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Human Coronavirus in Young Children Hospitalized for Acute Respiratory Illness and Asymptomatic Controls

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Abstract

Background—Human coronaviruses (HCoVs) have been detected in children with upper and lower respiratory symptoms but little is known about their relationship with severe respiratory illness.

Objective—To compare the prevalence of HCoV species among children hospitalized for acute respiratory illness and/or fever with asymptomatic controls and to assess the severity of outcomes among hospitalized children with HCoV compared with other respiratory viruses.

Methods—From December 2003–April 2004 and October 2004–April 2005, we conducted prospective, population-based surveillance of children <5 years of age hospitalized for ARI/fever in three U.S. counties. Asymptomatic outpatient controls were enrolled concurrently. Nasal/throat swabs were tested for HCoV species HKU1, NL63, 229E, and OC43 by RT-PCR. Specimens from hospitalized children were also tested for other common respiratory viruses. Demographic and medical data were collected by parent/guardian interview and medical chart review.

Results—Overall, HCoV was detected in 113 (7.6%) of 1,481 hospitalized children (83 [5.7%] after excluding 30 cases coinfected with other viruses) and 53 (7.1%) of 742 controls. The prevalence of HCoV or individual species was not significantly higher among hospitalized children than controls. Hospitalized children testing positive for HCoV alone tended to be less ill

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than those infected with other viruses, while those coinfected with HCoV and other viruses were clinically similar to those infected with other viruses alone.

Conclusion—In this study of children hospitalized for acute respiratory illness and/or fever, HCoV infection was not associated with hospitalization or with increased severity of illness.

Keywords

coronavirus; hospitalizations; asymptomatic controls; children

INTRODUCTION

There are currently five coronaviruses (family *Coronaviridae*, genus *Coronavirus*) known to infect humans: the four human coronaviruses (HCoVs) HKU1, NL63, 229E, OC43, and the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV). HCoVs 229E and OC43 were discovered in the 1960s.[1–3] Studies of cell and organ culture, serology, and human volunteer challenges performed in the 1960s and 1970s demonstrated that infection with 229E and OC43 was associated with viral replication and interference with ciliary action, as well as upper respiratory tract illness and a marked antibody rise.[4–7] Humans infected with HCoVs displayed a wide range of symptoms, with many also asymptomatic. In late 2002, the emergence of SARS-CoV fueled concern about the virulence and possible unrecognized burden of illness due to HCoVs.[8] Soon after the outbreak of SARS ended, HCoVs NL63 and HKU1 were identified.[9–12] Although HCoVs were typically detected among individuals with upper respiratory illnesses (i.e., "the common cold")[4, 7, 13, 14], some reports have suggested that they may have a role in pediatric lower respiratory infections and hospitalizations[15–18]. In contrast, several recent publications that included asymptomatic controls for comparison have questioned whether HCoVs have any role in severe respiratory illness and hospitalization among young children.[19–21] However, these studies were limited by relatively small sample size, short study duration, and single geographic site.

The primary objective of this study was to use prospective, population-based surveillance to compare the detection rates for HCoVs HKU1, NL63, 229E, and OC43 among children <5 years of age hospitalized for acute respiratory illness and/or fever (ARI/fever) with rates in asymptomatic control children of similar ages over two winter seasons in three geographic sites. In addition, the study compared the clinical characteristics between children hospitalized with confirmed HCoV and those hospitalized with other respiratory viruses. Finally, by combining these data with the data from three prior years of hospital surveillance that did not include asymptomatic control children[22], we describe the seasonality of HCoV detections over five seasons.

METHODS

Study Design

ARI Surveillance in Hospitalized Children—As part of the surveillance activities of the New Vaccine Surveillance Network (NVSN)[23–25], study staff prospectively enrolled hospitalized children <5 years of age with an admission diagnosis of ARI/fever that resided in the 3 counties surrounding Rochester NY, Nashville TN, and Cincinnati OH, USA during the period of October 2003 through April 2005. Hospital surveillance was conducted 4 days/week during 2003–04, 7 days/week during the months when influenza was circulating in each region in 2004–05 and 3–4 days/week when influenza was not circulating. Surveillance hospitals accounted for >95% of the pediatric hospitalizations in each county. ARI admission diagnoses included acute respiratory illness, apnea, asthma, bronchiolitis, croup, cystic fibrosis exacerbation, febrile neonate, febrile seizure, fever without localizing signs,

hypothermia, influenza, otitis media, other respiratory infection, paroxysmal cough, pharyngitis, pneumonia, respiratory distress, RSV, rule-out sepsis, sinusitis, tonsillitis, upper respiratory illness, and wheezing. Children were excluded if they had been hospitalized during the prior 4 days, were newborns hospitalized since birth, had neutropenia from chemotherapy, had a known non-respiratory cause for the hospitalization, or had been sick >14 days when screened; all others were eligible. The same protocol was used to carry out hospital surveillance at the Rochester and Nashville sites during the preceding three years.

Asymptomatic Control Enrollment—Children <5 years of age currently without ARI/fever who resided within the 3 counties were systematically enrolled as asymptomatic controls from 8–10 (depending on the year) large urban and suburban outpatient practices during 2 days/week from December 2003–April 2004 and October 2004–April 2005. These children will hereafter be referred to as "controls." Study staff prospectively identified eligible control children by reviewing clinic visit logs for well-child visits and spoke to the parent/guardian to determine that the child did not currently have ARI symptoms (i.e., chief complaints of a respiratory illness including fever, cough, earache, nasal congestion/runny nose, shortness of breath/rapid or shallow breathing, sore throat, vomiting after cough, or wheezing). In addition, the parent or guardian of each control child was asked to report the most recent prior medical visit for fever or respiratory symptoms during the surveillance period. Of the enrolled control children, 4.5% were excluded from analysis because review of the clinical records indicated the child had signs of ARI during their visit, as noted by the clinician who conducted their physical examination. There was no follow-up to determine whether subjects became ill or not soon after their enrollment visit.

Data Collection—For all enrolled hospitalized and control children, study staff obtained clinical and epidemiologic data from parent/guardian interviews and medical records using standardized methods and collected combined nasal/throat swab specimens. Pre-existing high risk conditions among enrolled children were identified based on the Advisory Committee on Immunization Practices recommendations for influenza vaccination and included history of asthma, heart disease, sickle cell anemia, cystic fibrosis, diabetes mellitus, or neuromuscular conditions, such as seizures, cerebral palsy, or muscular dystrophy.[26] These conditions were considered present if noted in the medical record or if the parent/guardian responded that a health care provider told them the child had the condition. A history of asthma/wheezing included asthma, reactive airway disease, and recurrent or chronic wheezing.

The study was approved by the Institutional Review Boards of each site and the Centers for Disease Control and Prevention (CDC). Informed consent was obtained from each parent/guardian before enrollment.

Research Laboratory Methods—Nasal/throat specimens were tested for HCoV using realtime reverse-transcription polymerase chain reaction (RT-PCR) assays for HCoVs HKU1, NL63, 229E, and OC43.[19, 22] Specimens from hospitalized cases were also tested by RT-PCR for influenza A or B virus (IV), human respiratory syncytial virus (RSV), human parainfluenza virus 1, 2 and 3 (HPIV1–3), human metapneumovirus (HMPV), human rhinovirus (HRV), and human bocavirus (HBoV). Asymptomatic control specimens were not tested for other viruses.

Data Analysis

Analyses comparing HCoV infections among hospitalized children and controls and assessing clinical factors among hospitalized children were restricted to the 5- and 7-month periods when both cases and controls were enrolled (December 2003–April 2004 and

October 2004–April 2005). Repeat hospitalizations/visits occurring among cases and controls were not excluded or adjusted for in the analysis. There were eight children with a second hospitalization or visits within 30 days of the first, and none of the children were positive for HCoV on both occasions. Categorical data were assessed with Pearson chi-square and Fisher's exact tests. The medians and interquartile ranges (IQR) were calculated for continuous variables. SAS version 9.2 was used for all analyses (SAS Institute, Cary NC) and a 2-sided 0.05 significance level was applied for all statistical tests performed.

Comparison of HCoV Detections between Hospitalized and Control Children— Crude unadjusted odds ratios and 95% confidence intervals (CI) were calculated using logistic regression. Five conditional logistic regression models were also fit. One model estimated the adjusted odds (aOR) of HCoV detection among hospitalized children versus controls while controlling for age group (0–5, 6–11, 12–23, 24–59 months), county, and month of hospitalization/visit. Four analogous models were fit to assess each HCoV species separately. Differences between cases and controls were assessed both including and excluding the hospitalized HCoV cases coinfected with IV, RSV, HPIV, or HMPV, and the results were similar.

Clinical Outcomes among Hospitalized Children—To assess the severity of HCoV infections relative to other respiratory viruses, the hospitalized children were divided into three subgroups for comparison: 1) HCoV positive (HCoV+) children who were not coinfected with IV, RSV, HPIV, or HMPV; 2) HCoV+ children who were coinfected with either IV, RSV, HPIV, or HMPV, and 3) HCoV negative (HCoV−) children who were infected with IV, RSV, HPIV, or HMPV.

Overall Prevalence and Seasonality of HCoV from 2000–2005—Hospital-based surveillance for ARI/fever among children <5 years of age had been conducted during the previous three years by the Rochester and Nashville sites utilizing the same study protocols and testing methods (without enrolling healthy controls). The prevalence (1.8%) and clinical features of the 19 HCoV+ children hospitalized from October 2001 through September 2003 have been previously reported.[22] In the current study, the HCoV detection rates from the previous 3 years are combined with the data gathered during 2003–2005 to describe the prevalence and seasonality of HCoV during five seasons of active population-based surveillance.

RESULTS

HCoV among Hospitalized Children

During the 12 months from December 2003 through April 2004 and October 2004 through April 2005, 1610 (82%) of 1952 children hospitalized for ARI/fever were enrolled in the study; test results were available for one or more of the four HCoV species in 1481 (92%) of these children. Of these, 113 (7.6%) tested positive for HCoV. Among the species, OC43 was the most frequent, with 58 (3.9%) detections, followed by 26 (1.8%) NL63, 17 (1.1%) HKU1, and 15 (1.0%) 229E. (Table 1) Three cases were infected with more than one strain of HCoV: two with both HKU1 and OC43 and one with both NL63 and 229E.

Other Viral Infections among Hospitalized Children

Coinfections were identified in the 113 hospitalized children with HCoV infection: 7 (6%) also tested positive for IV, 17 (15%) for RSV, 1 (1%) for HPIV1–3, 6 (6%) for HMPV, 8 (7%) for HRV, and 3 (3%) for HBoV. Rates of coinfection for the four HCoV species were: 59% for HKU1, 40% for 229E, 36% for OC43, and 23% for NL63 (not statistically significantly different). Only one HCoV+ child was coinfected with two other respiratory

viruses (IV and RSV). Overall, 41 (36%) had a viral coinfection and 30 of the coinfections were with viruses known to be associated with serious ARI (IV, RSV, HPIV, and HMPV). After excluding these 30 cases, the proportion of hospitalized children with HCoV was 5.7%. Of the 496 hospitalized children who were HCoV negative but were infected with a virus associated with serious ARI (subgroup 3), 145 (29%) tested positive for IV, 276 (56%) for RSV, 29 (6%) for HPIV1–3, and 72 (15%) for HMPV.

HCoV among Control Children

During the same two study periods described above, 822 (89%) of 919 asymptomatic controls were enrolled and 742 (90%) had test results reported for HCoV. (Table 1) Of these 742 controls, 53 (7.1%) tested positive for HCoV. The most common species was OC43, with 20 (2.7%), followed by 18 (2.4%) NL63, 12 (1.6%) HKU1, and 3 (0.4%) 229E.

Comparison of HCoV Detections between Hospitalized and Control Children

When compared with the controls, with or without excluding coinfections, significantly higher detection rates were not observed among hospitalized cases for any HCoV or for any of the specific HCoV species. (Table 1)

Demographic Characteristics of Hospitalized and Control Children

Among the hospitalized and control groups, respectively, no significant differences existed in the demographic characteristics between those with and without HCoV infection (Table 2). More than half (52%) of the HCoV+ hospitalized children were <6 months of age whereas HCoV infection among controls was more evenly distributed between the age groups (p=0.001). However, the proportion of children with HCoV infection was not significantly different in any age group for hospitalized children when compared with controls (Table 3). Among those <6 months of age the difference was greater but still did not reach statistical significance when coinfected cases were included (8.1% versus 4.8%, p-value=0.09).

Medical History of Hospitalized and Control Children

The medical history and selected characteristics for hospitalized children and controls positive for HCoV overall and for each HCoV species are shown in Supplemental Digital Content 1. Among the children infected with species NL63, pre-existing high risk conditions were more common among hospitalized children than controls (33% versus 0%, p=.01). However, in both groups, the prevalence of high risk conditions was no different between NL63-positive and NL63-negative children. The results were the same when the cases coinfected with IV, RSV, HPIV, or HMPV were included, and no other significant differences were found between HCoV+ hospitalized children compared with HCoV+ controls. Statistical comparisons were not made between cases and controls for species HKU1 and 229E due to the small numbers in each group.

Adjusted Model Comparing HCoV Detections between Hospitalized and Control Children

Infection with any HCoV or with a specific HCoV species was not associated with hospitalization in models controlling for age, county, and month of hospitalization/visit and excluding hospitalized children that were coinfected with other respiratory viruses. The aORs (CI) of HCoV detection among hospitalized children versus controls were as follows: for all HCoV infections, 0.79 (0.53–1.17); for HKU1, 0.57 (0.23–1.44); for NL63, 0.63 (0.31–1.30); for 229E, 2.38 (0.63–9.05); and for OC43, 0.82 (0.45–1.49). The estimated crude ORs and aORs changed little when HCoV+ coinfected hospitalized children were included in the analyses.

Discharge Diagnosis and Severity of Disease among Children Hospitalized with HCoV Compared with Those Hospitalized with Other Respiratory Viruses

Children infected with respiratory viruses (IV, RSV, HPIV, or HMPV) (Table 4, subgroup 2 and 3) were more likely than children singly infected with HCoV (Table 4, subgroup 1) to have had a discharge diagnosis of pneumonia or bronchiolitis, a hospital stay ≥3 days, or to require supplemental oxygen, though the last difference was statistically significant only for subgroup 3 versus subgroup 1. No statistically significant differences were observed between the children coinfected with HCoV plus another respiratory virus (subgroup 2) and the children infected only with another virus (subgroup 3). Coinfected children (subgroup 2) had a discharge diagnosis of otitis media more often than those singly infected with HCoV (subgroup1). In addition, among those singly infected with HCoV, 5 out of the 7 with a discharge diagnosis of croup were infected with species NL63. Croup was also more common among those singly infected with species NL63 than among those infected only with a non-coronavirus respiratory virus (23.8% versus 5.8%, p=.001).

Overall Prevalence and Seasonality of HCoV from 2000–2005

The prevalence of HCoV varied over the five study years, with a higher proportion of children with HCoV detected during 2000–01 and during the two seasons from 2003 to 2005 that are the focus of this study (see Figure, Supplemental Digital Content 2). The proportion of children with HCoV detected each month was very similar among both hospitalized children and controls (see Figure, Supplemental Digital Content 3). The most frequently detected species, OC43, tended to emerge in fall and peak in winter whereas NL63, the next most common species, tended to emerge in winter and peak in spring. Aside from one cluster during the winter months of 2003–04, HKU1 was uncommon during the five seasons. 229E was only observed during winter months and was not detected at all between April 2001 and February 2004. No notable differences were observed in the seasonal detection rates for HCoV between the three study sites during each of the five years of surveillance, although the sample sizes were small (data not shown).

DISCUSSION

This is the first study that reports the frequency of the four recognized HCoV species among hospitalized children and asymptomatic controls in several regions of the United States during multiple years. No statistically significant increase was observed in the rates of detection for HCoV or for any of the four individual species of HCoV among the hospitalized cases when compared with the controls, regardless of whether the 27% of hospitalized children who were coinfected with IV, RSV, HPIV, or HMPV, were excluded. The children hospitalized for ARI/fever in whom HCoV alone was detected appeared to be less severely ill than children with IV, RSV, HPIV, or HMPV infections, and the particular association observed between species NL63 and croup was consistent with other studies[27–29]. In addition, children coinfected with HCoV and other respiratory viruses were clinically similar to those infected only with IV, RSV, HPIV, or HMPV. This suggests that the other viruses rather than HCoV were responsible for the hospitalization.

The prevalence of HCoV species appeared episodic over the five seasons, with two years of lower overall activity separating several years of higher activity. A similar episodic pattern was reported by another study.[7] However, a study of HCoV seasonality over 20 years that did not include species HKU1 showed a high degree of year-to-year variability without a clear episodic pattern.[17] While we cannot ascertain a definitive epidemic pattern with five years of data, this study confirms the variable nature of HCoV circulation using sensitive methods of molecular detection.

Overall, our finding of no association between HCoV infection and serious illness among hospitalized children bolsters the findings of several prior studies.[19–21] A 2004–05 study from Thailand among patients of all ages and asymptomatic outpatient controls found no association between HCoV infection and hospitalization for pneumonia.[19] However, they observed fewer cases, with detection rates of 1.8% among cases and 2.1% among controls, and the number of asymptomatic controls enrolled was relatively small compared with our study (280 over one year versus 742 over two years). A more recent study comparing hospitalized Alaskan Native children less than three years of age and asymptomatic community controls found HCoV detection rates were the same for cases and controls (4%).[20] In a prospective community-based birth cohort study, species 229E and OC43 were detected at similar frequencies among symptomatic (5.5%) and asymptomatic children (4.4%), and neither species was detected in a specimen taken during an ARI episode that required hospitalization.[21] In contrast to our study, a three-year study of pediatric and adult inpatients and outpatients from the United Kingdom noted that 1.71% of those with lower respiratory tract infection were singly infected with HCoV compared with 1.08% among those with no respiratory symptoms.[18] However, the age distribution and sample size for those without symptoms were not described and a test for statistical significance was not provided.

Limitations of our study include the fact that the three geographic areas in this study may not be representative of the rest of the United States. Also, we did not assess bacterial coinfections or antibiotic use, which could have impacted the clinical outcomes for those children who were hospitalized. Our study did not collect data about respiratory symptoms before or after enrollment. Both cases and controls may have tested positive for HCoV from a very recent infection and developed symptoms after enrollment. Since prior studies have noted that HCoV may be shed at least 14 days after acute infection[30, 31], it is possible that controls with HCoV detected may have been shedding HCoV from a recent, symptomatic infection. However, this is also true for the hospitalized children, and few children with HCoV had medically-attended visits for respiratory illness in the month prior to enrollment. Another possible limitation is that asymptomatic children were not enrolled year-round, but the peak periods of HCoV circulation were included. Finally, we did not test the controls for the additional respiratory viruses for which the hospitalized children were tested.

This large prospective, multicenter, population-based study of HCoV infections among both cases and controls over several seasons found no association between hospitalization for ARI/fever and HCoV infection. This type of study, however, cannot rule out the possibility that the infection was causal in a subset of the children. It is possible that host factors are of primary importance in responding to HCoV infections, and further study of the relevance of host or other co-factors in symptomatic illness would help move the field forward. Furthermore, since very few studies of the known HCoVs have included a robust sample size, multiple years, and a control group, more studies would be helpful to verify the findings of this study. Given the low prevalence of hospitalized HCoV cases, the frequency of viral coinfection, and the differences in yearly circulation patterns, conducting future studies with larger numbers of cases and well-matched controls will be challenging. However, new multipathogen PCR platforms may provide opportunities for future studies of respiratory disease that include HCoV. Biopsy and autopsy studies with *in situ* identification of HCoV and microscopic assessment of fatal cases might also help elucidate viral etiology. Studies utilizing a variety of research strategies are needed to better delineate the role of HCoV infections among children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Number and percent testing positive for HCoVs among ARI/fever hospitalizations and asymptomatic controls, during the 12 months when controls were enrolled, December 2003 through April 2004 and October 2004 through April 2005.

	Hospitalized						Asymptomatic Controls		
	Coinfections included			Coinfections excluded*					
	N	n	%	N	n	%	N	n	%
Any HCoV	1481	113	7.6	1451	83	5.7	742	53	7.1
HKU1	1479	17	1.1	1449	9	†0.6	741	12	1.6
NL63	1478	26	1.8	1449	21	1.4	740	18	2.4
229E	1478	15	1.0	1449	13	0.9	740	3	0.4
OC43	1479	58	3.9	1450	41	2.8	741	20	2.7

*excluding HCoV+ hospitalizations coinfected with IV, RSV, HPIV or HMPV

†p<.05 by chi-square test for comparison with controls. No other comparisons between hospitalized children and asymptomatic controls reached statistical significance.

Table 2

Demographic characteristics of children hospitalized for ARI/fever (excluding those coinfected with IV, RSV, HPIV and HMPV) and asymptomatic controls with and without HCoV during the 12 months when controls were enrolled.

	Hospitalized ARI Cases		Asymptomatic Controls	
	HCoV+ N=83 %	HCoV− N=1368 %	HCoV+ N=53 %	HCoV− N=689 %
Age Group*				
<6 months	51.8	47.5	22.6	34.8
6–11 months	7.2	14.3	26.4	18.9
12–23 months	22.9	18.7	26.4	23.2
24–59 months	18.1	19.5	24.5	23.1
Female	41.0	43.2	56.6	48.6
Race/ethnicity				
White Non-Hispanic	50.6	48.6	32.1	37.9
Black Non-Hispanic	32.5	33.6	54.7	45.6
Hispanic	13.3	11.0	9.4	9.0
Other	3.6	6.8	3.8	7.1
Public Insurance or No Insurance	63.9	63.9	73.6	69.5

* Hospitalized HCoV+ children were more likely to be in the youngest age group than asymptomatic HCoV+ controls ($p<.01$ by chi-square test). All other differences between hospitalized children and asymptomatic controls or between cases or controls that were HCoV+ or HCoV− were not statistically significant.

Table 3

Age-specific HCoV detection rates (%) among ARI hospitalizations and asymptomatic controls during the 12 months when controls were enrolled.

	Hospitalized (Coinfections Excluded)*	Asymptomatic Controls
<6 months	6.2	4.8
6–11 months	3.0	9.7
12–23 months	6.9	8.0
24–59 months	5.3	7.6
Total	5.7	7.1

* excluding 30 cases coinfected with IV, RSV, HPIV or HMPV

Note: There were no statistically significant differences in HCoV detections between hospitalizations and controls.

Table 4

Discharge diagnoses and severity of illness among children hospitalized for ARI/fever.

	Subgroup 1 (N=83) HCOV+ & IV/RSV/HPIV/HMPV−	Subgroup 2 (N=30) HCOV+ & IV/RSV/HPIV/HMPV+	Subgroup 3 (N=496) HCOV− & IV/RSV/HPIV/HMPV+
	%	%	%
Discharge Diagnosis			
Pneumonia or Bronchiolitis	26.5	*60.0	*68.1
Croup	8.4	6.7	5.8
Otitis Media	12.0	*30.0	17.9
Length of Stay			
Median (IQR)	2 (1)	2 (2)	2 (2)
≥3 days	16.9	*36.7	*35.1
≥6 days	6.0	3.3	9.5
Admitted to ICU	2.4	0.0	5.4
Required Mechanical Ventilation	1.2	0.0	3.2
Required Supplemental Oxygen	19.3	33.3	*47.1

* $p < 0.05$ for comparison with Subgroup 1. None of the differences between Subgroup 2 and Subgroup 3 reached statistical significance.