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Hospitalized Children With Common Human Coronavirus Clinical Impact of Codetected Respiratory Syncytial Virus and Rhinovirus

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Background: The clinical impact of common human coronavirus (cHCoV) remains unclear. We studied the clinical manifestations of pediatric cHCoV infections and the possible modifying effects of codetected human rhinovirus (RV) and respiratory syncytial virus (RSV).

Methods: We used data from an 11-year-long prospective study of hospitalized children with community-acquired respiratory tract infections. Nasopharyngeal aspirates were analyzed with real-time polymerase chain reaction assay for cHCoV OC43, NL63, HKU1 and 229E, and 15 other respiratory viruses. We assessed disease severity based on the clinical factors hospitalization length, oxygen requirement, other respiratory support and supplementary fluids.

Results: cHCoV was detected in 341 (8%) of 4312 children. Among 104 children with single cHCoV detections, 58 (56%) had lower respiratory tract infection (LRTI) and 20 (19%) developed severe disease. The proportion with severe disease was lower among single cHCoV detections compared with single RSV detections (338 of 870; 39%), but similar to single RV detections (136 of 987; 14%). Compared with single cHCoV, codetected cHCoV-RSV was more often associated with LRTI (86 of 89; 97%) and severe disease (adjusted odds ratio, 3.3; 95% confidence interval: 1.6–6.7). LRTI was more frequent in codetected cHCoV-RV (52 of 68; 76%) than single cHCoV, but the risk of severe disease was lower (adjusted odds ratios, 0.3; 95% confidence interval: 0.1–1.0).

Conclusions: cHCoV was associated with severe LRTI in hospitalized children. Viral codetections were present in two-thirds. Codetections of cHCoV-RV were associated with lower proportions of severe disease, suggesting a modifying effect of RV on HCoV.

Key Words: common coronaviruses, respiratory infections, respiratory viruses, hospital medicine

(*Pediatr Infect Dis J* 2022;41:e95–e101)

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) outbreak[1,2] has drawn global attention toward all types of coronaviruses.[3,4] Today, we lack knowledge on the disease severity in children caused by infection of the four most common endemic human coronaviruses (cHCoVs): OC43, NL63, 229E and HKU1. Using sensitive polymerase chain reaction (PCR) methods, cHCoVs are commonly detected in children with respiratory tract infections (RTIs).[3,5] These viruses have been considered as agents of mild RTIs,[6] but recent evidence suggests that cHCoV may cause severe lower respiratory tract infections (LRTIs) in children, such as bronchiolitis and pneumonia.[7–13] However, high rates of codetected respiratory viruses have made it challenging to determine the clinical manifestations and severity associated with cHCoV in hospitalized children with RTI.[7,14–16] Further, epidemiologic studies and cell culture studies suggest possible interactions between respiratory viruses that may alter the course of a virus infection, but we lack information from clinical studies regarding interactions between common respiratory viruses.

In this study, we have used data from an 11-year-long observational cohort study of children hospitalized with RTI. The objectives were to describe the clinical manifestations of cHCoV and assess the possible impacts of codetected human rhinovirus (RV) and respiratory syncytial virus (RSV). We compared cHCoV to RSV and RV because both viruses are frequently codetected with HCoV, and their clinical manifestations are well known.

METHODS

Study Population and Setting

This analysis is based on a large observational cohort study of RTIs in hospitalized children, set up to study clinical manifestations and the effects of viral codetections in pediatric RTIs. In short, we have prospectively followed the disease course of children <16 years of age with community-acquired RTIs admitted to the Children's Clinic at St. Olavs Hospital, Trondheim University Hospital, Norway. The study was conducted from November 2006 to September 2017. Children's Clinic is the pediatric reference center for approximately 59,000 children in Trøndelag County. Enrollment assumed that a nasopharyngeal aspirate (NPA) was sampled for respiratory virus analyses on a clinical indication. Exclusion criteria were (1) refusal to participate, (2) not community-acquired RTI, such as hospital-acquired RTIs including newborns not dismissed from the hospital and ongoing cytostatic and/or immunodeficiency and (3) insufficient registration of clinical data. Most participants were enrolled during their stay at the hospital, with some retrospective inclusions.

Clinical Investigation, Classification of Diseases and Calculation of Severity Score

All children were routinely examined and treated by physicians at the pediatric department in accordance with the hospital's routines. Clinical data were recorded in standardized forms by physicians and nurses during hospitalization. For children

Accepted for publication December 2, 2021

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This study was supported by Central Norway Regional Health Authority (grant number 96987/2008). The Central Norway Regional Health Authority had no role in the design or conduct of the study.

The authors have no conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/22/4103-0e95
DOI: 10.1097/INF.0000000000003433

included after discharge, data were collected from medical records by members of the study group. Blood samples were collected to measure C-reactive protein concentration in mg/L and white blood cell count $\times 10^9$/L. Parents or legal guardians were asked to fill out additional clinical information forms about the child and the current RTI episode. "Chronic disease" included asthma or other lung diseases, neurologic, neuromuscular and metabolic disorders, in addition to congenital heart diseases. Preterm birth was defined as gestational age <36 weeks.

Included children were diagnosed with either an upper respiratory tract infection (URTI) or an LRTI with or without URTI. URTIs were classified as rhinopharyngitis, otitis, conjunctivitis and/or tonsillitis. We categorized LRTI into four categories based on clinical manifestations and radiologic findings, in prioritized order: (1) Pneumonia required the presence of consolidations on chest radiographs in addition to clinical manifestations from lower airways. (2) Bronchiolitis was defined as wheezing and/or fast breathing with retractions in children younger than 2 years of age. (3) Bronchitis was diagnosed in children older than 2 years of age with lower airway obstruction. Children discharged with the ICD-10 diagnosis J22 "unspecified acute lower respiratory infection" who did not meet the above criteria for LRTI were classified as (4) other LRTIs. Virus-induced asthma exacerbation was classified as bronchiolitis or bronchitis.

The severity of the RTI episodes was assessed using a self-composed severity score ranging from 0 to 10 points. The severity score was the sum of (1) oxygen therapy or respiratory support, with a need for oxygen therapy to maintain oxygen saturation ≥93% (1 point), high-flow nasal cannula (2 points), continuous positive airway pressure and bilevel positive airway pressure (3 points), noninvasive positive pressure ventilation with synchronized assisted ventilator pressure and pressure control as standard setting (4 points) and invasive respirator (6 points). Only the highest treatment modality was calculated if a child received several treatment modalities within oxygen therapy or respiratory support. (2) Use of intravenous fluids and/or nasogastric feeding tube (2 points), and (3) length of stay ≥5 days (2 points). A severity score ≥3 corresponding to or above the 75th percentile among all virus-positive children with RTI was defined as a "severe disease."

Laboratory Methods

Sampled NPAs were routinely placed into a standard virus transport medium without antibiotics. A total of 94% of all NPAs were sampled during the first 2 days of hospitalization. Clinical laboratory technicians performed in-house TaqMan real-time PCR tests to detect respiratory pathogens as previously described.[17] We routinely analyzed three species of cHCoV: OC43, NL63 and 229E. In 2015, all previous samples were reanalyzed for HKU1. Thirteen other viruses were also routinely tested for human adenovirus, human bocavirus, human enterovirus, human parechovirus, human metapneumovirus, influenza virus A and B, parainfluenza virus types 1–4, RSV, and RV in addition to *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae.* The same transport medium as described above was also used to culture bacteria with standard agarose media. We recorded the growth of *Hemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*.[18] Semiquantitative results for cHCoV were reported based on the cycle threshold value (C_t value), with a high viral load defined as a C_t value <30. A C_t value >42 was regarded as a negative test. The PCR methods were unchanged during the whole study period.

As codetections with other respiratory viruses interfere with the interpretation of cHCoV impact on clinical presentations, we divided cHCoV-positive children into three groups: "single

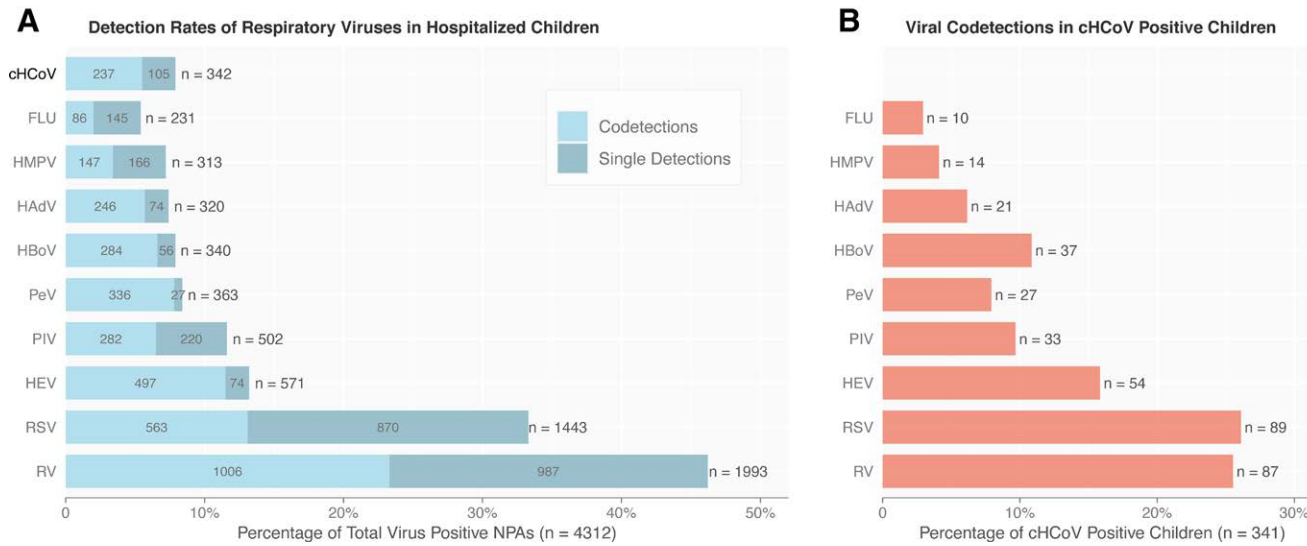

FIGURE 1. A: Detection rates of respiratory viruses in 4312 virus-positive NPAs from hospitalized children with RTI. For each virus, the absolute numbers of codetections with other viruses (light blue color) and the absolute numbers of single virus detections (dark blue color) are listed. The total detections rates for each virus are listed outside the bars. The length of the bars corresponds to the detection frequencies in percentages of 4312 virus-positive NPAs. B: Codetection rates of other respiratory viruses in 341 cHCoV-positive NPAs. The total detection rates for each virus are listed outside the bars. The length of the bars corresponds to the detection frequencies in percentages of 341 cHCoV-positive NPAs. cHCoV, common human coronavirus; FLU, Influenza virus A and B; HAdV, human adenovirus; HBoV, human bocavirus; HEV, human enterovirus; HMPV, human metapneumovirus; PeV, human parechovirus; PIV, parainfluenza virus types 1-4; RSV, respiratory syncytial virus; RV, human rhinovirus.

cHCoV-detections," "codetections with RSV" and "codetections with RV." If a child had codetections with both RSV and RV, the child was categorized as "codetections with RSV."

Statistical Analyses

Descriptive data were reported with counts and percentages, mean and standard deviations or median and interquartile range (IQR), as appropriate. Hypotheses were tested with Pearson chi-squared test. Multivariate logistic regressions were performed to study associations with LRTI and severe disease in "single cHCoV detection," "cHCoV with codetected RSV" and "cHCoV with codetected RV," adjusted for age (continuous), gender (female/male), chronic diseases and/or preterm birth (yes/no). The strength of the associations was reported with odds ratios (ORs) or adjusted odds ratios (aORs) and 95% confidence intervals (CIs). For all tests, a P value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 27. Illustrations were made with ggplot2 software package and Adobe Illustrator.

Ethics

Ethical considerations regarding this study are thoroughly described elsewhere.[15] 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

From November 2006 to September 2017, we included 4312 virus-positive NPAs from children younger than 16 years of age admitted with an acute RTI (see Figure, Supplemental Digital Content 1; http://links.lww.com/INF/E608). cHCoV was detected in 341 RTI episodes. Codetections with other viruses occurred in 70% (237 of 341) of cHCoV-positive NPAs, with RSV (89 of 341) and RV (68 of 341) as the most frequently codetected viruses (Fig. 1). The codetection rates of each respiratory virus among cHCoV-positive children were proportionally similar to the detection rates of the same viruses in the total cohort population (Fig. 1). However, this was not true for RSV, which had a higher codetection rate among cHCoV-positive children compared with the total sample (26% vs. 13%; OR, 1.8; 95% CI: 1.4–2.4; $P < 0.001$) (Fig. 1). An overview of all codetected viruses and bacteria in cHCoV-positive samples is reported (see Table, Supplemental Digital Content 2; http://links.lww.com/INF/E609).

Clinical Presentation of Children With RTI and Single cHCoV Detections

Two of three children with single cHCoV detections were boys, and one of three had a chronic disease and/or preterm birth (Table 1). In total, 83% (86 of 104) of children with single cHCoV detections had symptoms from the upper airways. Less than half

TABLE 1. Background Variables and Clinical Characteristics

	Single cHCoV (n = 104) No. (%)	cHCoV+RSV (n = 89) No. (%)	cHCoV+RV (n = 68) No. (%)
Background characteristics			
Female gender	38 (37)	38 (43)	22 (34)
Age in months, median (IQR)	7.7 (1.8–31.8)	10.3 (3.2–19.2)	16.9 (10.9–24.6)
Age <2 years	72 (69)	79 (89)	50 (74)
Chronic disease or preterm birth*	31 (30)	31 (35)	18 (26)
Selected signs and symptoms			
Fever	69 (66)	53 (60)	37 (54)
Rhinorrhea	54 (52)	48 (54)	36 (53)
Cough	71 (68)	74 (83)	48 (71)
Wheezing or dyspnea	25 (24)	62 (70)	40 (59)
Chest wall retractions	27 (26)	58 (65)	27 (40)
Abnormal lung auscultation	55 (53)	76 (85)	46 (68)
Vomiting and/or diarrhea	29 (28)	26 (29)	14 (21)
Measurements			
Hospitalized ≥24 hours	55 (53)	71 (80)	34 (50)
O_2 saturation ≤92%	8/97 (8)	13/88 (15)	9/62 (15)
Body temperature ≥38.0°C	49/96 (51)	48/88 (55)	28/64 (44)
Peak CRP >50 mg/L	24/97 (25)	21/83 (25)	12/61 (20)
Peak WBC $\times 10^9$/L, mean (SD)†	12.2 (6.1)	12.3 (4.9)	13.8 (5.9)
Chest radiograph performed	51 (49)	55 (62)	27 (40)
Main diagnosis			
Upper RTI	46 (44)	3 (3)	16 (24)
Lower RTI	58 (56)	86 (97)	52 (76)
Pneumonia	16 (15)	13 (15)	10 (15)
Bronchiolitis	25 (24)	64 (72)	26 (38)
Bronchitis	7 (7)	8 (9)	10 (15)
Other LRTI	10 (10)	1 (1)	6 (9)
Treatment			
Inhalations	51 (49)	82 (92)	45 (66)
Antibiotics	22 (21)	20 (22)	12 (18)
Supplemental fluids‡	26 (25)	26 (29)	12 (18)
Corticosteroids	18 (17)	29 (33)	23 (34)
Oxygen and/or respiratory support§	20 (19)	48 (54)	17 (25)

*Either asthma or other lung diseases, neurologic, neuromuscular and metabolic disorders, congenital heart diseases or gestational age <36 weeks.

†Missing data in 10 children with single cHCoV detection, 9 with codetected RSV and 7 with codetected RV.

‡Use of intravenous fluids and/or nasogastric feeding tube.

§Either high-flow nasal cannula, bilevel positive airway pressure, continuous positive airway pressure, noninvasive positive pressure ventilation (NIPPV) with synchronized assisted ventilator pressure and pressure control as standard setting or invasive ventilator.

cHCoV, human coronavirus; CRP, C-reactive protein; IQR, interquartile range; LRTI, lower RTI; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RV, human rhinovirus; SD, standard deviation; WBC, white blood cell count.

were diagnosed with URTI without LRTI; rhinopharyngitis and otitis occurred in 67 and 23 children, respectively. Children with URTI without LRTI were younger than those with LRTI (age in months; median [IQR], 2.5 [17.9] vs. 14.1 [31.7]). More than half of all children with single cHCoV detection were diagnosed with LRTI (Table 1). One in four had bronchiolitis, and one in seven met our criteria for pneumonia. Half of all children were treated with inhalations, and approximately one in five received antibiotics (Table 1).

Clinical Manifestations in Children With Single cHCoV Detections Compared With Children With Codetected cHCoV-RSV and cHCoV-RV

Children with single cHCoV detections were more likely to be >2 years of age (OR, 3.5; 95% CI: 1.6–7.6; $P = 0.001$), compared with children with codetections of cHCoV-RSV (Table 1). They were less likely to have LRTI (OR, 0.04; 95% CI: 0.01–0.15; $P < 0.001$), bronchiolitis (OR, 0.1; 95% CI: 0.07–0.2; $P < 0.001$), to be hospitalized ≥24 hours (OR, 0.3; 95% CI: 0.1–0.5; $P < 0.001$), receive treatment with inhalations (OR, 0.1; 95% CI: 0.04–0.2; $P < 0.001$), corticosteroids (OR, 0.4; 95% CI: 0.2–0.9; $P = 0.01$) and oxygen and/or other respiratory support (OR, 0.2; 95% CI, 0.1–0.4; $P < 0.001$).

Background characteristics were similar for children with single cHCoV compared with children with cHCoV and codetections with RV (Table 1). Children with single cHCoV detections were less likely to present with wheezing or dyspnea (OR, 0.4; 95% CI: 0.2–0.7; $P = 0.001$) and having an O_2 saturation ≤95% (OR, 0.3; 95% CI: 0.2–0.8; $P = 0.009$) compared with cHCoV-RV codetections. Further, they were less likely to develop LRTI (OR, 0.4; 95% CI: 0.2–0.8; $P = 0.006$), bronchiolitis (OR, 0.5; 95% CI: 0.3–1.0; $P = 0.05$) and to receive treatment with inhalations (OR, 0.5; 95% CI, 0.3–0.9; $P = 0.03$) and/or corticosteroids (OR, 0.4; 95% CI: 0.2–0.8; $P = 0.01$) in unadjusted analyses. Although children with single cHCoV detections were less likely to have LRTI compared with cHCoV-RV codetections, there were no differences in length of hospitalization ≥24 hours or use of oxygen and/or other respiratory support between the groups (Table 1).

When we adjusted for age differences, gender and chronic diseases/preterm birth, children with single cHCoV were still less likely to have LRTI compared with those with codetections of cHCoV-RSV and cHCoV-RV (cHCoV-RSV: aOR, 0.04; 95% CI: 0.01–0.1; $P < 0.001$; cHCoV-RV: aOR, 0.4; 95% CI: 0.2–0.7; $P = 0.005$).

Disease Severity in Children With Single cHCoV Detections Compared With Single RSV and RV Detections and Codetections of cHCoV-RSV and cHCoV-RV

Twenty-one percent (71 of 341) of cHCoV-positive children had severe disease. We compared disease severity in children with single cHCoV detections to children with single RSV and RV, in addition to those with cHCoV and codetected RSV or RV (Table 2). cHCoV with codetected RSV resembled the group of single RSV detections. In both groups, two of five were classified with a severe disease. Compared with both single RSV detections and cHCoV with codetected RSV, we found that children with single cHCoV detections had a lower risk of LRTI, shorter length of stay and a lower risk of severe disease.

Children with single cHCoV were less likely to have an LRTI compared with both single RV and cHCoV with codetected RV, but only single RV was significantly more likely to receive oxygen treatment and less likely to receive supplementary fluids. Nevertheless, children with single cHCoV detections had a tendency of higher frequency of severe disease (19%) compared with single RV detections (14%) and cHCoV with codetected RV (7%), although only the last comparison was statistically significant (Table 2).

Figure 2 illustrates disease severity in cHCoV-positive children according to cHCoV genomic loads and viral codetections. Adjusted logistic regression models with single cHCoV detection as reference showed that cHCoV-RSV more often (aOR, 3.3; 95% CI: 1.6–6.7; $P < 0.001$), and cHCoV-RV less often (aOR, 0.3; 95% CI: 0.1–1.0; $P = 0.04$) were associated with severe disease compared with single cHCoV detections (Table 3). Neither various cHCoV species (NL63, OC43, HKU and 229E), bacterial codetections nor cHCoV genomic load was associated with severe disease in unadjusted analyses (Table 3). However, children with single cHCoV detections were more likely to have a high cHCoV genomic load with a C_t value <30 compared with those with cHCoV and codetections of RV (OR, 4.0; 95% CI: 2.0–7.7; $P < 0.001$) and RSV (OR, 5.0; 95% CI: 2.6–9.3; $P < 0.001$), respectively.

TABLE 2. Severity Scores by Groups

	Single cHCoV (n = 104)	Single RSV (n = 870)		cHCoV+RSV (n = 89)		Single RV (n = 987)		cHCoV+RV (n = 68)	
	No. (%)	No. (%)	OR (95% CI)§	No. (%)	OR (95% CI)§	No. (%)	OR (95% CI)§	No. (%)	OR (95% CI)§
LRTI	58 (56)	834 (96)	18.4 (11.0–30.6)	86 (97)	22.7 (6.7–76.6)	781 (79)	3.0 (2.0–4.6)	52 (76)	2.6 (1.3–5.1)
Oxygen treatment	14 (13)	350 (40)	4.3 (2.4–7.7)	33 (37)	3.8 (1.9–7.7)	270 (27)	2.4 (1.4–4.3)	15 (22)	1.8 (0.8–4.1)
Respiratory support, any	6 (6)	131 (15)	2.9 (1.2–6.7)	15 (17)	3.3 (1.2–8.9)	63 (6)	1.1 (0.5–2.6)	2 (3)	0.5 (0.1–2.5)
Noninvasive*	6 (6)	113 (13)		13 (15)		61 (6)		2 (3)	
Invasive	0	18 (2)		2 (2)		2 (0)		0	
Supplemental fluids†	26 (25)	307 (35)	1.6 (1.0–2.6)	26 (29)	1.2 (0.7–2.3)	147 (15)	0.5 (0.3–0.8)	12 (18)	0.6 (0.3–1.4)
Length of stay ≥5 days	14 (13)	297 (34)	3.3 (1.9–6.0)	33 (37)	3.8 (1.9–7.7)	135 (14)	1.0 (0.6–1.8)	5 (7)	0.5 (0.2–1.5)
Severity score‡ ≥3	20 (19)	338 (39)	2.7 (1.6–4.4)	34 (38)	2.6 (1.4–5.0)	136 (14)	0.7 (0.4–1.1)	5 (7)	0.3 (0.1–0.9)

*Either high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or noninvasive positive pressure ventilation (NIPPV) with synchronized assisted ventilator pressure and pressure control as standard setting.

†Intravenous fluids or nasogastric feeding tube.

‡Sum of respiratory support (either oxygen treatment [1 point], HFNC [2 points], CPAP/BiPAP [3 points], NIPPV [4 points] or invasive respirator [6 points]), supplemental fluids (2 points) and length of stay ≥5 days (2 points).

§Compared with single cHCoV.

cHCoV, common human coronavirus; CI, confidence interval; LRTI, lower respiratory tract infection; OR, odds ratio; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RV, human rhinovirus.

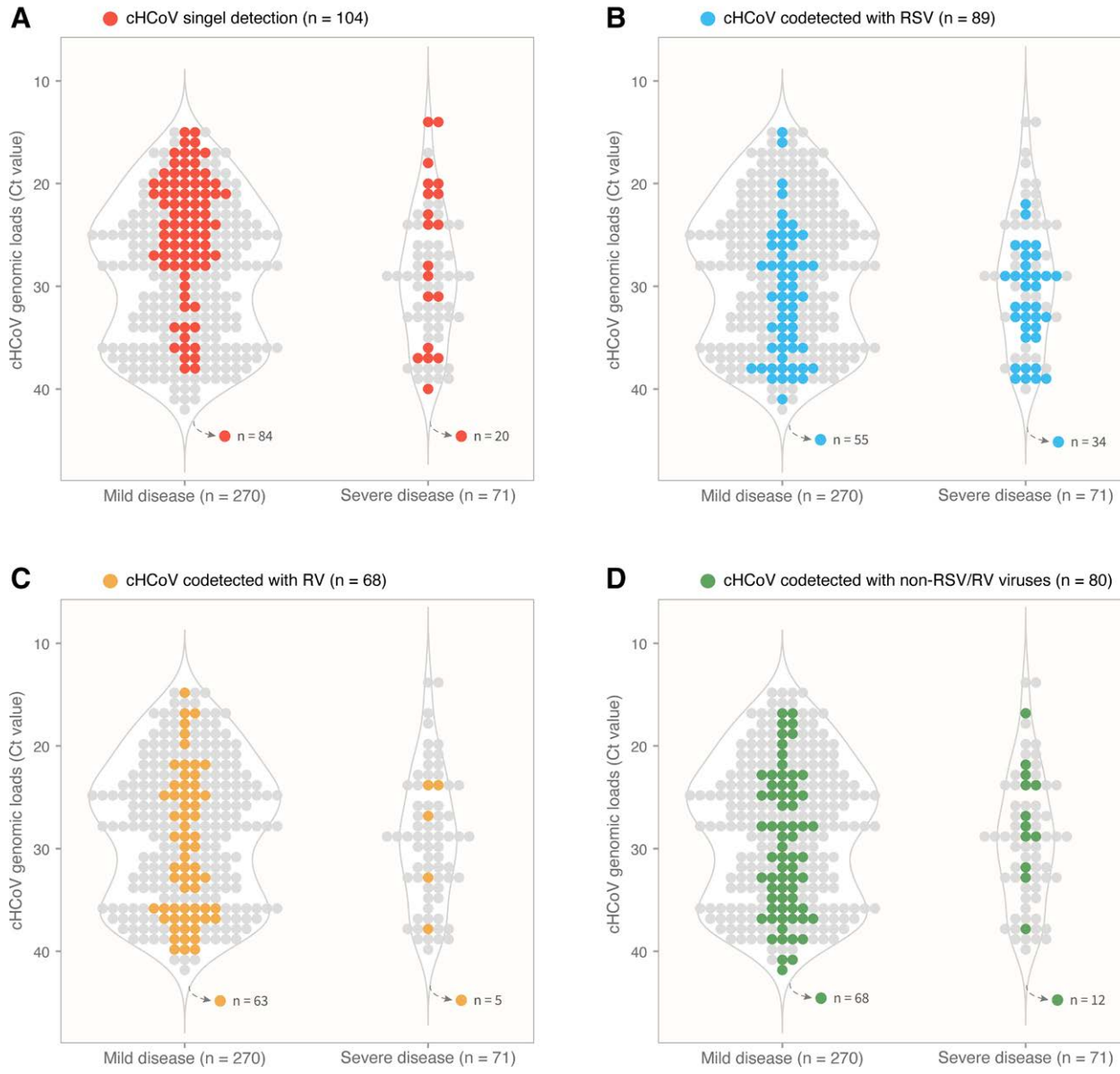

FIGURE 2. cHCoV genomic load and disease severity in 341 cHCoV-positive children hospitalized with RTI. A "severe disease" was defined as a severity score ≥3 corresponding to or above the 75th percentile among all virus-positive children with RTI based on the clinical factors hospitalization length, oxygen requirement or other respiratory support and supplementary fluids. A "mild disease" corresponded to a severity score <3. A: single cHCoV detections (red), (B) cHCoV with codetected RSV (blue), (C) cHCoV with codetected RV (yellow), (D) cHCoV with other codetections than RSV or RV (green). Gray dots represent all other cHCoV detections.

DISCUSSION

Main Findings

We found that over half of children hospitalized with RTI and single cHCoV detections were diagnosed with LRTI. Hence, cHCoV is not only detected in children with URTI, but also in children with more severe illnesses. Two-thirds of children with cHCoV had viral codetections. cHCoV codetected with RSV resembled single RSV detections and resulted in more frequent development of severe diseases than single cHCoV detections. The findings in relation to RV showed a different pattern. Similar rates of children with single RV and single cHCoV detections developed severe disease, but cHCoV in the presence of RV was associated with a lower rate of severe disease and lower cHCoV genomic loads compared with single cHCoV. These results suggest a modifying effect of RV on codetected cHCoV in children with RTIs.

Clinical Manifestations of cHCoV

In the present study, we found HCoV in 8% of children admitted with RTI to a Norwegian public hospital providing pediatric service to an entire county population during an 11-year-long period. Using the same dataset, we have previously reported similar detection rates of cHCoV in hospitalized children with RTI and asymptomatic controls,[15] in line with other studies.[19–21] However,

TABLE 3. Factors Associated With Severe RTI in cHCoV-positive Hospitalized Children (n = 261)*

	Unadjusted analyses		Adjusted analyses†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Virus detections				
Codetection with RV	0.3 (0.1–0.9)	0.04	0.3 (0.1–1.0)	0.04
Codetection with RSV	2.6 (1.4–5.0)	0.004	3.3 (1.6–6.7)	<0.001
Single cHCoV detection (reference)				
Male gender	1.3 (0.7–2.3)	0.38	1.0 (0.5–2.0)	0.94
Age (months)	1.0 (1.0–1.0)	0.01	1.0 (1.0–1.0)	0.005
Chronic disease or premature birth‡	2.4 (1.3–4.3)	0.004	1.8 (0.9–3.5)	0.08
cHCoV C_t value <30§	1.6 (0.9–2.8)	0.14		
cHCoV species¶				
OC43	1.1 (0.6–2.0)	0.65		
NL63	1.7 (0.9–3.0)	0.09		
HKU1	1.4 (0.2–1.5)	0.24		
229E	0.7 (0.2–2.4)	0.53		
Bacterial codetections‖				
Streptococcus pneumoniae	1.0 (0.5–1.8)	0.91		
Haemophilus influenzae	0.8 (0.4–1.4)	0.39		
Moraxella catarrhalis	1.2 (0.6–2.2)	0.56		

*Including 104 children with single cHCoV detection, 89 children with cHCoV and codetected RSV and 68 children with cHCoV and codetected RV.

†Gender, age (continuous) and chronic diseases or preterm birth, in addition to variables with *P* value <0.05 in the univariate analysis were included in the multivariate analysis.

‡Either asthma or other lung diseases, neurologic, neuromuscular and metabolic disorders, congenital heart diseases or gestational age <36 weeks.

§cHCoV-positive samples with C_t value ≥30 as reference.

¶For each comparison, the reference group included all other cHCoV species.

‖For each comparison, the reference group was a negative PCR test/culture growth for the respective bacterium.

cHCoV, common human coronavirus; CI, confidence interval; C_t, cyclic threshold; OR, odds ratio; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RV, human rhinovirus.

the children with RTI were more likely to have a low C_t value, that is, a high cHCoV genomic load, supporting a causal role of cHCoV in children with severe RTI. Hence, in the present study, we aim to describe clinical and virologic details in children with RTI, and the impact of codetected RSV and RV. We found that most children were younger than 2 years of age, and one in three had preexisting medical conditions. Although approximately two in three had viral codetections, more than half of children with a single cHCoV had pneumonia or bronchiolitis and received inhalations, and one in five received antibiotics and were treated with oxygen or other respiratory support. Some pneumonia cases might have been missed because only half of the cHCoV-positive children had a chest radiograph. These findings resemble recent hospital studies, reporting LRTI in 29%–86%,[7,22] pneumonia in 4%–10%[7,16,22] and oxygen treatment and respiratory support in 9%–25%[7,13,22,23] of children with cHCoV.

The new SARS-CoV-2 virus shares some similarities with cHCoV. Most hospitalized children with SARS-CoV-2 belong to the youngest age group and presents with fever and mild respiratory symptoms.[24–26] Data from this study, alongside previous reports, suggest that cHCoV sometimes may cause severe LRTI in need of intensive care.[7,13,23,27] SARS-CoV-2 does also in some cases cause severe LRTI, for example, oxygen or respiratory support has been required for 10%–49% and 2%–35% have been admitted to intensive care units.[24–26,28–33]

Codetections With RSV and RV

We found that cHCoV most often was codetected with RSV and RV. RSV dominated over cHCoV, as the proportions of LRTI and severe disease among single RSV detections resembled cHCoV-RSV codetections. Further, children with codetected cHCoV-RSV had lower cHCoV genomic loads than single cHCoV detections. cHCoV and RSV were frequently codetected, as previously reported.[7,13,14,16,27,34–36] Future studies should investigate whether cHCoV infections might facilitate subsequent RSV infections as suggested by van der Hoek et al,[37] or whether such apparent interactions are manifestations of their similar seasonality.

A recent cell culture study revealed that RV inhibits influenza A virus infections by activating the host antiviral defense (interferon response) in the target tissue.[38] With a similar approach, Dee et al[39] found that RV inhibits SARS-CoV-2 replication by triggering a rapid innate immune response within the respiratory epithelium. We speculate that the ability of RV to rapidly trigger innate immune responses may also prevent cHCoV replication. This might explain why we found that children with codetections of cHCoV and RV had lower cHCoV genomic loads and developed less severe disease compared with single cHCoV-infected children.

Strengths and Limitations

A strength of our study is that we have used the same method for the inclusion of symptomatic children during the whole study period, and the long study period reduces the risk of bias due to seasonal fluctuations. The study was conducted at a single center, although it is the only center providing pediatric service to an entire county population. We used a nonvalidated severity score developed to mirror clinical routines at the hospital, as there is a lack of acknowledged validated scores for this purpose. All NPAs were sampled with a standardized procedure and the PCR methods were unchanged during the whole study period. The use of C_t values as a proxy for viral genomic loads may, however, have some limitations, because low-quality NPAs might not express the true viral genomic load in the nasopharynx. Due to the cross-sectional design of the study, virus causality and interaction analyses should be interpreted carefully. Finally, the cHCoV detection rate may be too low, because we were not able to complete reanalyses of cHCoV-HKU1 in NPAs collected after 2015, due to a lack of available resources during the COVID-19 pandemic.

CONCLUSION

This study suggests that cHCoV is associated with severe illness in children, although codetections with other viruses appeared in two of three children. Children with codetected cHCoV-RSV more often presented with LRTI and severe disease, resembling those of children with single RSV detections. On the contrary, codetections of cHCoV and RV were associated with less severe disease compared with single cHCoV, suggesting an interaction where RV impairs cHCoV infections.

ACKNOWLEDGMENTS

The authors acknowledge nurses and doctors at the Children's Clinic, St. Olavs Hospital for the collection of clinical data. The authors also acknowledge the staff at the Department of Medical Microbiology, St. Olavs Hospital for all virologic analyses. The authors would especially like to thank Dr Per Eirik Hæreid for important statistical contributions to their study, in addition to research nurse Siv Anita Myhre.

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