J, et al. Demographic and clinical characteristics of pediatric COVID-19 in Arkansas: March-December 2020. *Medicine (Baltimore).* Oct 21 2022;101(42):e31058.
15. Control CfD. New ICD-10-CM code for the 2019 novel coronavirus (COVID-19). https://www.cdc.gov/nchs/data/icd/Announcement-New-ICD-code-for-coronavirus-19-508.pdf. Accessed September 2022.
16. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr.* Aug 8 2014;14:199.
17. McElfish PA, Willis DE, Shah SK, et al. Parents' and Guardians' Intentions to Vaccinate Children against COVID-19. *Vaccines (Basel).* Feb 25 2022;10(3).

18. Markham JL, Richardson T, Teufel RJ, et al. Impact of COVID-19 on Admissions and Outcomes for Children With Complex Chronic Conditions. *Hosp Pediatr.* Apr 1 2022;12(4):337-353.
19. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. *JAMA Netw Open.* Jun 1 2021;4(6):e2111182.
20. Whittaker R, Greve-Isdahl M, Boas H, Suren P, Buanes EA, Veneti L. COVID-19 Hospitalization Among Children <18 Years by Variant Wave in Norway. *Pediatrics.* Sep 1 2022;150(3).
21. Boehme KW, Kennedy JL, Snowden J, et al. Pediatric SARS-CoV-2 Seroprevalence in Arkansas Over the First Year of the COVID-19 Pandemic. *J Pediatric Infect Dis Soc.* Jun 22 2022;11(6):248-256.
22. Hoffmann M, Kruger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell.* Feb 3 2022;185(3):447-456 e411.
23. Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature.* Feb 2022;602(7898):657-663.
24. Cao Y, Yisimayi A, Jian F, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature.* Aug 2022;608(7923):593-602.
25. Kronman MP, Gerber JS, Newland JG, Hersh AL. Database Research for Pediatric Infectious Diseases. *J Pediatric Infect Dis Soc.* Jun 2015;4(2):143-150.
26. Control CfD. COVID-19 Vaccination Coverage and Vaccine Confidence Among Children. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children.html. Accessed 11/3/2022.
27. Chemaitelly H, AlMukdad S, Ayoub HH, et al. Covid-19 Vaccine Protection among Children and Adolescents in Qatar. *N Engl J Med.* Nov 2 2022.