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Impact Of Different Human Coronaviruses (Hcovs) On Pediatric Patients At A Tertiary Pediatric Hospital – Retrospective Study

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IMPACT OF DIFFERENT HUMAN CORONAVIRUSES (HCOVS) ON PEDIATRIC PATIENTS AT A TERTIARY PEDIATRIC HOSPITAL – RETROSPECTIVE STUDY

by

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PUBLIC HEALTH

ABSTRACT

Background: Human Coronaviruses (HCoV) are important pathogens associated with respiratory disease in humans and animals. The majority of HCoVs are emerging human pathogens with 7 known types causing human disease and 5 being identified in the last 2 decades.

Methods: We performed a retrospective review of all encounters with known HCoV at a tertiary pediatric hospital from January 2015 until January 2018. Electronic medical records (EMRs) were reviewed for demographic data, HCoV type, viral copathogens, time to testing, admission, need for increased intensity of care (HLC), requirement for supplemental oxygen, radiographic findings suggestive lower respiratory tract disease (LRT) when available and the length of hospitalization (LOS).

Results: We analyzed 450 encounters for 430 different patients. OC43 was the most common HCoV type. Seasonality was evident during winter and spring months. Nosocomial infections were identified in 11.43% of the encounters. HCoV type and the presence of copathogens were not associated with a requirement for hospitalization, need for either HLC or supplemental oxygen support. Patients < 5 years of age were more likely to be admitted to the hospital, need HLC and have nosocomial infections compared to patients > 5 years of age.

Conclusion: HCoV are important respiratory pathogens in pediatric populations especially patients < 5 years of age. Different types of HCoVs have a similar impact on patients. HCoV may have bigger impact on nosocomial infections as compared to community acquired infections.

Keywords: Human coronaviruses (HCoV), pediatric patients, respiratory viral infections, nosocomial infections.

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Background

Human corona viruses (HCoVs) are a group of single stranded, positive sense RNA viruses recognized to cause infections in humans and animals [1]. Currently there are seven HCoVs recognized as human pathogens of which five have been identified during the last two decades [2]. Most of these viruses are considered emerging human pathogens as their origin has been linked to different animals. HCoV are divided into four groups (alpha, beta, gamma, and delta) with human pathogens belonging to the first two groups. Alpha HCoV include 229E, and NL63. Beta coronaviruses include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), SARS-CoV-2, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), OC43, and HKU1 [2]. SARS-CoV-2, a novel coronavirus strain, was recently identified as responsible for the current ongoing pandemic, Corona Virus Infectious Disease 2019 (COVID-19) that has rapidly become a major global health threat [3].

The severity of disease attributed to different HCoV varies. Endemic HCoV (OC43, NL63, 229E, and HKU1) primarily cause upper respiratory tract infections, particularly among children [4], and occasionally lower respiratory tract infections in all age groups [5] [6], but especially in immune compromised patients [7].

The spectrum of HCoV disease in pediatric populations has been the focus of recent studies. The purpose of this study was to examine the impact of HCoV on the clinical

course and outcome of children at a tertiary pediatric hospital to improve understanding of disease severity, and outcomes.

Methods

We performed a retrospective chart review of all children with a positive test for HCoV who received care, whether inpatient or outpatient, at Children's of Alabama (COA), a tertiary pediatric hospital,. The study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB).

Patients

All children with a positive viral respiratory panel (VRP) by PCR for HCoV were included in the analysis. Visits spanned the period from January 2015 to January 2018. Data collection was completed utilizing REDCap [8]. Only the first encounter was analyzed when the same patient presented on more than one occasion for the same HCoV since prolonged shedding or reinfection could not be differentiated. Patients with recurrent presentations are described separately.

Data Collection

Electronic medical records (EMRs) were reviewed; data collected included demographics (date of birth, gender, and race/ethnicity), admission status, chest x-ray (CXR) findings (when available), need for more intense care (HLC, defined as admission to the intensive care (pediatric, neonatal or cardiac) or special care units), HCoV type, viral copathogens, time to testing, oxygen requirement, and length of stay (LOS). Underlying medical co-

morbidities were also recorded, including prematurity (<37 week-gestation), immune suppression (cancer, primary immune deficiency or use of chemotherapy, steroid or immune modulators), chronic lung disease (CLD), cystic fibrosis (CF) or asthma), cardiac disease, baseline oxygen requirement, presence of tracheostomy tube, neuromuscular disease (cerebral palsy, seizure disorder, or muscular atrophy), and complex medical problems (chronic diagnoses not included above like congenital malformations, genetic disorders and end-stage renal disease).

Definitions

Age was calculated in days from date of birth to encounter date and dichotomized for age, < 5 years or ≥ 5 years. Encounters are considered inpatient if classified as inpatient in the EMR or the patient was admitted for >24 hours. CXR findings were recorded for lower respiratory tract (LRT) disease (peri-bronchial thickening, consolidations, patchy infiltrates or worsening of chronic parenchymal disease). Oxygen requirement and presence of tracheostomy tube was determined based on physicians' notes. Oxygen support is recorded as positive if the patient developed a new oxygen requirement or had an increase in oxygen supplementation relative to baseline. Infections are considered nosocomial if the patient tested positive 3 days or more after admission with new onset of symptoms.

Statistical Analysis

Descriptive statistics used proportions and percentages for categorical variables, and median with interquartile range (IQR) for continuous variables. Bivariate analysis is

conducted using Chi-Square or Fisher exact tests (when appropriate). Significance was set to be below .05. LOS is rounded to the nearest integer and analyzed using non-parametric tests for bivariate and Poisson distribution in multivariate model. Multivariate analysis was done using generalized linear mixed models with random intercepts. Adjusted odds rations (aOR) with 95% confidence intervals (95% CI) and p values are presented. Analyses were performed using SAS 9.3 (USA, NC). Patients with mixed HCoV (more than one type simultaneously, n=7) were excluded from analyses due to small number of observations.

Results

Population

The dataset included 455 encounters from 430 different patients (407 patients had 1, 21 patients had 2 and 2 patients had 3 encounters). Recurrent encounters for the same patient had to have different HCoV detected. Table 1 provides the different demographic characteristics and spectrum of clinical disease for the population. The majority of visits (85%) were inpatient encounters; OC43 was the most commonly identified virus (60%). Viral infections were more common during the winter and spring months (Figure 2). OC43 was more likely to have viral copathogens (59.78%) while NL63 was the least likely to have viral copathogens (28%) as compared to other HCoV (229E had copathogens in 43% and HKU1 had copathogens in 46%, p <.0001).

The distribution of HCoV types and the presence of viral copathogens were not different by age, gender or race/ethnicity group. The detection of viral copathogens was associated with younger patients (57% vs. 39%, p= .0006), immunocompetent patients (54% vs,

38%, p= .0131) and those without neuromuscular disorders (54% vs. 42%, p= .0377). Although different HCoV (excluding mixed) were not different by immune status, patients with chronic lung disease had more encounters due to OC43 (68% vs. 57%) and fewer encounters due to NL63 (8% vs. 16%, p= .0414). HCoV and viral copathogens were not different by prematurity, cardiac disease, complex medial problems, oxygen at baseline or presence of tracheostomy tube.

Clinical Outcomes

Inpatient encounters were more frequent in patients <5 years (89% vs. 77%) than in those >5 years, p= .0008), patients with a history of prematurity (92% vs. 84% in term infants, p= .0424), presence of tracheostomy at baseline (95.83% vs. 84.50%, p= .034) and immunocompetent patients (87% vs. 76%, p= .018). Presence of pre-existing respiratory disease, the need for oxygen at baseline, cardiac disorders, neuromuscular disease, complex medical problems, HCoV (excluding mixed) or the presence of viral co-pathogens were not different between inpatient and outpatient encounters.

Among inpatient encounters, HLC was associated with younger patients (65% vs. 42%, p <.0001), immunocompetent (62% vs. 38%, p= .0015) those without underlying respiratory disease (66.16% vs. 42.15%, p <.0001), and those with no complex medical problems (62% vs. 46%, p= .0104). Need for HLC was not associated with prematurity, cardiac disorders, neuromuscular diseases, the need for baseline respiratory support, HCoV (excluding mixed) or presence of viral co-pathogens.

Among inpatient encounters, supplemental oxygen was associated with the presence of oxygen support at baseline (91% vs. 56%, p <.0001), tracheostomy (91% vs. 58%, p

<.0001), prematurity (73% vs. 59%, p= .0125), cardiac disease (80.65% vs. 58.70%, p= .0011), neuromuscular disorders (84% vs. 56%, p< .0001), and immunocompetent (66.27% vs. 36.54%, p< .0001). Need for oxygen support during admission was not associated with age category, presence of respiratory disease, the presence of complex medical problems, HCoV subtypes (excluding mixed), or the presence of viral-copathogens.

Among encounters where an X-ray was obtained, findings suggestive of LRT disease were associated with patients <5 years (62% vs. 49%, p= .021), patients with complex medical problems (69% vs. 55%, p= .0279), those with no cardiac disorders (60.52% vs. 46.03%, p= .036), and encounters positive for viral co-pathogens (62.70% vs. 51.68%, p= .0426). Immune suppression, chronic respiratory disease, prematurity, neuromuscular disease, need for oxygen or tracheostomy at baseline, and HCoV subtypes were not associated with LRT disease findings on X-rays.

LOS was analyzed using non-parametric test for inpatient encounters. The median LOS in days was longer for immunocompromised (6.5 with IQR 3 – 32 vs. 5.0 with IQR 2 – 11, p= .0304), premature (6 with IQR 3 – 16 vs. 5.0 with IQR 2 – 11, p= .0423), neuromuscular disease (7 with IQR 3 – 21 vs. 4 with IQR 2 – 10, p= .0044), cardiac disease (8 with IQR 3 – 28 vs. 5 with IQR 2 – 11, p= .0042), need for oxygen at baseline (8 with IQR 3 – 20 vs. 5 with IQR 2 – 11, p= .0124), presence of tracheostomy at baseline (8 with IQR 4 – 140 vs. 5 with IQR 2 – 11, p= .0011) and absence of viral copathogens (6 with IQR 3 – 18 vs. 5 with IQR 2 – 10, p= .0094). LOS was not different by age category, HCoV (excluding mixed), presence of underlying respiratory disease or presence of complex medical problems.

Multivariate Analysis

A model predicting inpatient admission adjusting for immune suppression, age and prematurity suggests only patients <5 years were more likely to be admitted to the hospital as compared to older patients (aOR 2.04, 95% CI 1.12 – 3.70). A model predicting the HLC among admitted patients (adjusting for age, immune suppression, chronic respiratory disease, and complex medical problems) showed that younger patients were more likely to need HLC (aOR 1.78, 95% CI 1.03 – 3.08). Patients with immune suppression (aOR 0.27, 95% CI 0.12 – 0.53), respiratory disease (0.31, 95% CI 0.18 – 0.53) and complex medical problems (aOR 0.51, 95% CI 0.29 – 0.91) were less likely to have needed HLC.

A model predicting the need for oxygen during hospitalization (adjusting for prematurity, cardiac disease, neuromuscular disease, oxygen or tracheostomy, and immune suppression) revealed that patients who need oxygen at baseline (aOR 5.66, 95%CI 2.06 – 15.61), have neuromuscular disorders (aOR 2.73, 95% CI 1.31 – 5.68), and or cardiac disorders (aOR 3.63, 95% CI 1.66 – 7.97) were more likely to need oxygen during admission while patients with immune suppression were less likely to need oxygen during admission (aOR 0.36, 95% CI 0.17 – 0.74). A multivariate model for the LOS using Poisson distribution (adjusting for HCoV types, neuromuscular disorders, cardiac disease, presence of baseline oxygen and presence of a tracheostomy) showed that encounters with 229E as compared to OC43 (adjusted ratio 1.7, 95% CI 1.14 – 2.55, p= .0174), presence of neuromuscular disorders (adjusted ratio 1.43, 95% CI 1.02 – 2.02, p= .0433), presence of cardiac disease (1.76, 95% CI 1.20 – 2.57, p= .0113), and presence of

baseline oxygen support (1.52, 95% CI 1.04 – 2.24, p= .0361) were associated with longer LOS while the presence of tracheostomy tube at baseline was associated with shorter LOS (adjusted ratio 0.64, 95% CI 0.43 – 0.96, p= .0356).

Multisystem Inflammatory Syndrome in Children (MIS-C)

Four patients had clinical presentations similar to MIS-C and are briefly described here.

A 13 years old female admitted with hypermobility admitted with septic shock and required vasopressors, fluid resuscitation and oxygen support with no intubation. The VRP was positive for NL63 and no other reason was identified for her shock presentation. She recovered and was discharged on hospital day 4.

An 11 years old male with no medical history admitted with atypical Kawasaki's Diseases (KD) and required intensive care for vasopressors and intubation. He received intravenous immune-globulin (IVIG), aspirin, stress doses of steroids, and broad-spectrum antibiotics. An echocardiogram showed decreased left ventricular function and a dilated right ventricle; improvement was noted on hospital day 5. The VRP was positive for OC43 and Rhinovirus/ Enterovirus.

A 9 years old male with global developmental delay, shunted hydrocephalus and seizure disorder was admitted with fever, vomiting, diarrhea and septic shock requiring fluid resuscitation and intubation for respiratory decompensation. The VRP was positive for OC43. He also had elevated liver enzymes and acute kidney injury.

An 8 year old male with prior history of asthma and prematurity was admitted with acute encephalitis. He presented with headache and vomiting and later developed persistent seizures. The electroencephalogram (EEG) showed left hemisphere discharges and MRI

confirmed left supratentorial acute-subacute anoxic brain injury. He required decompressive craniotomy and had complicated medical course. The VRP was positive for NL63. A work up for the encephalitis and cerebrovascular accident was unrewarding, including autoimmune panel.

Nosocomial Infections

Infections classified as nosocomial were found in 52 (11%) encounters with a median of 26.5 days (IQR 7.50 – 99) before the VRP results became available. Nosocomial infections were associated with longer median hospital stay 87.49 days (IQR 27.49 – 222.77) as compared to community-acquired infection (median 3.86, IQR 2.03 – 8.59, p<.0001). Nosocomial infections were more likely in younger patients (16% vs. 7%, p= .0322), those immunosuppressed (27% vs. 11%, p= .002), presence of tracheostomy at baseline (28% vs. 11%, p= .0016), absence of viral copathogens (19% vs. 8% of those with copathogens, p= .0044), and need for HLC (16.89% vs. 8.54%, p= .0168). Nosocomial infections were not associated with presence of underlying respiratory diseases, prematurity, neuromuscular disorders, complex medical problems, cardiac disorders, baseline oxygen requirement or different HCoV types (excluding mixed HCoV).

Recurrent and Mixed Infections

Among the 48 encounters, 23 patients had more than one HCoV infection during the study period; 54% were in patients >5 years of age, 85% were inpatients, 28% were immune compromised, 44% had a viral copathogen, 33% had chronic respiratory disease,

and 23% were classified as nosocomial. Oxygen supplementation was provided to 67% of the encounters and only 38% needed HLC. Seven patients were found to have 2 HCoV simultaneously, Table 2 provides a summary of those patients.

Discussion

Our findings show that OC43 was the most common HCoV detected during the study period. In Hong Kong and Japan NL63 [9] [10] or in Italy 229E [11] has been identified as the most common HCoV in children. Similar to our findings, others have also identified OC43 as the predominant subtype in the United States [7] [12] and China [13]. While others show some differences in clinical presentation among different HCoV subtypes [13], we found HCoV subtypes were similarly distributed among most patient groups and the clinical impact of the different HCoV subtypes was similar for the outcomes of interest (admission to the hospital, need for HLC, need for oxygen supplement and presence of LRT findings on CXR). Similarly, Ogimi et al found no significant differences between HCoV subtypes with disease severity or outcome [7] [11]. A notable exception is LOS as 229E was associated with longer duration of hospitalization.

The higher rates of inpatient encounters and need for HLC in our study group likely reflects the culture of utilizing PCR testing in our institution where it is usual to reserve PCR-based testing to patients with significant underlying chronic conditions or patients requiring escalation of care.

Seasonal changes in detected HCoV infections were similar throughout the study period (Figure 2) for all different types. The sharp increase in annual HCoV-positive tests is

likely due to increase utilization of the PCR-based testing at our institution (101 encounters in 2015, 134 in 2016, and 199 in 2017). Different seasonal distribution of HCoV subtypes have been reported in some studies [7] [9]. The detection of multiple HCoV types in one sample was found in approximately 1.5% of the encounters analyzed from our institution during the study period. Simultaneous detection of HCoV subtypes has been previously reported with varying frequencies [7] [11] [12] [14]. However, due to the small sample size (n=7), it is unclear whether having more than one HCoV subtype simultaneously is associated with different presentation or outcomes.

HCoVs are important pathogens in hospital acquired infections as they were detected in 13.37% of the inpatient encounters in this study. Gagneur and colleagues, utilizing indirect immunofluorescence and cell culture, found that HCoVs were the most common reason for viral nosocomial infections in a neonatal intensive care unit with higher rates for oxygen supplementation (85%). [15]. The lower rates of viral copathogens in nosocomial infections compared to community-acquired infections highlights the importance of HCoV as hospital-acquired infections and warrants active surveillance.

Twenty-three patients presented with separate 48 encounters (21 patients had 2 and 2 patients had 3) with more than one encounter due to different HCoV types during the study period highlighting how common HCoV infections are in children. The majority were inpatient encounters and for patients aged 5 years or older.

Twenty-nine encounters (from 12 patients) were recurrent presentation for the same HCoV type. Seventeen encounters were not analyzed because interim testing was not done; thus, we could not identify prolonged shedding versus recurrent infections. Those encounters raised the question regarding the possibility of reinfection with the same

HCoV strain. We postulate that most of these encounters were less likely due to reinfection as the interval between the two infections were relatively short (within 2 months). Three immunocompromised patients had more than two months intervals between the tests (2 had more than 6 months), all of these encounters were due to OC43. Although these were immunocompromised patients, prolonged shedding of the virus for more than 6 months would be unusual. In a cohort of 44 immunocompromised patients with HCoV, Ogimi et al reported that 17 patients had viral shedding for more than 21 days while none had viral shedding more than 60 days [16]. Their study included mostly adult patients (only 2 pediatric cases) and showed no difference in shedding duration between HCoV types. Kiyuka et al studied the patterns of HCoV-NL63 endemic infections in coastal Kenya and found that repeated infections due to NL63, 229E and OC43 were possible with varying intervals between reinfections [17]. In their study, they noted higher viral load with NL63 re-infections as compared to the original infection. Re-infections were less frequent with 229E and OC43. The immune response to endemic HCoV infections may not be long-lasting in some patient populations and re-infections may be possible.

Younger age (< 5 years) is associated with admission to the hospital and need for HLC in this cohort. Lee et al showed that HCoV OC-34 and NL63 were common viral pathogens in this age group with high disease burden [18]. Similar results were also shown in other studies conducted in the US where patients of young age were more likely to develop severe disease [7] [12]. In a study by Gerna et al, 47 HCoV infections were detected in patients admitted to the hospital with respiratory symptoms , with 28 detected in children up to 5 years of age [14].

In this cohort, individuals immunocompromised and those with underlying respiratory disease were less likely to be admitted to the hospital, require escalation of care or have severe disease. This finding may reflect widespread utilization of PCR at our institution and would not be interpreted as these factors to be associated with milder disease or better outcomes than healthier counterparts. At our institution, especially in the early stages of the PCR deployment, it was not unusual to test high risk patients with milder disease while testing of their healthier counterparts is only reserved for when escalation of care is needed. Ogimi et al, reviewed pediatric patients with HCoV infections and reported that immune suppression was associated with severe lower respiratory tract (LRT) disease and having underlying respiratory disease was associated with a higher risk of developing LRT disease and severe LRT disease [7]. Varghese et al, also reviewed pediatric patients with HCoV infections and identified respiratory conditions, cardiovascular disease and congenital diseases, but not immune suppression, to be associated with need of respiratory support. They also identified congenital/genetic disease to be a risk factor for intensive care admission [12]. The variabilities in these results likely due to differences in cohorts, methodologies and practice differences at the institution-level in utilizing PCR tests for various groups. Longer hospitalization was evident in multiple high-risk groups in this cohort (immunocompromised, premature, neuromuscular disorders and cardiac diseases, but not those with tracheostomy or those with complex medical problems) and for 229E (but not other types) as compared to OC43. The longer hospital stays for the high-risk groups could be explained by the complexity of underlying problems.

MIS-C has been recently descried in children and is temporally linked to SARS-CoV-2 infection [19] [20]. We briefly described four patients who presented with clinical presentations that are similar to the MIS-C. We hypothesize that multisystemic hyperinflammation may be induced by other HCoVs.

Limitations

Limitations including the retrospective nature of the study and reliance on information as recorded in the EMRs. Moreover, the study is limited by the under-representation of pediatric patients who do not have major risk factors or severe disease.

Conclusion

HCoVs are important pathogens in the pediatric population with higher need for hospitalization and need for escalation for care in younger patients. The clinical impact of the four different types of HCoVs is similar. HCoVs may have a bigger impact on nosocomial infections as compared to community-acquired infections. Future prospective studies are warranted to delineate the roles of HCoV infections in the pediatric population, especial in the high-risk groups.

Table 1

Summary of demographic characteristics and clinical disease for analyzed encounters (N=455)

Gender	
Females, n (%)	192 (42.20%)
Males, n (%)	263 (57.80%)
Race/ Ethnicity	
White, n (%)	307 (67.47%)
Black/African American, n (%)	142 (31.21%)
Other race or ethnicity [a], n (%)	6 (1.32%)
Age	
< 5 years	315 (69.23%)
≥ 5 years	140 (30.77%)
Inpatient, n (%)	389 (85.49%)
Outpatient, n (%)	66 (14.51%)
Length of stay (LOS) in days, median (IQR) for inpatient encounters (n= 389)	5 (2-11)

HCoV	
OC43, n (%)	271 (59.56%)
HKU1, n (%)	68 (14.95%)
NL63, n (%)	60 (13.19%)
229E, n (%)	49 (10.77%)
Mixed [b], n (%)	7 (1.54%)
Nosocomial, n (%)	52 (11.43%)
Viral copathogens present, n (%)	234 (51.43%)
RhV/ EV, n (%)	123 (27.03%)
RSV, n (%)	64 (14.07%)
Adenovirus, n (%)	30 (6.59%)
PINF, n (%)	25 (5.49%)
HMN, n (%)	18 (3.96%)
Influenza (A or B), n (%)	17 (3.74%)
Clinical course	
Required oxygen, n (%)	242 (53.19%)
Higher level of care, n (%)	225 (49.45%)
CXR obtained, n (%)	339 (74.51%)

X-ray with lower respiratory tract findings, n (%)	196/339 (57.82%)
Underlying chronic conditions	
Premature, n (%)	110 (24.18%)
Immune suppression, n (%)	69 (15.16%)
Respiratory disease, n (%)	151 (33.19%)
Tracheostomy at baseline, n (%)	49 (10.77%)
Oxygen need at baseline, n (%)	79 (17.36%)
Cardiac disease, n (%)	71 (15.60%)
Neuromuscular disease, n (%)	96 (21.10%)
Complex medical problems, n (%)	100 (21.98%)

[a] Other race/ethnicity include: Hispanic (1), Alaskan (3) and Declined (2).

[b] Mixed HCoV encounters include: OC43, 229E (3), OC43, NL63 (2), OC43, HKU1 (1), and HKU1, NL63 (1).

Table 2

Features and disease outcome in patients with more than one HCoV infection (mixed HCoV)

Patient number	1	2	3	4	5	6	7
Age category	≥5 years	<5 years	≥5 years	<5 years	<5 years	≥5 years	<5 years
Premature	No	No	No	Yes	Yes	No	No
Immune suppressed	No	No	No	No	No	Yes	No
Respiratory disease	Yes	Yes	Yes	Yes	Yes	No	No
Need for oxygen at baseline	Yes	No	No	No	Yes	No	No
HCoV	OC43 NL63	OC43 229E	OC43 229E	OC43 HKU1	OC43 229E	OC43 NL63	HKU1 NL63
Viral copathogen	None	None	PINF	RSV	ADN Rh/EV	None	None

Hospital admission	Yes	No	Yes	Yes	Yes	No	Yes
Need for oxygen during admission	Yes	No	No	Yes	Yes	No	No
HLC admission	No	No	No	No	No	No	No

ADN: Adenovirus, HCoV: Human coronavirus, HLC: higher-level care, PINF: Parainfluenza virus, Rh/EV: Rhinovirus / Enterovirus, RSV: Respiratory syncytial virus.

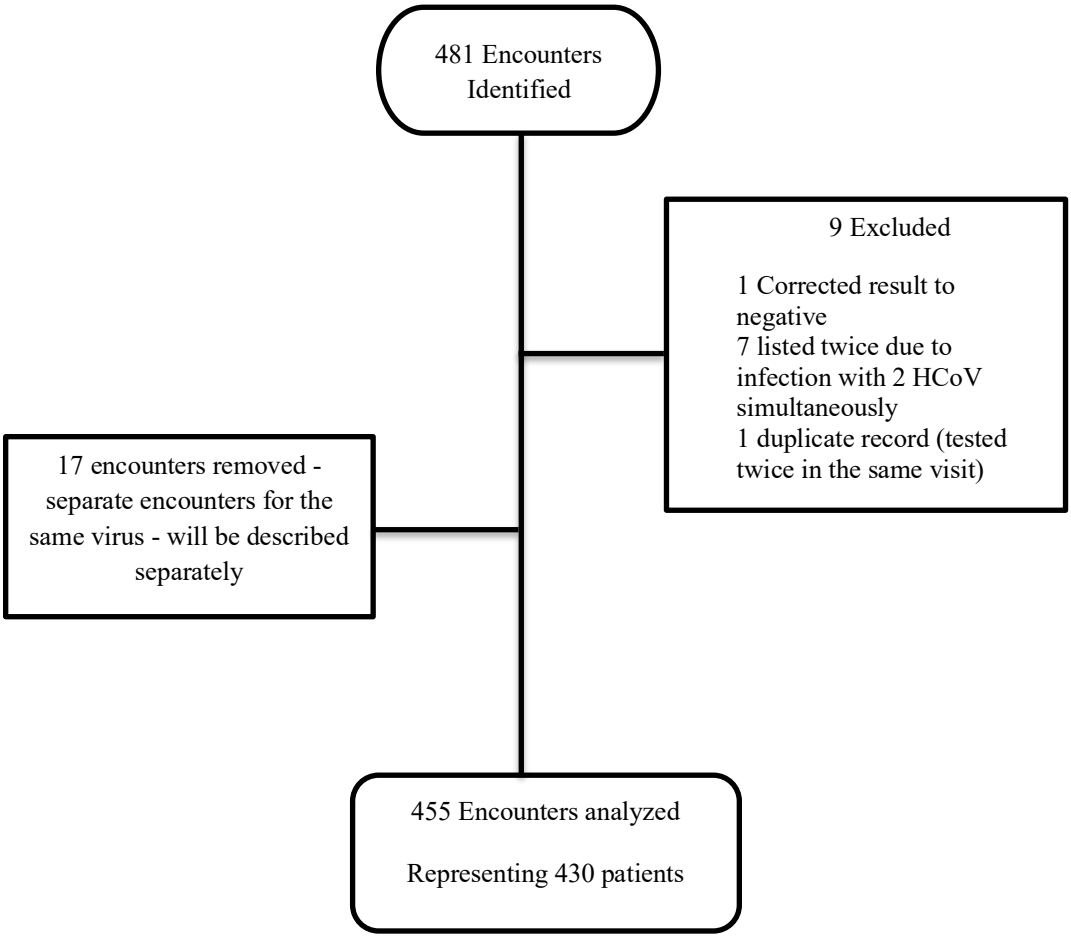

Figure1

Flow chart showing the original and final dataset and participants.

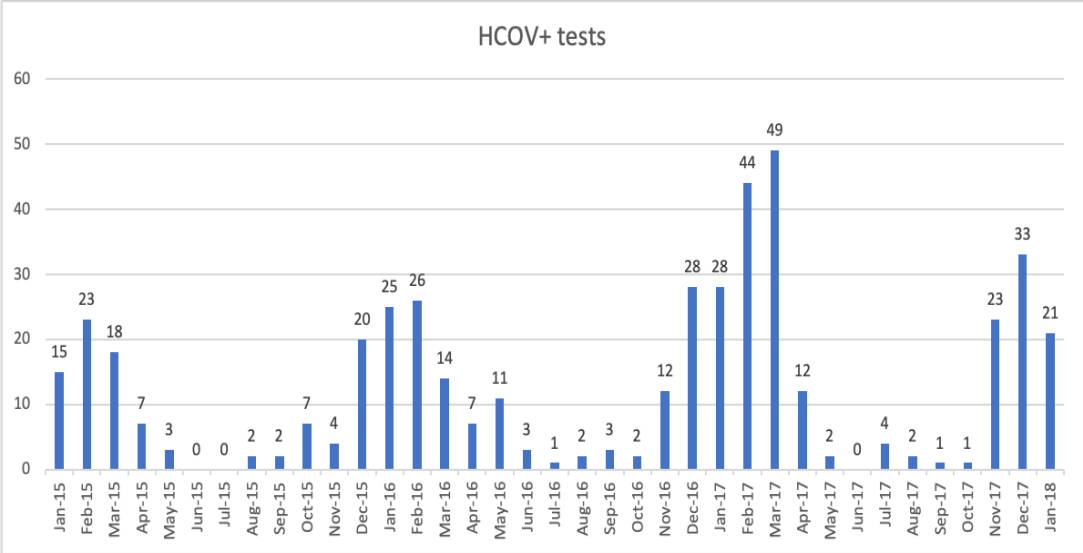

Figure 2

Distribution of encounters with positive total HCoVs over the study period

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Appendix: IRB Approval Letter

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Alsulami, Abdulsalam O

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 27-Nov-2019

RE: IRB-300002148
Impact of Different Human Coronaviruses (HCoVs) on Pediatric Patients at a Tertiary Pediatric Hospital – Retrospective Study and Assessment of Interve

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The IRB reviewed and approved the Continuing Review submitted on 27-Nov-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	5
Determination:	Approved
Approval Date:	27-Nov-2019
Approval Period:	One Year
Expiration Date:	26-Nov-2020

The following populations are approved for inclusion in this project:

- Children – CRL 1

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA
- Waiver of Informed Consent
- Waiver of Parental Permission

Documents Included in Review:

- ipr.191127.pdf.pdf

GROUP NAME	INFORMED CONSENT	POPULATION
All participants	Waiver of HIPAA, Waiver of Informed Consent, Waiver of Parental Permission	Children - CRL 1