

# Coronavirus Causes Lower Respiratory Tract Infections Less Frequently Than RSV in Hospitalized Norwegian Children

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**Background:** We have described occurrence and clinical manifestations of human coronaviruses (HCoV) in hospitalized Norwegian children with respiratory tract infection (RTI) and compared them with a group of respiratory syncytial virus (RSV)-infected children.

**Methods and Population:** We used in-house TaqMan multiplex real-time polymerase chain reaction to test nasopharyngeal samples from 536 RTI episodes in 452 children who were admitted during the 2006–2007 winter. Twenty-one viruses, including HCoV-OC43, HCoV-NL63, HCoV-229E, HCoV-HKU1, and RSV were tested. The amount of viral nucleic acid was recorded semiquantitatively based on the cycle threshold value.

**Results:** A total of 665 positive polymerase chain reaction tests were recorded in 536 nasopharyngeal specimens. Coronavirus was found in 68 (12.7%): HCoV-OC43,  $n = 44$  (8.2%), and HCoV-NL63,  $n = 24$  (4.5%). Only RSV and rhinovirus were detected more frequently. Neither HCoV-229E nor HCoV-HKU1 was detected. Among children with HCoV-OC43, 73.0% tested positive for at least one other virus, compared with 41.2% with HCoV-NL63 and 40.3% with RSV ( $P = 0.03$  and  $P < 0.01$ , respectively). Children with HCoV-OC43 and HCoV-NL63 were older than children with RSV (median age, 19 vs. 10 months,  $P = 0.01$ ). Lower respiratory tract infection (LRTI) was half as common in children with HCoV-OC43 (48.6%) and HCoV-NL63 (47.1%) as in children with RSV (82.3%) (both  $P < 0.01$ ). After adjusting for age, chronic disease, LRTI, and co-detection of other viruses in a multiple logistic regression analysis, HCoV was associated with a shorter fever period and shorter hospitalization time than RSV.

**Conclusions:** HCoV-OC43 and HCoV-NL63 are common among hospitalized Norwegian children with RTI. Children with HCoV-OC43 and HCoV-NL63 have LRTI less frequently and may need a shorter hospital stay than children with RSV.

**Key Words:** coronavirus, RSV, respiratory tract infection, children

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Two human coronaviruses, HCoV-229E and HCoV-OC43, have been known as causes of the common cold since the 1960s.<sup>1–3</sup> The discovery of coronavirus as the causative agent for SARS,<sup>4,5</sup> has led to renewed interest in coronavirus. Shortly after the severe acute respiratory syndrome epidemic, 2 more coronaviruses were identified. HCoV-NL63 was first detected in 2003 by van der Hoek

et al<sup>6</sup> in a 7-month-old girl with bronchiolitis, and shortly after by Fouchier et al<sup>7</sup> in an 8-month-old boy with pneumonia. In 2005, another coronavirus, HCoV-HKU1, was isolated by Woo et al.<sup>8</sup>

Coronaviruses in humans have been detected worldwide,<sup>9–13</sup> and they are likely to have a seasonal distribution.<sup>9,14–18</sup> The proportion of respiratory tract infections caused by coronavirus vary from year to year.<sup>14,15,19,20</sup> In children, coronaviruses may cause asymptomatic infections and upper respiratory tract infections (URTI),<sup>11,21,22</sup> while their contribution to lower respiratory tract infection (LRTI) is not clear. However, using banked nasal secretions collected during a 20-year-long period in the United States, human coronaviruses, in particular OC43 and NL63, were detected in 8.4% of nonhospitalized children with LRTI, and in 4.7% with URTI.<sup>23</sup> Among hospitalized children, laryngitis has been reported, in particular, in association with HCoV-NL63,<sup>11,17,24</sup> while bronchiolitis and pneumonia have been reported at varying frequencies in children with HCoV-NL63 and OC43.<sup>17,18</sup>

We have studied human coronavirus infections in Norwegian children. We report clinical and virologic findings of 68 coronavirus-infected children who were admitted to a hospital during the winter of 2006 to 2007, and compare with a group of human respiratory syncytial virus (RSV)-infected children who were hospitalized during the same period. Our aims were to describe occurrence and clinical manifestations, and to compare severity of coronavirus and RSV infections.

## MATERIALS AND METHODS

### Study Population

The study was performed at the Departments of Pediatrics and Medical Microbiology, St Olavs University Hospital of Trondheim, Norway. The Department of Pediatrics provides emergency care for a population of approximately 58,000 children aged <16 years, of whom 18,000 are less than 5 years of age (Statistics Norway, 2010). From November 13, 2006 to June 15, 2007, 536 episodes of respiratory tract infection (RTI) in 452 children were included in the study. Median age of the children was 18 months (range, 3 days–16 years).

### Clinical Investigations and Diagnostic Criteria

The patients were examined, diagnosed, and treated routinely at the discretion of medical doctors. We extracted clinical information and laboratory data from the medical records to classify the children.

LRTI was diagnosed as the presence of characteristic manifestations of bronchiolitis, bronchitis, asthma exacerbation, or pneumonia. Bronchiolitis was diagnosed in children  $\leq 2$  years with (1) tachypnea, (2) signs of lower airway obstruction such as wheezing and retractions, and (3) either a normal radiogram or a radiogram with air trapping/hyperinflation, perihilar infiltrates, or atelectasis. Bronchitis was diagnosed in children  $> 2$  years with (1) tachypnea, (2) signs of lower airway obstruction, and (3) either a normal radiogram or a radiogram with air trapping/hyperinflation, perihilar infiltrates, or atelectasis. Asthma exacerbation was diagnosed in patients with (1) tachypnea, (2) signs of lower airway

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obstruction, and (3) either a current asthma diagnosis, 2 or more previous episodes of lower airway obstruction, or atopic disease. Pneumonia was diagnosed in patients with (1) tachypnea, (2) typical clinical findings such as crepitations, blasting breath, and muffled or bronchial respiratory sound, and (3) a radiogram with local infiltrates, consolidation, or pleura effusion. URTI was diagnosed in patients without manifestations from the lower respiratory tract, but with the presence of characteristic manifestations of rhinopharyngitis, tonsillitis, otitis media, or acute laryngitis.

### Laboratory Investigations

Nasopharyngeal aspirates were collected on a conventional virus transport medium without antibiotics, and viral nucleic acids were extracted from 200  $\mu$ L samples by Boom technology using NucliSENS easyMAG extractor (bioMérieux).<sup>25</sup> cDNA was synthesized using reverse transcription and random primers. Detection of viral pathogens was carried out using in-house TaqMan real-time polymerase chain reaction (PCR) assays and semiquantitative results were reported based on the Ct value (cycle threshold value). A high viral load was defined as a Ct value  $<30$ , and a low viral load as a Ct value  $\geq 30$ . The HCoV-229E real-time PCR was based on assays published by van Elden et al,<sup>26</sup> and a multiplex assay was used for the detection of HCoV-OC43<sup>26</sup> and HCoV-NL63.<sup>7</sup> Multiplex PCR tests for RSV (target: nucleocapsid, not published) and rhinovirus<sup>27</sup> were also performed. In addition, real-time assays were carried out for the following viruses: bocavirus,<sup>28</sup> human metapneumovirus,<sup>29</sup> enterovirus (target: '5-UTR, not published), adenovirus,<sup>30</sup> influenza virus A<sup>31</sup> and B,<sup>32</sup> and parainfluenza virus 1–3.<sup>33</sup> In addition, real-time PCR assays for Epstein-Barr virus (target: BamHI-fragment, not published), cytomegalovirus (target: DNA polymerase, not published), herpes simplex virus 1 and 2,<sup>34</sup> human herpesvirus 6,<sup>35</sup> and parainfluenza virus 4<sup>36</sup> were performed until May 21, 2007. Conventional viral cultures were performed as well. In 2010, 330 available nasopharyngeal samples (RNA stored at  $-80^{\circ}\text{C}$ ) were tested by a real-time PCR for the detection of HCoV-HKU1.<sup>19</sup>

### Data Analysis

Categorical variables were compared with the Pearson  $\chi^2$  test or the 2-tailed Fisher exact test. Continuous and nearly normal

distributed variables were analyzed with the Student *t* test or the analysis of variance test, and nonparametric variables were compared by use of either Mann-Whitney *U* or Kruskal-Wallis tests. Multiple logistic regression analyses were used to compare severity of HCoV and RSV infection. We entered duration of hospital stay, duration of oxygen treatment, and fever as independent variables, and adjusted for potentially confounding factors (age, chronic disease, LRTI, and presence of codetected viruses). The strength of the associations was expressed by the odds ratio (OR) with 95% confidence intervals (CI), and corresponding *P* values. A 2-sided *P*  $< 0.05$  was considered statistically significant. All analyses were performed using the Statistical Package of Social Science, Version 16.0.

## RESULTS

### Viral Detections

One nasopharyngeal sample was collected in each of 536 episodes of RTI in 452 children (some children had more than 1 RTI episode). In these 536 samples, we detected 665 positive PCR tests (Table 1), while 123 samples (22.9%) were negative for all PCR tests. The most frequently detected viruses were RSV (*n* = 142), rhinovirus (*n* = 91), and coronavirus (*n* = 68) (Table 1). HCoV-OC43 was detected in 44 (8.2%) and HCoV-NL63 in 24 (4.5%) samples (Table 1). Neither HCoV-E229 nor HCoV-HKU1 was detected. An HCoV-OC43 outbreak occurred, starting in the middle of November 2006 and lasting to the end of January 2007. In November, the virus was found in 6 samples, while in December HCoV-OC43 was the most frequently detected virus, found in 25 of 92 samples with positive findings (27.2%). The frequency of HCoV-OC43 declined throughout the 2 first months of 2007 with 8 detections in January and 3 in February. Most of the samples with HCoV-NL63 or RSV were collected after the HCoV-OC43 outbreak, from the middle of January to the end of April 2007. We detected 2 positive PCR tests for HCoV-NL63 in January, 5 in February, 8 in March, 5 in April, and 3 in June. RSV peaked in February 2007 with 47 samples, and the RSV outbreak lasted until the middle of May 2007.

### Study Groups With Coronavirus and RSV

To study the clinical manifestations of coronavirus we included every second RSV-positive child in a comparison group.

**TABLE 1.** Virus Detections in 536 Episodes of Respiratory Tract Infection (RTI) Among 452 Children

Viruses	N (%)	Group A, HCoV-OC43 (n = 37)	Group B, HCoV-NL63 (n = 17)	Groups C + D, HCoV-OC43 or HCoV-NL63 + RSV (n = 14)	Group E, RSV (n = 62)
HCoV-OC43	44 (8.2)*	37	0	7	0
HCoV-NL63	24 (4.5)	0	17	7	0
HCoV-229E	0	0	0	0	0
HCoV-HKU1	0	0	0	0	0
RSV	142 (26.5)	0	0	14	62
Rhinovirus	91 (17.0)	6	2	1	3
Human bocavirus	55 (10.3)	8	1	1	5
Human metapneumovirus	55 (10.3)	5	0	0	4
Enterovirus	53 (9.9)	10	1	1	4
Adenovirus	44 (8.2)	2	1	0	5
Influenza virus A	33 (6.2)	0	0	0	1
Parainfluenza virus 2	1 (0.2)	0	0	0	0
Parainfluenza virus 3	34 (6.0)	4	1	0	1
Parainfluenza virus 4	7 (1.3)	1	0	0	0
Epstein-Barr virus	20 (3.7)	4	0	1	2
Cytomegalovirus	48 (9.0)	4	0	2	3
Human herpes virus 6	14 (2.6)	1	2	2	1

Distribution of codetected viruses among children with human coronavirus (HCoV)-OC43 (Group A), HCoV-NL63 (Group B), HCoV-OC43 + RSV (Group C), HCoV-NL63 + RSV (Group D), and every second RSV-positive RTI (Group E).

No positive tests for influenza virus B, parainfluenza virus 1, and herpes simplex virus 1 and 2 were detected.

\*Number (percentage of 536 episodes).

HCoV indicates human coronaviruses; RSV, respiratory syncytial virus.

Some of these children also tested positive for HCoV-OC43 (n = 7) and HCoV-NL63 (n = 7). Thus, for the study of clinical manifestations we included a total of 37 children/RTI episodes with HCoV-OC43 without RSV (Group A), 17 children/RTI episodes with HCoV-NL63 without RSV (Group B), 7 children/RTI episodes with HCoV-OC43 and RSV (Group C), 7 children/RTI episodes with HCoV-NL63 and RSV (Group D), and 62 children/RTI episodes with RSV without coronavirus (Group E).

**Clinical Characteristics and Laboratory Measurements**

Children with HCoV-OC43 and HCoV-NL63 (Groups A and B) were older than children with RSV (Group E) (median age, 19 months vs. 10 months, *P* < 0.05)(Table 2) and tended to have a chronic disease (other than asthma) more often (19/54 vs. 13/62, *P* = 0.09) (Table 2). Among all the children with HCoV and RSV (Groups A–E), chronic disease other than asthma was most common among the oldest (10/16 [62.5%] of those >5 years vs. 24/114 [21.1%] of those ≤5 years, *P* = 0.001). Respiratory symptoms and findings (dyspnea, wheezing, retractions, tachypnea, and crepitations) were more common among children with RSV (Table 2). There were, however, no differences in C-reactive protein levels, white blood cell counts, and x-ray findings between the groups (Table 2).

**Diagnoses**

Of the children with HCoV-OC43 (Group A), 18 (48.6%) had URTI and 18 (48.6%) had LRTI. One (2.7%) child had monosymptomatic fever. Among the children with LRTI, 8 (21.6%) had pneumonia, 6 (16.2%) bronchiolitis, 3 (8.1%) bronchitis, and 1 (2.7%) asthma exacerbation. Of the children with

HCoV-NL63 (Group B), 9 (52.9%) had URTI and 8 (47.1%) had LRTI. One (5.9%) had pneumonia, 4 (23.5%) bronchiolitis, 1 (5.9%) bronchitis, and 2 (11.8%) asthma exacerbation. There were no differences in distribution of the various LRTI between the 2 coronaviruses (Groups A and B). All 14 children in Group C (HCoV-OC43 + RSV) and Group D (HCoV-NL63 + RSV) were diagnosed with LRTI. Five (35.7%) had pneumonia, 7 (50%) bronchiolitis, and 2 (14.3%) asthma exacerbation. Among the children with RSV (Group E), 11 (17.7%) had URTI and 51 (82.3%) had LRTI. Of those with LRTI, 17 (27.4%) had pneumonia, 27 (43.5%) bronchiolitis, 2 (3.2%) bronchitis, and 5 (8.1%) asthma exacerbation.

Signs of URTI were found among a majority of those with LRTI: Group A, 15 of 18 (83.3%); Group B, 6 of 9 (66.7%); Group C, 7 of 7 (100%), Group D, 7 of 7 (100%), Group E, 48 of 51 (94.1%). Among children with isolated URTI, there were no differences in the rates of diagnoses between Group A (rhinopharyngitis, n = 17 [94.4%]; tonsillitis, n = 3 [16.7%]; otitis media, n = 2 [11.1%]; laryngitis, n = 4 [22.2%]), Group B (rhinopharyngitis, n = 7 [77.8%]; otitis media, n = 2 [22.2%]; tonsillitis, n = 1 [11.1%]), and Group E (rhinopharyngitis, n = 8 [72.7%]; otitis media, n = 1 [9.1%]; tonsillitis, n = 1 [9.1%]).

**Viruses Codetected With HCoV and RSV**

Among children in Group A, 27 of 37 (73.0%) had one or more viruses detected in addition to HCoV-OC43 (Table 1). Codetection of other viruses was also present in 7 of 17 (41.2%) children in Group B with HCoV-NL63, and in 25 of 62 (40.3%) children in Group E with RSV. Compared with Group A with HCoV-OC43, fewer children with HCoV-NL63 (Group B) and

**TABLE 2.** Clinical Characteristics of Children With Acute Respiratory Tract Infection Classified on the Basis of Whether Human Coronavirus (HCoV)-OC43 or HCoV-NL63, Respiratory Syncytial Virus (RSV), or Both Viruses Were Present

	Group A, HCoV-OC43 (n = 37)	Group B, HCoV-NL63 (n = 17)	Groups C + D, HCoV-OC43 or HCoV-NL63 + RSV (n = 14)	Group E, RSV (n = 62)	<i>P</i> *
Age (months) <sup>†</sup>	23.0 (1–183)	12.0 (1–177)	8.5 (1–31)	10.0 (1–95)	0.01
Sex (male) <sup>‡</sup>	23 (62.2)	7.0 (41.2)	11.0 (78.6)	36.0 (58.1)	0.79
Chronic disease <sup>§</sup>					
Asthma <sup>‡</sup>	1 (2.7)	1.0 (5.9)	2.0 (14.3)	5.0 (8.1)	0.45
Other chronic disease <sup>§§</sup>	11 (29.7)	8.0 (47.1)	2.0 (14.3)	13.0 (21.0)	0.09
Cough <sup>‡</sup>	35 (97.2)	14.0 (87.5)	13.0 (92.9)	61.0 (100)	0.09
Dyspnea <sup>‡</sup>	19 (59.4)	10.0 (71.4)	12.0 (85.7)	47.0 (85.5)	<0.01
Wheezing <sup>‡</sup>	15 (40.5)	7.0 (41.2)	8.0 (57.1)	44.0 (73.3)	<0.001
Retractions <sup>‡</sup>	13 (39.4)	5.0 (29.4)	11.0 (84.6)	44.0 (71.0)	<0.001
Tachypnea <sup>‡</sup>	17 (45.9)	6.0 (37.5)	12.0 (92.3)	51.0 (85.0)	<0.001
Creptitations <sup>‡</sup>	5 (14.3)	3.0 (17.6)	9.0 (64.3)	32.0 (53.3)	<0.001
Ronchi <sup>‡</sup>	14 (40.0)	3.0 (17.6)	9.0 (64.3)	30.0 (50.8)	0.05
CRP maximum (mg/L) <sup>†</sup>	17.0 (<5–398)	21.0 (<5–119)	51.0 (<5–255)	22.0 (<5–192)	0.96
Leukocytes maximum (× 10 <sup>9</sup> /L) <sup>†</sup>	12.9 (4.7–45.7)	10.4 (1.3–23.4)	15.0 (5.4–45.9)	12.5 (5.5–35.2)	0.19
Chest x-ray taken <sup>‡</sup>	16.0 (43.2)	8.0 (47.1)	12.0 (85.7)	35.0 (56.5)	0.20
Local infiltrate <sup>‡</sup>	5 (35.7)	1.0 (14.3)	6.0 (50.5)	18.0 (54.5)	0.06
Perihilar infiltrate <sup>‡</sup>	4 (28.6)	4.0 (57.1)	8.0 (66.7)	19.0 (57.6)	0.16
Days in hospital <sup>†</sup>	1.0 (0–11)	1.5 (0–10)	4.5 (0–115)	4.0 (0–44)	<0.001
Days with O <sub>2</sub> <sup>†</sup>	0.0 (0–12)	0.0 (0–8)	0.0 (0–4)	0.5 (0–16)	<0.01
Minimum O <sub>2</sub> level (%) <sup>†</sup>	96.0 (65–100)	97.0 (78–100)	89.0 (60–99)	90.0 (55–100)	<0.01
Days with fever <sup>†</sup>	1.0 (0–5)	2.0 (0–5)	2.0 (0–24)	2.0 (0–14)	0.03
Maximum temperature (Celsius) <sup>¶</sup>	38.7 (1.1)	38.7 (1.1)	38.9 (1.1)	39.0 (1.1)	0.18
Antibiotic treatment <sup>‡</sup>	13 (35.1)	9.0 (52.9)	10.0 (71.4)	27.0 (43.5)	0.76

All percentages calculated on the basis of available data excluding missing values.

\*Group A + Group B versus Group E.

<sup>†</sup>Median (range).

<sup>‡</sup>Number (percent).

<sup>§</sup>Other chronic diseases: heart disease, neurologic disease, pulmonary disease, immunodeficiency, others. One patient in Group B had both asthma and another chronic disease.

<sup>¶</sup>Mean (standard deviation).

CRP indicates C-reactive proteins.



RSV (Group E) had codetections ( $P = 0.03$  and  $P < 0.01$ , respectively).

For HCoV-OC43, HCoV-NL63, and RSV, there were no associations between codetection of other viruses and (1) whether the infection was located in the upper or lower respiratory tract, (2) length of hospital stay, or (3) duration of oxygen treatment, respectively (data not shown).

### Viral Load of HCoV and RSV

Using sensitive semiquantitative PCR tests we studied whether a relationship existed between viral load in the nasopharyngeal sample and clinical diagnosis (URTI or LRTI). No such association for any of the viruses was found (data not shown). Nor was any association found between viral load of the same 3 viruses and (1) length of hospital stay and (2) duration of oxygen treatment, respectively (data not shown).

### Disease Severity of HCoV Compared With RSV

LRTI and bronchiolitis were less common among the coronavirus-infected children (Groups A and B) than among those with RSV (Group E) (both  $P < 0.01$ ) or those with coronavirus and RSV (Groups C and D) (both  $P < 0.01$ ). A univariate logistic regression analysis comparing LRTI in Groups A and B with Group E similarly showed that the odds of developing LRTI were 5 times lower among those with HCoV-OC43 and HCoV-NL63 (OR, 0.20; 95% CI, 0.09–0.47;  $P < 0.001$ ). Adjusting for differences in age, chronic disease, and the presence of codetected viruses by use of multiple logistic regression analysis strengthened this association (OR, 0.15; 95% CI, 0.05–0.40;  $P < 0.001$ ). Similar results were found for bronchiolitis (data not shown). Children with HCoV-OC43 and HCoV-NL63 infection less frequently had respiratory symptoms or findings related to the lower airways compared with those with RSV infection (Table 2). However, when we adjusted for differences in age, chronic disease, the presence of codetected viruses, and whether the children had LRTI, none of these associations persisted (data not shown). Children with HCoV-OC43 and HCoV-NL63 had fever for a shorter period than children with RSV (Table 2), and this finding persisted after adjusting for the same 4 covariates (OR, 0.66; 95% CI, 0.47–0.93;  $P = 0.02$ ). Children with HCoV-OC43 and HCoV-NL63 infections were treated with oxygen for a shorter period compared with children with RSV (Table 2), but after adjustment this difference was no longer present (data not shown). On the other hand, HCoV-OC43 and HCoV-NL63 infections were associated with a shorter hospital stay both in univariate analysis (Table 2) and when we adjusted for the same 4 covariates (OR, 0.84; 95% CI, 0.71–0.98;  $P = 0.03$ ).

### DISCUSSION

During the winter season 2006–2007, there was an outbreak of coronavirus infection among children in Mid-Norway. Coronavirus was detected in 12.7% of the nasopharyngeal samples collected from children who were admitted with an acute respiratory tract infection. Only RSV and rhinovirus were detected more frequently. During the last 4 weeks of 2006, HCoV-OC43 was the most common virus found in more than one-fourth of the samples. HCoV-NL63 was seen regularly after the HCoV-OC43 outbreak, while neither HCoV-229E nor the recently described coronavirus HKU1 were detected during the study period. Our findings agree with previous knowledge that some serotypes may dominate one year with others being dominant in the next.<sup>21,23</sup> It has also been shown that the incidence of coronavirus can vary considerably during 1 season,<sup>11,14–17,20</sup> as we found for both HCoV-OC43 and HCoV-NL63. HCoV-HKU1 has been reported infrequently from Western Europe.<sup>9,22</sup> We later tested for HCoV-HKU1 in the

samples that were available in 2010 (60%), but detected no HCoV-HKU1. This finding suggests that HCoV-HKU1 might not be a common cause of severe respiratory tract infection in children.

We found that children with coronavirus were older than children with RSV and tended to have chronic disease (other than asthma) more often, as it also was reported recently by Kuypers et al.<sup>16</sup> Children with HCoV-OC43 and HCoV-NL63 displayed wheezing and other symptoms related to the lower respiratory tract less frequently than those with RSV infection. These differences were not related to the viruses per se, but to the fact that coronavirus-infected children had LRTI less frequently. We also found that children with coronavirus had a shorter fever period and a shorter hospital stay, which could not be explained by their older age, that fewer with coronavirus had LRTI and more had chronic diseases, or the possible influence of codetected viruses. Only a few previous studies have compared RSV and coronavirus infections in children. In accordance with our findings, both McIntosh et al and van der Hoek et al found that coronavirus caused a mild disease more frequently than RSV.<sup>13,17</sup> In our study all children with positive tests for both RSV and either HCoV-OC43 or HCoV-NL63 developed a lower respiratory tract infection with clinical characteristics much like those with solitary RSV infection (younger age, longer hospitalization), illustrating the significance of RSV over coronavirus. Nevertheless, it should not be forgotten that HCoV-OC43 or HCoV-NL63 may also cause severe lower respiratory tract infections. Among our patients, a 3-year old boy with pneumonia and solitary HCoV-OC43 was hospitalized for 11 days with initial severe hypoxia (oxygen saturation level of 65%). He had a maximum C-reactive protein level of 79 mg/L and recovered without antibiotics.

We found a high rate of viral codetections in the coronavirus-positive samples: nearly 75% of the children with HCoV-OC43 and 40% with HCoV-NL63 tested positive for one or more viruses in addition to coronavirus. Other recent studies using sensitive PCR technology have reported similar findings.<sup>16,18,19</sup> It is difficult to determine whether a causal relationship between the detection of specific viral nucleic acids and clinical manifestations exists, especially when more viruses are detected in the same sample. Regamey et al found that shedding of viral nucleic acids 3 weeks after onset of acute respiratory tract infection occurred in 30% of patients with coronavirus, and the shedding may last even longer.<sup>9</sup> Long-time viral shedding has also been reported for other viruses, such as rhinovirus<sup>37</sup> and bocavirus,<sup>38</sup> and may explain codetection of these viruses. Several of our findings suggest that codetections may not be causally related to RTI. RSV, which is the most common and well-known cause of RTI, had a codetection rate that was comparable to the high rates in the coronaviruses. Furthermore, the children with both RSV and coronavirus had a disease with clinical characteristics very similar to a solitary RSV infection. We also found that disease severity (more severe expressed as a higher rate of LRTI than URTI, longer duration of oxygen treatment, and longer length of hospital stay), was not associated with codetection of other viruses in children with HCoV-OC43, HCoV-NL63, or RSV.

We studied whether viral load could be related to disease severity since such a dose-response relationship might support a causal relationship between viral detection and clinical infection. Although we found no associations between disease severity and viral load of HCoV-OC43, HCoV-NL63, and RSV, these findings should be interpreted with caution, because the virus concentrations were not determined at standardized time points after the onset of the infection in our patients.

Our study has limitations that warrant careful interpretation and further studies to confirm the findings. We have only studied

the most severely ill children who were admitted to the hospital. Furthermore, the study was performed during 1 single winter season which might explain the high HCoV-OC43 incidence and the absence of HCoV-229E and HCoV-HKU1. Our data may also be biased because nasopharyngeal samples were collected on clinical indication, and because patients were not treated according to a standardized protocol. Although we have used RSV infected children as controls, the lack of a healthy control group limits the ability to evaluate casual relationships between virus detections and clinical manifestations.

We conclude that HCoV-OC43 and HCoV-NL63 are common among hospitalized Norwegian children with RTI. HCoV-OC43 and HCoV-NL63 cause hospitalization from upper or lower respiratory tract infections in weak and somewhat older children with underlying chronic conditions more often than RSV, while RSV primarily causes hospitalization due to lower respiratory tract infections in previously healthy infants.

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