MAJOR ARTICLE

Title: Human Coronavirus in Hospitalized Children with Respiratory Tract Infections: A Nine-year-long, Population-based Study from Norway

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Brief summary: During a nine-year long period, human coronaviruses (HCoV) OC43, NL63, HKU1 and 229E occurred at similar rates in hospitalized children with respiratory tract infections and asymptomatic controls, but infected children had higher genomic loads, supporting a causal role in infection.

ABSTRACT

Background: The burden of Human Coronavirus- (HCoV) associated respiratory tract infections (RTIs) in hospitalized children is poorly defined. We studied the occurrence and hospitalization rates of HCoV over nine years.

Methods: Children from Sør-Trøndelag County, Norway, hospitalized with RTIs and asymptomatic controls, were prospectively enrolled from 2006 to 2015. Nasopharyngeal aspirates were analyzed with semi-quantitative polymerase chain reaction (PCR) tests for HCoV subtypes OC43, 229E, NL63 and HKU1, and 13 other respiratory pathogens.

Results: HCoV was present in 9.1% (313/3458) of all RTI episodes: 46.6% OC43, 32.3% NL63, 16.0% HKU1 and 5.8% 229E. Hospitalization rates for HCoV-positive children with lower RTIs were 1.5 and 2.8 per 1,000 <5 and <1 years of age, respectively. The detection rate among controls was 9.4% (60/639). Co-detections occurred in 68.1% of the patients and 73.3% of the controls. In a logistic regression analysis, high HCoV genomic loads (cycle threshold <28 in PCR-analysis) were associated with RTIs (OR = 2.16, *P* = .032) adjusted for relevant factors.

Conclusions: HCoVs occurred in one out of 11 hospitalized children with RTIs and asymptomatic controls. A high HCoV genomic load was associated with RTI. HCoVs are associated with a substantial burden of RTIs in need of hospitalization.

Keywords: Human Coronaviruses, children, hospitalization rates, respiratory tract infections, asymptomatic controls

INTRODUCTION

Human Coronaviruses (HCoV) are commonly detected in nasopharyngeal aspirates (NPAs) from children with respiratory tract infections (RTIs). They were first described in the 1960s as agents of the common cold [1-3]. Recently, HCoV has obtained renewed interest, due to both more sensitive diagnostic methods and increased attention towards HCoV after the SARS outbreak in 2002, thereby resulting in the identification of new HCoV subtypes [4-7].

Six species of HCoV infects humans: OC43, 229E, SARS, NL63, HKU1 and MERS. While SARS and MERS are feared for their potential for severe illness and pandemics [8], the other subtypes have traditionally been associated with milder upper RTIs. In children, however, HCoV may also cause lower respiratory tract infections (LRTIs) in need of hospitalization [9-12], but only a few population-based reports have precisely estimated the risk of HCoV-associated hospitalizations [13-16].

OC43, NL63, 229E and HKU1 are distributed worldwide [17-19], and their detection frequency varies [15, 19-21]. Some studies found similar [21-23], or even lower [24], detection rates of HCoV among hospitalized children compared to controls. Nonetheless, long-term studies of HCoV are rare, and most previous studies lack the inclusion of asymptomatic controls. Hence, the significance of HCoV detections in children with LRTIs, the seasonality and the overall burden of HCoV in hospitalized children remains poorly defined.

To address these needs, we used data from a nine-year-long prospective population-based survey of children admitted to St. Olavs Hospital in Norway. Our primary aim was to determine the occurrence of HCoV detections in children hospitalized with RTI and the hospitalization incidence rates for HCoV-associated LRTIs in children. To help evaluate the role of HCoV in RTIs, we compared the presence and genomic loads of HCoVs between hospitalized children with RTIs and an asymptomatic control group.

METHODS

Study Setting

The study was conducted at the Children's Department at St. Olavs Hospital in Trondheim, Norway. The Department of Pediatrics is the sole pediatric reference center for approximately 59,000 children in Sør-Trøndelag County.

Study Population

From November 2006 to July 2015 we conducted a prospective surveillance study, enrolling all children admitted to the Children's Department at St. Olavs Hospital with symptoms and signs of RTIs. Most patients were enrolled during their stay at the hospital, and some were retrospectively included after hospital discharge. Children hospitalized <24 hours were further defined as outpatients.

Exclusion criteria were: 1) age over 16 years, 2) hospital-acquired RTIs, including newborns not dismissed from the hospital, 3) ongoing cytostatic and/or immune-suppressive treatment, and 4) a non-RTI primary infectious diagnosis. The same child could be included more times with different RTI episodes.

Children admitted to elective surgery from 2007 to 2015 were monthly recruited as the control group. Their caregivers were asked to confirm that they were asymptomatic for RTIs the previous two weeks. Moreover, children undergoing ear, nose or throat surgery were not included in the control group.

Caregivers and older children (>12 years) received both oral and written information about the study during their stay at the hospital. Written consent to participate was collected from most caregivers. Invitation letters were sent to the children and their caregivers after discharge if they took NPAs for clinical purposes, but had not been asked to participate in the study due to practical challenges. No response after two weeks was regarded as passive consent.

Clinical Investigation and Disease Classifications

All children with RTI were examined, diagnosed and treated by physicians in accordance with the hospital's routines. A physician or member of the study group recorded relevant study information before discharge, whereas for children included after discharge, the data was collected from medical records. Participants were divided in two main groups: upper RTIs and LRTIs. Upper RTIs included a diagnosis of rhinosinusitis, pharyngitis, tonsillitis, otitis media and acute laryngitis without signs of LRTIs. A LRTI was defined as the presence of dyspnea, signs of lower airway obstruction (wheezing, retractions), and/or a chest roentgenogram with positive results such as infiltrates, atelectasis and/or air trapping [25].

Laboratory Methods

Nasopharyngeal aspirates (NPAs) were routinely collected from all children, and placed into a universal virus transport medium without antibiotics. A total of 94% of all NPAs were sampled during the first two days of hospitalization. Clinical laboratory technicians also performed inhouse TaqMan real-time polymerase chain reaction (RT-PCR) tests to detect respiratory pathogens [9]. We analyzed for four subtypes of HCoV: OC43, NL63, 229E and HKU1. Thirteen other viruses were also routinely tested for: human adenovirus (HAdV), human bocavirus (HBoV), human enterovirus (HEV), human parechovirus (HPeV), human metapneumovirus (HMPV), influenza virus A and B (Flu A/B), parainfluenza virus (PIV) types 1-4, respiratory syncytial virus (RSV) and human rhinovirus (HRV). Semi-quantitative results were reported based on the cycle threshold value (Ct-value), with a high genomic load defined as a Ct-value <28, a medium load defined as a Ct-value of 28-<35 and a low load defined as a Ct-value 35-40. Lastly, a Ct-value >40 was regarded as a negative test.

Epidemiologic Year and Incidence Calculations

We defined an epidemiologic year from the beginning of August to the end of July in the following year. The annual hospitalization (incidence) rates were estimated based on: 1) HCoV detection rates for children hospitalized ≥24 hours with a LRTI from our survey, 2) statistics on a LRTI diagnosis in need of hospitalization from the hospital's Patient Administrative System (PAS), and 3) population data for Sør-Trøndelag County provided by Statistics Norway. In the PAS, a LRTI was defined as a main diagnosis (ICD-10 code) of pneumonia (J10.0, J11.0, J12.0-J12.9 and J13-J15), bronchitis (J20), bronchiolitis (J21), unspecified LRTI (J22) and/or asthma exacerbation (J45-J46). We were not able to exclude children hospitalized <24 hours in the PAS.

Statistical Analysis

Data was described with mean, median, interquartile range or percentages, as appropriate. Categorical data was analyzed with a Pearson's χ^2 test or a Fisher's exact test, and reported with odds ratios (OR). Continuous and not normally distributed data (age) was tested with a Mann-Whitney *U* test.

To determine the relation between HCoV and RTIs, we conducted unadjusted analyses on relevant pre-defined variables, including genomic load, season, co-detection of severe RTI-causing viruses, age, gender and high-risk condition such as chronic disease and/or premature birth). A multivariate logistic regression was performed on the significant variables extracted from the unadjusted analyses to help determine the independent association of each variable with RTIs. The strength of the associations was reported with ORs and 95% confidence intervals.

For all tests, a *P*-value < .05 was considered statistically significant, and all analyses were performed using IBM SPSS Statistics 24 or SigmaPlot 14.0 software.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REC) Central in 2006 (No: 4.2006.2289) and 2012 (No: 2012.10.42).

RESULTS

Occurrence of Human Coronaviruses

During a nine-year-long period from November 2006 to July 2015, we included 3,458 episodes of RTIs in hospitalized children and 639 controls. HCoV were detected in 9.1% (313 of 3,458) of the episodes in the patient group, and were the fifth most common viruses after HRV (58.2%), RSV (29.3%), HEV (11.3%) and PIV type 1-4 (9.1%). A total of 39.3% (123 of 313) of the children with a positive HCoV infection were outpatients.

The detection rate of HCoV in the control group was 9.4% (60 of 639), and HCoV were the sixth most commonly detected viruses after HRV (55.4%), HEV (23.8%), HPeV (11.0%), PIV type 1-4 (10.8%) and HBoV (10.0%).

Characteristics of Patients and Controls

The prevalence of HCoV was equal in both groups, although detection rates of HCoVs in cases and controls differed when stratified by age (supplementary table 1). Children with RTIs were younger (*P* = .001) and more likely to have a high-risk condition such as chronic diseases and/or premature birth (*P* = .046) (Table 1).

Among the HCoV-positive patients, 46.6% (146 of 313) were positive for OC43, 32.3% (101 of 313) for NL63, 16.0% (50 of 313) for HKU1 and 5.8% (18 of 313) for 229E. Two children were infected with both NL63 and 229E.

In the control group, 40.0% (24 of 60) were positive for OC43, 31.7% (19 of 60) for NL63, 16.7% (10 of 60) for HKU1 and 15.0% (9 of 60) for 229E. Two controls were positive for both NL63 and 229E.

Seasonal and Annual Variations of HCoV in Hospitalized Patients

HCoV was detected among patients in all nine years. The average detection rate was 34.8 detections per season, with a range from 18 in 2013/2014 to 60 in 2006/2007 (Figure 1).

Overall, the majority of HCoV detections (71.9%) occurred during the period from November through March, with an average of 51 detections each month. From April to October, the average monthly detection rate was 8.3. During the study period, most detections were in December, and there was only one detection in August.

The detection pattern of HCoV varied with subtypes and seasons. OC43 was the most frequently detected HCoV, and we found a high number of OC43 detections every second season. This was also true for NL63, with the exception of the 2008/2009 season. In high-detection seasons (excluding 2008/2009), the average rate was 26 detections per year for OC43 and 20 for NL63.

In low-detection years, the average detection rate was six detections yearly for OC43 and four for NL63 (excluding 2008/2009).

During a nine-year period, OC43 was detected in all months, but not for *every* month each year. This was not true for NL63, which was never detected from August through October. OC43 was detected before NL63 in each season.

HKU1 appeared with high numbers every second season, when detection rates for OC43 and NL63 were low. In the high-detection seasons, HKU1 had an average detection rate of 12 detections, and 88% of HKU1 detections appeared in the months from November to February.

229E was seldom detected, with an average of only three detections per year.

Co-detections among Patients and Controls

Among HCoV-positive patients, 31.9% had a single HCoV infection, 41.9% had two viruses (including those with both OC43 and 229E) and 26.2% had ≥3 viruses detected (Table 2). For the control group, the corresponding figures were 26.7% with a single HCoV detection, 28.3% with two viruses detected and 45% with 3≥ viruses detected (Supplementary Table 2). Hence, it was not more likely to have a single HCoV detection in the patient group compared to the control group (OR = 1.28, *P* = .53).

The most common co-detections in the patient group were HRV (24.9%), RSV (23.3%) and HEV (16.6%) (Table 2). In total, 36.7% had co-detections of viruses known to cause severe RTIs in need of hospitalization (RSV, HMPV, PIV type 1-3 and Flu A/B).

In the control group, the most common co-detections were HRV (43.3%), HEV (33.3%) and PIF 1-4 (20.0%), while the detection of viruses known to cause severe RTIs were rare in this group (Supplementary Table 2).

Hospitalized children with RTI and HCoV detection were more likely to have a co-detection with a severe RTI-causing virus (RSV, HMPV, PIV type 1-3 and Flu A/B) than the control group (OR = 5.2, *P* = < .001).

Comparison of HCoV Genomic Loads between Patients with RTIs and Asymptomatic Controls

A total of 43.5% of the children with RTIs had a high genomic load, 30.7% had a medium load and 25.9% had a low load. For the controls, the corresponding numbers were 28.3%, 36.7% and 35.0%, respectively.

HCoV-positive children with RTIs more often had a high genomic load compared to asymptomatic controls (OR = 1.94, *P* = .029) (Table 3). Among children with RTIs, a high genomic load was detected in 67.0% with a single HCoV detection, 24.3% with co-detections of severe RTI-causing viruses and 41.8% with co-detections of other viruses (*P* < .001). Patients with a sole HCoV detection were more likely to have a high genomic load of HCoV compared to patients with co-detections of severe RTI-causing viruses (OR = 6.3, *P* < .001). In contrast, there were no significant differences in genomic load between controls with single detections and controls with co-detections (OR = 1.21, *P* = 1.00).

The Relation between HCoV and RTIs

We investigated the relation between HCoV detection and RTIs in consideration of other factors in a multiple regression model. A high genomic load of HCoV was independently associated with RTIs (OR = 2.16, *P* = .032), and adjusted for the co-detection of severe RTI-causing viruses, age, gender and high-risk conditions (Table 3).

Hospitalization Rates

A total of 60.7% (190 of 313) of the HCoV-positive children with RTIs were hospitalized for more than 24 hours. In this group, 73.7% were diagnosed with a LRTI. From November 2006 to December 2015, the average yearly hospitalization rate of children with HCoV and LRTIs was 1.5 per 1,000 children less than five years of age, and 2.8 per 1,000 children less than one year of age (Table 4). The yearly hospitalization rates ranged from .5 to 3.2 per 1,000 children less than five years of age and .9 to 5.5 per 1,000 children less than one year of age (Table 4).

It is difficult to determine the real burden of HCoV due to influencing factors such as co-detections and genomic loads estimations. We therefore also calculated separate hospitalization rates for the detection of OC43 or NL63, including single infections and the detection of high genomic loads (Supplementary Table 3). For children less than five years of age, approximately one-third of the OC43 and NL63 detections had a high genomic load, with one-fifth single infections. Thus, the hospitalization rate for children <5 years of age with a high genomic load of OC43 was 3.0 per 10,000, and 1.6 for a high genomic load of NL63.

DISCUSSION

Main Findings

HCoV occurred in approximately one out of 11 hospitalized children with RTIs and controls during a nine-year-long period. The four investigated HCoV subtypes had different detection rates and different seasonal distributions. Although more than two-thirds in both groups had co-detections with other viruses, our data support that HCoV leads to a substantial burden of RTIs in need of hospitalization. The average hospitalization rate of children with LRTIs and HCoV detection was 1.5 per 1,000 children <5 years old, and 2.8 per 1,000 children <1 year old.

Seasonal Variations of HCoV Subtypes

Almost half of all HCoV detections were OC43 and one-third were NL63, whereas HKU1 and 229E appeared more seldom. All HCoV subtypes were primarily detected in wintertime from November through March, with some detections throughout the year. Our data verifies findings from studies in both the US and Europe, which reports the highest detection rates in the winter and spring seasons [10, 17, 18, 26-29]. Others have reported that in Asia, HCoV may peak during all parts of the year [19, 22, 30, 31]. Consequently, the seasonal circulation of HCoVs is possibly dissimilar in temperate and tropical regions [30].

In our study, OC43 and NL63 appeared in winter epidemics with clear biennial peaks, whereas HKU1 appeared in alternating winter outbreaks with low OC43 and NL63 activity. HKU1 was rarely detected outside outbreaks, and 229E only appeared sporadically. Djikman et al. diagnosed HCoV infections by serology, and observed a similar pattern [20]. On this basis, the authors hypothesized that cross-reacting antibodies may be induced during OC43 and NL63 infections, thereby explaining why other HCoV subtypes seldom have outbreaks at the same time, and the lower detection rates of HKU1 and 229E [20].

The Relation between HCoV and RTIs in Need of Hospitalization

Using PCR, the average detection rate of HCoV in hospitalized children with RTIs in the present study was 9.1%, varying with a factor of 3.3 between seasons. Previous studies of a shorter duration have reported HCoV detection rates with larger variations from 1 to 15% [15, 19-21]. We also found that the control group had a detection rate of similar magnitude (9.4%), as has been reported before [21, 23]. This finding may question whether HCoVs are the causal pathogen of RTIs when HCoVs are detected in nasopharyngeal aspirates. Another prominent finding was the high viral co-detection rates in more than two-thirds of the infected children, as well as in the controls. Previously, somewhat lower co-detection rates have been reported [10, 17, 18, 22, 30], but our finding might simply reflect the high number of virus types analyzed in our study. In the current study, children with RTIs were more likely to have a co-detection of RSV and other viruses known for their potential to cause severe RTIs, whereas controls more often had a co-detection of less pathogenic viruses. This finding might also question whether HCoV caused the present RTIs. However, we made three observations on the basis of genomic loads estimations which support that HCoV causes RTIs among hospitalized children. First, assuming that a high genomic load more than a low genomic load usually indicates an active infection, we found that children with RTIs were more likely to have a high HCoV genomic load than the controls. Second, children with a single HCoV infection were more likely to have a higher genomic load (67%), compared to those with a co-detection of rhinovirus and other less pathogenic viruses (41.8%), and those with co-detections of RSV and other viruses with the potential to cause severe RTIs (24.3%). van der Hoek et al. have previously published similar findings for HCoV subtype NL63 [16]. Finally, a high genomic load of HCoV was independently associated with RTIs in multiple logistic regression analyses, adjusted for severe viral co-detections and other confounder variables.

In the control group, HCoV genomic load did not differ between those with single- and co-detections. On the basis of this observation, we suggest that detections of low levels of nucleic-acids from HCoV in the controls are more likely to be traces from previous infections, rather than an expression of ongoing asymptomatic infections, for which we would have expected higher HCoV loads to be present. Unfortunately, serologic analyses were not available, and cultures are not helpful, as HCoV does not grow in conventional cell lines.

Hospitalization Rates of Children with HCoV and LRTIs

The average hospitalization rate of children with LRTIs and HCoV detection was 1.5 per 1,000 children <5 years old. Children <1 year had a higher rate, 2.8 per 1,000 children. These figures may be an overestimation due to the possible contribution of RSV and other co-detected viruses, but since the exact causal contribution of each co-detected virus is difficult to ascertain, we decided to report incidence rates based on the total number of HCoV positives. Our incidence rates were calculated only for lower RTIs, because upper RTIs are underreported in our hospital patient administrative system. Previously, only a few studies have reported hospitalization rates in HCoV-infected children, and this data is difficult to compare with ours [13-16]. On the basis of calculations in our dataset, we have recently published a somewhat higher hospitalization rate for HMPV compared to HCoV (1.9 LRTIs per 1,000 children <5 years old), and RSV appeared seven times more often (10.5 LRTIs per 1,000 children <5 years old) [25].

To give a more precise estimation of the burden of HCoV, we also reported on the LRTI hospitalization rates for detections with high genomic loads and single detections of OC43 and NL63. On the other hand, these figures may be underestimations, because the presence of other viruses or a low HCoV load cannot exclude a possible causal contribution by HCoVs. For children under five years of age, the hospitalization rates for a high genomic load of OC43 and NL63 infections were 3.0 and 1.6 per 10,000 children, respectively. In a comparable study over five consecutive years, van der Hoek et al. reported a somewhat higher hospitalization rate for NL63 (2.2 per 10,000 children <3 years old), even when they defined a NL63 infection as a single NL63 detection with high genomic loads (>10,000 copies/ml in nasopharyngeal aspirate) [16].

Limitations

The strengths of the present study are the population basis and prospective enrollment of children with infections from the same county in Norway over a nine-year-long period. It is also an advantage that during the entire study period we have used the same PCR tests for a high number of virus types, and the use of semi-quantitative genomic loads estimations. Although the cross-sectional design is not optimal, the inclusion of asymptomatic controls allowed us to study causal relations between HCoV and infection. The nasal swabs from the control group were sampled during anaesthesia, which might have resulted in higher viral detection rates. Age and gender differed among cases and controls, but was controlled for in the analyses.

Conclusion

Our nine-year-long population-based study show that the HCoV subtypes OC43, NL63, 229E and HKU1 appear in hospitalized Norwegian children with characteristic outbreak patterns, primarily in the wintertime. Although detection rates were equal between children with RTIs and controls, still our data support that HCoVs contribute to respiratory tract infections in hospitalized children.

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FOOTNOTES

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Potential conflicts of interests All authors declare that they have no commercial or other associations that might pose a conflict of interests.

Presentation of data on meetings Preliminary analyses have been presented at the European Society for Clinical Virology (ESCV) meeting, September 2017, Stresa, Italy. Abstract number 013 (poster).

FIGURE LEGENDS

Figure 1. Monthly Distribution of Human Coronavirus (HCoV) Subtypes in Nasopharyngeal Aspirates from Children Hospitalized with Respiratory Tract Infections from November 2006 to July 2015.

Gray shade represent the total number of HCoV-detections, with numbers at the Y-axis. Colored area represent HCoV subtypes OC43 (red), NL63 (blue), HKU1 (green) and 229E (orange).

Table 1. Characteristics of Children with Respiratory Tract Infections and Asymptomatic Controls with an Human Coronavirus Detection

	Children with HCoV, No. (%)[1]	
Characteristics	Patients (n = 313)	Controls (n = 60)
Age, median (IQR), mo	14.8 (4.9-27.3)	34.3 (22.8-64.4)
Age group		
<6 mo	89 (28.4)	1 (1.7)
6-11 mo	45 (14.4)	2 (3.3)
12-23 mo	89 (28.4)	12 (20.0)
24-59 mo	63 (20.1)	28 (46.7)
≥60 mo	27 (8.6)	17 (28.3)
Female	123 (39.3)	7 (11.7)
High-risk condition	90+ (29.2)	10 (16.7)
Premature birth (gestational age <36 wk)	52++ (17.0)	5 (8.3)
≥1 chronic disease[2]	58 (18.5)	6 (10.0)
Season		
Aug-Oct	12 (3.8)	6 (10.0)
Nov-Jan	173 (55.3)	27 (45.0)
Feb-Apr	105 (33.5)	21 (35.0)
May-Jul	23 (7.3)	6 (10.0)
RTI		
LRTI	44 (14.1)	
Combined LRTI and URTI	165 (52.7)	
URTI	104 (33.2)	

[1] Data represent No. (%) of children unless otherwise specified.

[2] Chronic disease: heart disease, neurologic disease and/or pulmonary disease.

+Missing data in 5 patients.

++Missing data in 8 patients.

Abbreviations: HCoV, Human Coronaviruses; RTI, Respiratory Tract Infection; No., number; IQR, Interquartile Range; mo, month; Ct, Cycle Threshold; LRTI, lower RTI; URTI, upper RTI.

Table 2. Virus Detections and Codetected Viruses in Human Coronaviruses-Positive Nasopharyngeal Aspirates from Children with Respiratory Tract Infections from 2007 to 2015.

	HCoV-detections, in total and after subtypes, No. (%)				
	Total HCoV (N= 313)	OC43 (n= 146)	NL63 (n= 101)	HKU1 (n= 50)	229E (n= 18)
Respiratory viruses					
Rhinovirus	78 (25.0)	35 (24.0)	21 (20.8)	16 (32.0)	7 (38.9)
Respiratory syncytical virus	73 (23.4)	33 (22.7)	28 (27.8)	10 (20.0)	2 (11.2)
Enterovirus	52 (16.7)	23 (15.8)	14 (13.9)	12 (24.0)	4 (22.3)
Human bocavirus	35 (11.2)	17 (11.7)	10 (10.0)	6 (12.0)	2 (11.2)
Parainfluenza virus types 1-4	31 (10.0)	12 (8.3)	9 (9.0)	7 (14.0)	3 (16.7)
Human parechovirus	22 (7.1)	9 (6.2)	7 (7.0)	5 (10.0)	1 (5.6)
Adenovirus	20 (6.4)	13 (9.0)	4 (4.0)	2 (4.0)	1 (5.6)
Human metapneumovirus	15 (4.8)	6 (4.2)	2 (2.0)	6 (12.0)	1 (5.6)
Influenzavirus A/B	8 (2.6)	3 (2.1)	5 (5.0)		
No. of detections					
Single HCoV-detection	100 (32)	50 (34.3)	32 (31.7)	12 (24.0)	6 (33.4)
HCoV + 1 codetection	132 (42.2)	60 (41.1)	45 (44.6)	22 (44.0)	6 (33.4)
HCoV + ≥2 codetections	81 (25.9)	36 (24.7)	24 (23.8)	16 (32.0)	6 (33.4)

HCoV, Human Coronaviruses.

Table 3. Relations between HCoV and RTI, comparing children with RTI (N= 313) and asymptomatic controls (N= 60)

	Univariate analysis			**Adjusted analysis**		
	OR	**(95% CI)**	***p*-value**	**OR**	**(95% CI)**	***p*-value**
HCoV viral load						
Ct-value <28	1.94	(1.06, 3.57)	0.029	2.16	(1.07, 4.37)	0.032
Ct-value >28 (reference)						
Season						
Aug-Oct	0.52	(0.14, 1.97)	ns			
Nov-Jan	1.67	(0.62, 4.48)	ns			
Feb-Apr	1.30	(0.47, 3.59)	ns			
May-Jul (reference)						
Co-detection severe virus[1]	5.23	(2.18, 12.5)	<0.001	4.59	(1.78, 11.9)	0.002
Age						
0-2 y	9.36	(4.20, 20.9)	<0.001	8.36	(3.39, 20.6)	<0.001
2-5 y	1.41	(0.67, 3.01)	ns	1.25	(0.53, 2.97)	ns
> 5 y (reference)						
Female	4.90	(2.16, 11.1)	<0.001	4.22	(1.76, 10.1)	0.001
High-risk condition[2]	2.06	(1.00, 4.25)	0.046	3.44	(1.51, 7.80)	0.003

Variables with *p*-value < 0.05 in the univariate analysis were included in the multivariate analysis.

[1] Includes Respiratory syncytial virus, Human metapneumovirus, Influenza virus type A and B, and Parainfluenza virus types 1-3.

[2] High-risk condition: heart disease, neurologic disease and pulmonary disease.

Abbreviations: RTI, respiratory tract infection; HCoV, Human coronaviruses; OR, odds ratios; CI, confidence interval; Ct, cycle threshold; y, year(s).

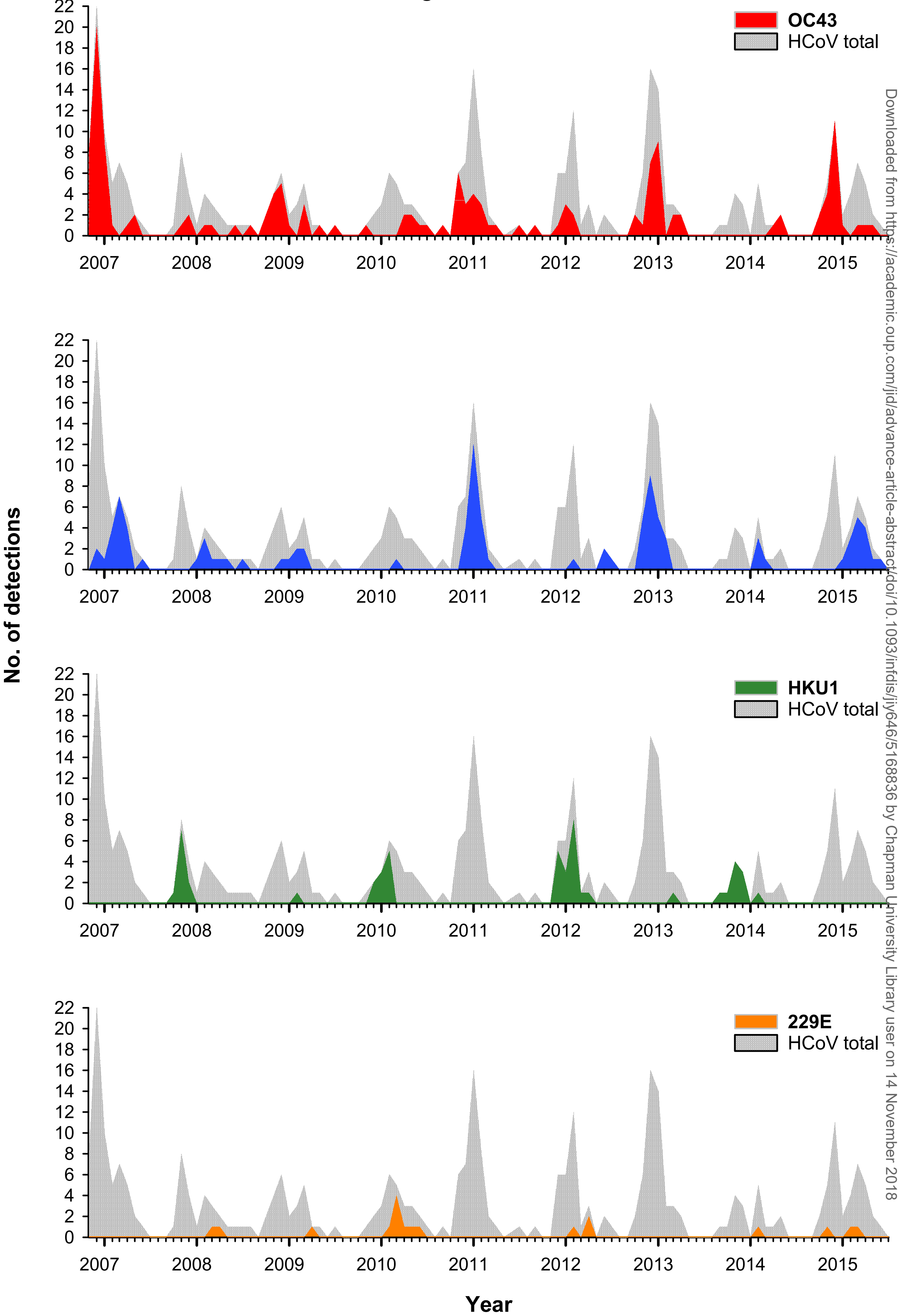
Table 4. Hospitalization* Incidence Rates in Children with LRTI and HCoV detection, by Age and Season

	Hospitalization per 1,000 Children with LRTI				
Seasons	**0-11 mo**	**12-23 mo**	**24-59 mo**	**5-16 y**	**0-59 mo**
2006-2007	5.5	3.6	1.0	0.1	2.5
2007-2008	1.8		0.2		0.5
2008-2009	2.7	2.8		0.2	1.2
2009-2010	1.7	2.0	0.1		0.8
2010-2011	1.7	2.5	0.6	0.1	1.1
2011-2012	1.5	4.3	0.2		1.3
2012-2013	4.6	3.9	1.3	0.1	2.4
2013-2014	0.9	0.5	0.5		0.6
2014-2015	4.9	4.8	2.4	0.1	3.2
Mean	2.8	2.7	0.7	0.1	1.5
(95% CI)	(1.7, 3.9)	(1.7, 3.7)	(0.2, 1.2)	(0.0, 0.1)	(0.9, 2.1)

CI, Confidence Interval; HCoV, Human Coronaviruses; LRTI, Lower Respiratory Tract Infection; mo, Months; y, Years.

*Children hospitalized ≥24 hours.

Figure 1


OC43
HCoV total
HKU1
HCoV total
229E
HCoV total
No. of detections
22
20
18
16
14
12
10
8
6
4
2
0
2007
2008
2009
2010
2011
2012
2013
2014
2015
Year