

# Severity and Outcome Associated With Human Coronavirus OC43 Infections Among Children

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**Background:** Human coronaviruses are known causes of the common cold. Subtype OC43 (HCoV-OC43) is the more prevalent human coronavirus in several parts of the world. Recent studies have suggested these viruses can cause severe lower respiratory tract illnesses in children.

**Objective:** We sought to determine the epidemiology, clinical characteristics, outcomes and severity of illness associated with HCoV-OC43 infections in a pediatric population.

**Methods:** We retrospectively identified patients with positive HCoV-OC43 respiratory specimens between December 2009 and December 2010 in a pediatric hospital in Montreal. Each case was compared with 2 controls (tested negative for HCoV-OC43). Clinical characteristics, underlying conditions, outcomes and disease severity were reviewed for both groups. Risk factors and independent predictors of disease severity were also assessed.

**Results:** During the study period, 68 patients were identified as infected with HCoV-OC43 (1.8% of specimens tested, 4.2% of all respiratory viruses identified by reverse transcription polymerase chain reaction). The majority (77%) occurred in November 2010. Chief symptoms of HCoV-OC43 infection were fever (in 78% of cases), cough (67%) and upper respiratory tract infection symptoms (57%). HCoV-OC43 infection was not more frequent in children with preexisting conditions. Coinfection with other respiratory viruses was associated with lower respiratory tract infections in HCoV-OC43-infected cases, but did not lead to increased rates of hospitalization, admission to intensive care unit or death.

**Conclusions:** In our population, HCoV-OC43 infections generally caused upper respiratory tract infection, but can be associated with lower respiratory tract infection especially in those coinfecting with other respiratory viruses.

**Key Words:** coronavirus, HCoV-OC43, severity, risk factors, children

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Coronaviruses were first discovered in the 1960s as the cause of self-limited upper respiratory tract infections (URTIs) in humans and a wide variety of diseases in other mammals and in birds. The identification of a novel coronavirus as the etiologic agent of severe acute respiratory syndrome in late 2002 led to concerns that these pathogens may potentially cause more severe disease than previously appreciated, including involvement of other organ systems.<sup>1</sup> There are now 5 coronaviruses recognized as human pathogens (HCoV): HCoV-OC 43, HCoV-229E, HCoV-

HKU1, HCoV-NL63 and severe acute respiratory syndrome-CoV. Although the recently discovered HCoV-NL63 and HCoV-HKU1 are detected in only 5% of symptomatic patients tested for respiratory viral agents,<sup>2</sup> HCoV-OC43 and HCoV-229E are thought to account for about 15% of URTI overall, but can contribute to as many as 35% of URTI during times of peak viral activity.<sup>3–5</sup> A recent study has shown that the majority of children seroconvert to human coronaviruses early in childhood (before 2 years of age) and that HCoV-OC43 appears to be the most prevalent.<sup>6</sup> Additionally, some studies are suggesting that HCoV may play a role in lower respiratory tract infections (LRTIs) and cause hospitalizations: HCoV have been detected in respiratory specimens of 14% of children younger than 2 years admitted to hospital with respiratory infections in the Netherlands,<sup>6</sup> and accounted for 4.4% of all pediatric admissions for respiratory tract infection in Hong Kong.<sup>7</sup> In other studies, HCoV infections were associated with lower respiratory tract disease requiring supplemental oxygen, mechanical ventilation and intensive care unit (ICU) admission, but severe disease appeared to be more frequent in cases coinfecting with other respiratory pathogens, and among children with comorbidities or born prematurely.<sup>8–10</sup> HCoV-OC43 has also been associated with outbreaks of severe respiratory diseases in children and the elderly,<sup>11–13</sup> but several other studies, which have included asymptomatic controls for comparison, have questioned whether HCoV plays any role in severe illness and hospitalization.<sup>14–17</sup>

In our institution, after the implementation of a multiplex reverse transcriptase polymerase chain reaction (RT-PCR) respiratory virus assay in September 2009, we noted that HCoV-OC43 accounted for 4.7% of all respiratory viruses identified in respiratory specimens during a one-year period, with a peak incidence in the fall months of October and November. The objective of this study was to use retrospective data to assess the epidemiology, clinical characteristics and severity of HCoV-OC43 infections in children, and to assess risk factors associated with hospitalization and severe disease in infected children, in comparison with non-HCoV-OC43-infected children presenting to the same institution during the study period.

## METHODS

### Study Setting

The Montreal Children's Hospital is a tertiary-care pediatric hospital with a medical and surgical emergency department that serves the Island of Montreal and its surroundings. On average, 200 children are seen daily in the emergency department, with a peak during winter months (January to March). Approximately 60% of these children are under 5 years of age, and 50% present for a respiratory illness. Patients with multiple comorbidities including malignancy, renal disease and congenital malformations are also treated at this hospital.

### Study Design

This was a retrospective case-control study, conducted on patients presenting to the Montreal Children's Hospital (Emergency

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Department, outpatient clinics or wards) between December 2009 and December 2010 and for whom testing for respiratory viruses was performed. Cases and controls were retrospectively identified from the microbiology laboratory database.

Cases were children who had a respiratory specimen (nasopharyngeal swab, nasopharyngeal aspirate, bronchoalveolar lavage or endotracheal secretions) that tested positive for HCoV-OC43 by RT-PCR. Study subjects were counted only once, even if they presented to hospital multiple times or had several specimens positive for HCoV-OC43.

Controls were children who were tested for respiratory viruses by RT-PCR but tested negative for HCoV-OC43 (but could be positive for other respiratory viruses). For each case, 2 controls tested for respiratory viruses within a 2-week period were randomly selected. Signs or symptoms of febrile or respiratory illness were not required for inclusion in the study.

## Variables and Definitions

Data were abstracted from medical and laboratory records using a standardized form. For each study patient, we obtained data on: patient demographics, preexisting conditions, presenting complaints, signs and symptoms, radiographic findings, microbiological results including the presence of other respiratory viruses by RT-PCR (influenza A and B, respiratory syncytial virus, parainfluenza 1–3, HCoV-229E, adenovirus, enterovirus/rhinovirus, human metapneumovirus [hMPV]), use of antivirals and antibiotics, use of bronchodilators, supplemental oxygen needs, ventilator requirements, admission to hospital, duration of hospitalization, admission to ICU and death. Preexisting diseases or conditions were categorized as prematurity, hematologic (including malignancy), sickle cell disease and chronic pulmonary or cardiac conditions. Data were extracted by 1 investigator, and completed data collection sheets were then reviewed with the senior author.

Principal diagnosis was classified as URTI, LRTI or pneumonia based on the treating physician's assessment on presentation to the emergency department, or on main diagnosis at admission based on clinical evaluation and investigations. Presence of apnoea, hypoxia or respiratory distress was indicative of LRTI, and radiographic evidence (infiltrates or consolidation) was required for a classification of pneumonia.

A symptom score, adapted from the Canadian Acute Respiratory Illness and Flu Scales,<sup>18</sup> was also used to compare both groups. This scoring system is based on a combination of 5 clinical symptoms (cough, rhinorrhea, headache, vomiting and fever), each worth 1 point for a maximal severity score of 5.

## Ethics

Approval from the Hospital Research Ethics Board was obtained to review patients' charts.

## Data Analysis

We used descriptive statistics to compare clinical characteristics between HCoV-OC43–infected children and controls. For continuous variables, medians and standard deviations were calculated. Categorical data were analyzed using Pearson and Fisher exact tests. Using logistic regression, crude odds ratios (ORs) and 95% confidence intervals (CIs) were first calculated to determine the risk of LRTI, admission and antibiotic use associated with HCoV-OC43. A multivariate analysis using logistic regression was then performed adjusting for 2 predictor variables: presence of underlying conditions and coinfection with other viruses. Two different models were fitted for the following dependent variables: risk of LRTI and risk of admission. These predictor variables were considered significant when their respective multivariate adjusted

OR 95% CI did not include 1. All analyses were done using SAS (SAS v9.2, SAS institute, Cary NC).

## RESULTS

### Epidemiology of HCoV-OC43

During the study period (December 2009 to December 2010), a total of 3847 pediatric respiratory specimens were tested by RT-PCR, of which, 1615 specimens were positive for at least 1 respiratory virus (42% positive). HCoV-OC43 was detected in 68 cases (1.8% of all specimens) and accounted for 4.2% of respiratory viruses detected that year. Of these cases, HCoV-OC43 was the only virus detected in 46 (68%) patients, whereas other respiratory viruses were detected in the remaining. Fifty-two (77%) of the HCoV-OC43 infections occurred during the month of November 2010.

### Demographic Characteristics and Preexisting Conditions

We compared 68 cases of HCoV-OC43–infected children with 136 controls. Cases were on average younger than controls (mean age of 1.04 years compared with 2.28 years for controls,  $P=0.001$ ), but the majority of patients in both groups were younger than 18 months of age (82% of the HCoV-OC43–infected children and 68% of the controls). There were also more male patients in both groups. Preexisting pulmonary, cardiac and hematologic conditions were less frequent in HCoV-OC43 cases than in the control group, but these differences were not statistically significant (Table 1).

### Comparisons of Clinical Features

Fever, cough and URTI symptoms were the most common clinical manifestations associated with HCoV-OC43 infection, and occurred with greater frequency in cases compared with controls. A little over one third of cases presented with gastrointestinal symptom. Pneumonia and febrile seizures were relatively rare occurrences in both groups. Overall, none of the differences in clinical features were statistically significant (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B438>).

### Other Viral Infections

Infection with other respiratory viruses was described in both groups: 22 (32%) of the cases were coinfecting with 1 or more other respiratory viruses, whereas 1 or more viruses were detected

**TABLE 1.** Baseline Characteristics of HCoV-OC43–infected Cases and Controls

Baseline Characteristics	HCoV-OC43 Infected N = 68 n (%)	Controls N = 136 n (%)	OR (95% CI)
Mean age in yrs (SD)	1.04 (1.36)	2.28 (3.88)	
Median age in yrs (IQR)	0.62 (0.2–1.1)	0.77 (0.1–1.9)	—
Age <18 mo	56 (82.4)	93 (68.4)	
Male, no. (%)	36 (53)	77 (57)	—
Prematurity	9 (13.2)	17 (12.5)	1.07 (0.45–2.54)
Hematologic disease	6 (8.8)	20 (14.7)	0.56 (0.21–1.47)
Sickle cell disease	3 (4.4)	4 (2.9)	1.52 (0.33–7.00)
Cardiac disease	8 (11.8)	22 (16.2)	0.69 (0.29–1.65)
Pulmonary disease	4 (5.9)	20 (14.7)	0.36 (0.12–1.11)

SD indicates standard deviation; IQR, interquartile range.

**TABLE 2.** Infection With Other Respiratory Viruses in HCoV-OC43–infected Cases and Controls

Viruses Detected by RT-PCR	HCoV-OC43–infected Cases N = 68 n (%)	Controls N = 136 n (%)
Adenovirus	12 (17.6)	7 (5.1)
Rhinovirus/enterovirus	6 (8.8)	30 (22.1)
Respiratory syncytial virus (A, B)	2 (2.9)	15 (11.0)
Parainfluenza (1–3)	3 (4.4)	3 (2.2)
Influenza (A, B)	0 (0)	3 (2.2)
HCoV-229E	0 (0)	0 (0)
hMPV	0 (0)	0 (0)
Overall*	22 (32.4)	62 (45.6)

\*Patients in which a respiratory virus other than HCoV-OC43 was detected by RT-PCR.

in 62 (46%) of the controls. Three HCoV-OC43 cases were coinfecting with 2 other respiratory viruses, whereas the remainder were coinfecting with only 1 other virus. Among cases, adenovirus was most frequently involved in coinfections, whereas rhinovirus/enterovirus were most frequently detected among controls (Table 2). Because the majority of the HCoV-OC43 infections occurred during the month of November, influenza and hMPV, which are more predominant during the winter months, were rarely detected among our cases and controls.

### Clinical Course and Outcomes

Overall, 20 (29.4%) patients in the HCoV-OC43 group met the criteria for LRTI, a proportion similar to controls (28.7%). Among the HCoV-OC43–infected cases, only 25 (36.8%) were hospitalized compared with 81 (59.6%) patients in the control group. This difference in hospitalization rates remained significant after stratifying by age younger than 18 months: controls were more likely to be hospitalized than cases irrespective of their age. Furthermore, the mean duration of hospital stay was shorter for HCoV-OC43–infected children (median 2 versus 6 days in the control group; the mean duration of hospitalization for the HCoV-OC43–infected group was 23.6 days, and 43.2 days for the controls).

A lower proportion of HCoV-OC43–infected cases, particularly in those younger than 18 months, received antibiotics (30.8% of cases overall versus 50% of controls; 25% of the cases

younger than 18 months versus 45% of the controls younger than 18 months). This difference was statistically significant, even after stratifying by age younger than 18 months.

There were fewer admissions to the ICU among cases compared with controls, and fewer deaths. In the HCoV-OC43–infected group, 7 (10.3%) patients were admitted to the ICU. Only one of these patients required admission for a complication of his viral illness (febrile seizure) whereas the others were admitted with, and not because of, HCoV-OC43. These patients had diagnoses of aspiration pneumonia, necrotizing enterocolitis, peritonitis, prematurity, herpetic encephalitis or were postcardiac surgery, respectively. There was 1 death in our cohort of HCoV-OC43–infected patients: the patient died from severe respiratory distress due to aspiration pneumonia.

Among the controls, 29 (21.3%) were admitted to the ICU. Of those, 3 were admitted for severe respiratory illness secondary to a viral infection (1 patient was infected with influenza H1N1 pandemic strain, and 2 patients were infected with enterovirus/rhinovirus). Other reasons for admission to the ICU in this group included aspiration or bacterial pneumonia, cardiac surgeries or cardiopulmonary malformations.

### Adjusted Analyses Comparing HCoV-OC43–infected Patients and Controls

In the multivariate analysis, presence of other coinfecting respiratory viruses in the HCoV-OC43–infected group appeared to be an independent predictor for the development of LRTI (OR: 2.04; 95% CI: 1.08–3.83). The only independent predictor for hospitalization was presence of underlying comorbidities (OR: 3.68; 95% CI: 1.91–7.10). But even after adjusting for underlying comorbidity and presence of coinfection, HCoV-OC43–infected cases were less likely than controls to be admitted (OR: 0.40, 95% CI: 0.21–0.76 and OR: 0.77, 95% CI: 0.42–1.41, respectively) (Table 3).

### DISCUSSION

Human coronaviruses have been associated with respiratory illnesses ranging from the common cold to high morbidity outcomes such as pneumonia and bronchiolitis. This study was designed to determine the epidemiology, the clinical features, the severity of illness and outcomes associated with HCoV-OC43 infections, the more prevalent of the human coronaviruses in Montreal, in a pediatric population.

**TABLE 3.** Outcomes in HCoV-OC43–infected Cases in Comparison to Controls

Outcomes	HCoV-OC43 Infected		Controls No. (%)		Crude OR (95% CI)	Crude OR (95% CI) <18 mo	Adjusted OR Adjusted for Comorbidities (95% CI)	Adjusted OR Adjusted for Coinfections (95% CI)
LRTI	20 (29.4)	17 (30.4)	39 (28.7)	29 (31.2)	1.04 (0.55–1.97)	0.96 (0.47–1.97)	0.98 (0.52–1.88)	2.04 (1.08–3.83)
Hospitalization	25 (36.4)	20 (35.7)	81 (59.6)	49 (52.7)	0.40 (0.22–0.72)	0.50 (0.25–0.99)	0.4 (0.21–0.76)	0.77 (0.42–1.41)
Length of hospitalization, median days (IQR)	2 (1.5–3.5)	2 (1–4)	6 (3–22)	7 (3–39)	—	—	—	—
Antibiotic use	21 (30.8)	14 (25.0)	68 (50.0)	42 (45.2)	0.45 (0.24–0.83)	0.40 (0.20–0.84)	—	—
Admission to ICU	7 (10.3)	6 (10.7)	29 (21.3)	20 (21.5)	0.42 (0.18–1.02)	0.44 (0.16–1.17)	—	—
Mortality	1 (1.5)	1 (1.8)	4 (2.9)	0 (0)	0.49 (0.05–4.49)	—	—	—

None of the comparisons between cases and controls in terms of LRTI, admission to ICU, duration of hospitalization and mortality reached statistical significance. IQR indicates interquartile range.

Previous published studies have focused on clinical and epidemiological descriptions of HCoV infections, or performed comparisons of HCoV-OC43 cases with asymptomatic controls. We compared HCoV-OC43-infected patients with symptomatic controls (with respiratory complaints) presenting to the hospital during a 1-year period, in order to directly assess the impact of HCoV-OC43 infections and the role of preexisting comorbidities and coinfections with other respiratory viral pathogens on the severity of illness.

We found that the great majority of children infected with HCoV-OC43 were younger than controls, and were more likely to present with higher fevers and symptoms of URTI. This is in agreement with published studies, which have shown that HCoV-OC43 infections tend to occur before 2 years of age and generally result in a febrile acute respiratory self-limited infection.<sup>6,16,19</sup> Of our HCoV-OC43-infected cases, 30% developed a LRTI, a proportion that was similar to the control group. However, after adjusting for coinfection with other respiratory viral pathogens, the risk of LRTI was increased in HCoV-OC43 cases compared with controls. This indicates that HCoV-OC43 infections involving other respiratory pathogens lead to more severe illness than HCoV-OC43 alone, in children. This is in agreement with several case reports and a recent study comparing hospitalized children with asymptomatic controls, in which patients infected with HCoV alone were less ill than those infected with either multiple pathogens or with viruses typically considered more virulent, such as influenza, respiratory syncytial virus and hMPV.<sup>16,20</sup>

About one third of our cases were coinfecting with at least 1 other respiratory virus, adenovirus being the most frequently detected other virus during the HCoV-OC43 season. The rate of coinfections is similar to that described in a recent study conducted in Scotland, in which other viral pathogens were detected in 42% of HCoV-OC43 infections.<sup>21</sup> Among our controls, 46% were infected with at least 1 respiratory virus, the most frequently detected being rhinovirus/enterovirus followed by respiratory syncytial virus.

In our study, fewer patients infected with HCoV-OC43 required hospitalization compared with controls (37% versus 60%, respectively), a statistically significant difference. Admitted cases also had shorter hospitalizations, on average, than controls. Only a minority of patients infected with HCoV-OC43 required ICU care, and most of these had multiple and severe comorbidities that prompted their admission. Even after adjusting for potential confounding variables such as preexisting conditions and coinfections with other respiratory viruses, we note that infection with HCoV-OC43 is not a significant risk factor for hospitalization nor for ICU admission, and that our controls were overall sicker than HCoV-OC43-infected cases. In the population studied, the rates of hospitalization were higher and the length of hospital stays were longer for both groups, than what has been described in other studies.<sup>10</sup> These differences probably reflect the fact that our institution is a tertiary-care centre providing services not only to a general pediatric population but also to children with multiple underlying illnesses including malignancies.

HCoV-OC43 was detected in nearly 2% of all specimens tested by RT-PCR and accounted for over 4% of all respiratory viruses detected during the study period, indicating this virus is more prevalent in Montreal than either Parainfluenza 1 or Parainfluenza 2. Previous reports have suggested that HCoV-OC43 emerges in the fall and peaks in the winter (late summer in the southern hemisphere).<sup>16,19,21–23</sup> In our setting, however, a significant proportion of the HCoV-OC43 infections occurred in November 2010 suggestive of a possible epidemic cluster in our population during that month, or a fall seasonality for this virus. From analysis of the epidemiological data for 2011 to 2012

(unpublished observations), it does indeed appear that HCoV-OC43 peaks in the late fall in Montreal, and not in the winter as previously expected.

The limitations of this study include the fact that our institution's patient population may not be reflective of the general pediatric population, and that our study is retrospective, with collection of information based on available data in medical records. Sample sizes were sometimes too small to permit robust stratification upon several factors. However, our study provides a specific comparison of HCoV-OC43 infections with symptomatic controls presenting with respiratory syndromes, rather than with asymptomatic controls as has been done in several other studies.

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