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Human metapneumovirus infections are associated with severe morbidity in hospitalized children of all ages

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SUMMARY

The impact of human metapneumovirus (HMPV) in children aged >5 years and the risk factors associated with disease severity for all ages have not been well characterized. A retrospective cohort study of 238 children aged 0–15 years hospitalized over a 3-year period was performed. Medical records were reviewed for demographic information, clinical parameters and outcomes. Multivariable analyses were performed to identify independent factors associated with worse disease severity assessed by length of hospital stay (LOS), need for ICU care, respiratory support, and a disease severity score. Pulmonary diseases were associated with all outcomes of care, while congenital heart disease (CHD) and neuromuscular disorders were associated with longer LOS, and CHD and trisomy 21 were associated with worse severity scores independent of other covariables. Fever, retractions, use of steroids and albuterol were also associated with enhanced disease severity. Understanding the determinants of HMPV disease in children may help design targeted preventive strategies.

Key words: Asthma, bronchiolitis, human metapneumovirus, respiratory infections.

INTRODUCTION

Human metapneumovirus (HMPV) is a common aetiological agent of lower respiratory tract infections (LRTIs) in children worldwide. Since its discovery in 2001, different studies have documented that the clinical manifestations caused by this virus are similar to those caused by respiratory syncytial virus (RSV) [1–3]. RSV and HMPV belong to the Paramyxoviridae family, and often cause bronchiolitis, pneumonia, croup, asthma exacerbations or reactive airway disease (RAD) in infants and children [2–10]. Both are responsible for the most severe forms of bronchiolitis in infants and young children, and the presence of underlying medical conditions seems to be a risk factor for enhanced disease severity [2–4, 7, 11–14]. Specifically, the following risk factors have been associated with severe HMPV infection in infants and children aged <5 years: prematurity, chronic lung disease (CLD) of prematurity, other pulmonary diseases, congenital heart disease (CHD), neuromuscular disorders, immunocompromised state,

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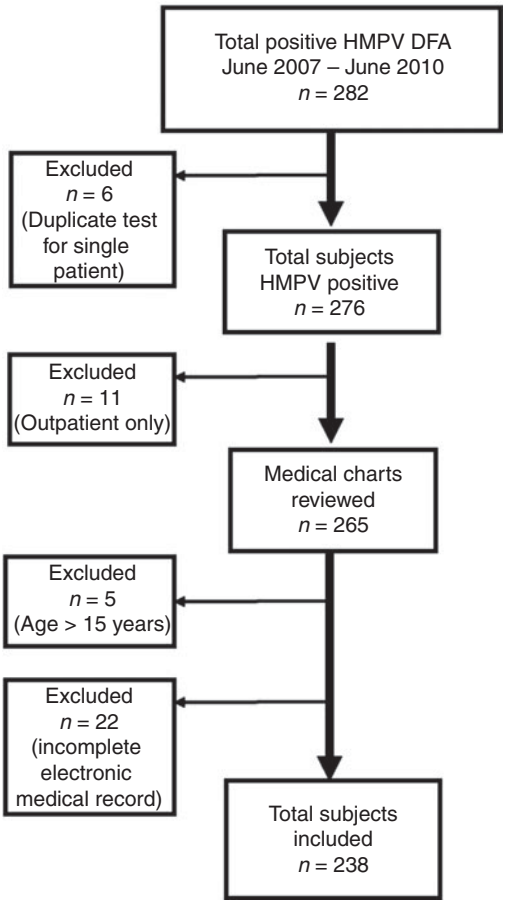

Fig. 1. Flow diagram of selection of eligible subjects for the study between June 2007 and June 2010. HMPV DFA, Human metapneumovirus direct fluorescent antibody.

and trisomy 21 [3, 5, 8, 9, 11, 13, 14]. The impact of these and other risk factors for severe disease in older children with HMPV infection and whether older children present with different manifestations have not been well characterized. In this study we sought to describe the spectrum of HMPV infection in a broader group of hospitalized children and to identify independent risk factors associated with disease severity across all age groups.

METHODS

Study patients

This retrospective cohort study was conducted at a single tertiary paediatric centre (Nationwide Children's Hospital; NCH) in Columbus, Ohio. With institutional IRB approval (IRB10-00142), children who tested positive for HMPV by direct fluorescent antibody (DFA) testing, sent at the discretion of the attending physician, were identified from microbiology reports from June 2007 to June 2010. Medical records from the identified subjects were screened and subjects were included in the study if they were: (1) hospitalized, (2) aged between 0 and 15 years, (3) found to have HMPV identified by DFA in respiratory samples, and (4) had a complete electronic medical record available (Fig. 1). Co-infection with other respiratory viruses was not an exclusion criterion.

Although polymerase chain reaction (PCR) has become the test of choice for rapid and sensitive diagnosis of acute viral respiratory tract infections, DFA for respiratory virus testing was the standard of care at our institution during the study period [15, 16]. DFA tests for detection of influenza A and B, parainfluenza 1, 2, and 3, adenovirus, RSV (Millipore, USA), and HMPV (Diagnostic Hybrids, USA) were routinely run together as a part of a respiratory panel, and were available year round. The sensitivity for HMPV by DFA is estimated at 60–95% [16–18]. Other respiratory pathogens were not included in the DFA panel and thus were not routinely tested for when testing for HMPV. Respiratory samples were obtained as either a nasopharyngeal swab or nasal wash and processed at the clinical microbiology laboratory at NCH.

Data collection

A standardized data collection form was used to gather information from medical records, including demographic information such as age, sex, race, date of hospital admission and date of discharge, and past medical history, including the presence of underlying medical conditions potentially associated with increased disease severity such as prematurity, pulmonary diseases, CHD, neuromuscular disease, immunocompromised state, and trisomy 21. Prematurity was defined as gestational age <37 weeks. Pulmonary diseases included CLD of prematurity (bronchopulmonary dysplasia/respiratory distress syndrome), asthma/RAD, and anatomical or congenital lung diseases such as tracheo/laryngomalacia. Presence of wheezing/bronchiolitis *per se* was excluded from this larger category due to concerns of potential overclassification, although asthma/RAD and history of wheezing were evaluated separately. CHD was limited to structural lesions. Neuromuscular disorders were limited to those with effects on muscle tone and included hypoxic-ischaemic encephalopathy, cerebral palsy, traumatic brain injury, myelomeningocele,

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spinal muscular atrophy, or infantile spasms. Diagnoses of primary seizure disorders or hydrocephalus with placement of ventriculo-peritoneal shunt were excluded. Immunodeficiency included primary immune defects or those secondary to use of immunosuppressive medications at time of illness. Data regarding presenting symptoms, physical examination, medications received (specifically bronchodilators, corticosteroids, antibiotics), laboratory tests (including blood, urine, lower respiratory bacterial cultures), imaging studies, discharge diagnoses, and outcomes of care including: length of hospital stay (LOS), duration and need for intensive care unit (ICU) care and respiratory support including type (mechanical ventilation, non-invasive positive pressure ventilation, oxygen supplementation), hospital re-admission within 1 week of discharge, and death were also collected.

Statistical analyses

Descriptive statistics were used to characterize the study population and parameters of HMPV disease severity. Inferential statistics performed included non-parametric Mann–Whitney *U* test or Kruskal–Wallis test for continuous variables, with data reported as medians and 25th and 75th interquartile ranges (IQR). Categorical variables were compared using χ^2 test or Fisher's exact test. *Z* test for proportions was used when appropriate. These tests were performed using SigmaPlot (SPSS Science, USA). We also performed multivariable logistic regression analyses and selected LOS, ICU care, need for any type of respiratory support (mechanical ventilation, non-invasive positive pressure ventilation, oxygen supplementation) and a disease severity score as outcome measures for severe disease. To generate the disease severity score one point was assigned for the presence of each outcome (0–3), as done in previous studies [14]. The severity score was then categorized into a binary outcome and compared subjects whose hospital course did not include any components of the severity score (score = 0) (LOS $\leqslant$ 4 days, no ICU care, no respiratory support) *vs.* those subjects whose hospital course included all three components of the severity score (score = 3). LOS was also categorized into a binary outcome by its median value ($\leqslant$4 days, >4 days). Independent risk factors associated with disease severity were selected based on biological plausibility and/or prior association in univariate analyses, and a full sequence model with no selection method of exclusion was generated. To further explore the effect of age on disease severity adjusted for the presence of comorbidities, we built a separate model that only included demographic information (gender and age stratified into five different groups) and the presence of underlying medical conditions. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. A two-sided *P* value $<0{\cdot}05$ was considered significant. All logistic regression analyses were conducted in SAS v. 9.3 (SAS Institute Inc., USA).

RESULTS

Epidemiology and demographic characteristics

During the study period 9246 viral DFA tests were performed and 282 (3%) tested positive for HMPV in 276 subjects while 1608 were positive for RSV (17·4%, $P<0{\cdot}001$). Eleven children with positive tests were not hospitalized and therefore were excluded. Of 265 hospitalized children reviewed for age at the time of treatment and completeness of the medical record, 238 subjects met study criteria (Fig. 1). During the study period only 126 respiratory samples were tested for HMPV by PCR with one positive result; this child was not included in the study. Co-detection of *Bordetella pertussis* by PCR and RSV by DFA were identified in two separate previously healthy children; no other respiratory viruses were co-detected with HMPV infection.

The proportion of children diagnosed with HMPV by DFA was similar across the study years (3·8% for June 2007–May 2008, 3·7% for June 2008–May 2009 and 2·2% for June 2009–May 2010). Sixty-one percent of subjects were hospitalized in winter ($n=145$, 21 December–20 March), and 29% in spring ($n=69$, 21 March–20 June). The median age at the time of hospitalization was 14 (IQR 6–29) months, and one-third of subjects ($n=74$, 31%) were older than 24 months. Fifty-three percent ($n=127$) of subjects were male, and 56% ($n=134$) were of white race. The majority of children had at least one identifiable traditional risk factor for severe disease ($n=161$, 68%) and were older compared to those without any risk factors ($P<0{\cdot}001$). (Table 1) The most common underlying medical condition was pulmonary disease ($n=107$, 45%), followed by prematurity ($n=96$, 40%) and CHD ($n=42$, 18%). Sixty-three percent ($n=149$) of subjects had at least one of these diagnoses (Fig. 2).

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Table 1. *Demographic characteristics and differences in outcomes of children with human metapneumovirus infection with and without traditional risk factors*

	Risk factor ($n=161$)	Previously healthy ($n=77$)	P value
Demographic characteristics			
Age, months, median (IQR)*†	20 (9·75–38)	8 (3–17)	**<0·001**
Gender, *n* (%)‡			
Male	89 (55%)	38 (49%)	0·472
Female	72 (45%)	39 (51%)	
Race, *n* (%)*‡			
White	99 (61%)	35 (45%)	**0·021**
Black	44 (25%)	21 (27%)	
Other	22 (13%)	21 (27%)	
Disease severity			
LOS, days, median (IQR)*†	5 (3–7)	3 (2–4)	**<0·001**
Need for ICU, *n* (%)§	35 (22%)	8 (10%)	0·039
Any type of respiratory support§	116 (72%)	48 (62%)	0·159
(*a*) MV as maximal support			
Need for MV, *n* (%)§	12 (7%)	1 (1%)	0·097
Length of MV, days, median (IQR)†	8 (7–14)	4 (4–4)	0·178
(*b*) PPV as maximal support			
Need for PPV, *n* (%)§	15 (9%)	6 (8%)	0·992
Length of PPV, days, median (IQR)*†	6 (3–12)	3 (2–3)	**0·017**
(*c*) Supplemental O_2 as maximal support			
Need for O_2, *n* (%)§	89 (55%)	41 (53%)	0·995
Length of O_2, days, median (IQR)*†	4 (2–6)	2 (2–3)	**<0·001**

ICU, Intensive care unit; IQR, interquartile range; LOS, length of hospital stay; MV, mechanical ventilation; O_2, oxygen; PPV, positive pressure ventilation.
Traditional risk factors include the following: prematurity, pulmonary disease, congenital heart disease, neuromuscular disorders, immunocompromised state, and trisomy 21.
* Statistically significant if $P<0·05$.
† Mann–Whitney U test.
‡ χ^2 test.
§ Z test.

Clinical characteristics, interventions and discharge diagnoses

The most common clinical signs and symptoms at presentation were cough ($n=220$, 92%), fever ($n=199$, 84%), coryza ($n=193$, 81%), increased work of breathing ($n=140$, 59%) or wheezing ($n=134$, 56%). Decreased oral intake ($n=111$, 47%), vomiting ($n=101$, 42%), diarrhoea ($n=51$, 21%), otalgia ($n=40$, 17%), and cyanosis ($n=17$, 7%) were also described. On initial physical examination, crackles or rhonchi ($n=142$, 60%), wheezing ($n=134$, 56%), rhinorrhoea or congestion ($n=129$, 54%), and retractions ($n=125$, 53%) were the findings most commonly documented. Otitis ($n=46$, 19%), pharyngitis ($n=10$, 4%), and conjunctivitis ($n=8$, 3%) were also present.

During their hospitalization, 79% ($n=189$) of subjects were treated with albuterol (median 3, IQR 2–6 days), 51% ($n=122$) with corticosteroids for more than 24 h (median 4, IQR 3–6 days), and 68% ($n=161$) received antibiotics (median 3, IQR 2–5 days). Corticosteroids and bronchodilators were used equally in younger and older children (>5 years), while older children were more likely to receive antibiotics ($P<0·001$).

Blood cultures were obtained in 50% ($n=119$) of subjects; 15% ($n=35$) had a urine culture and 11% ($n=26$) had a lower respiratory culture performed. All previously healthy children had negative cultures

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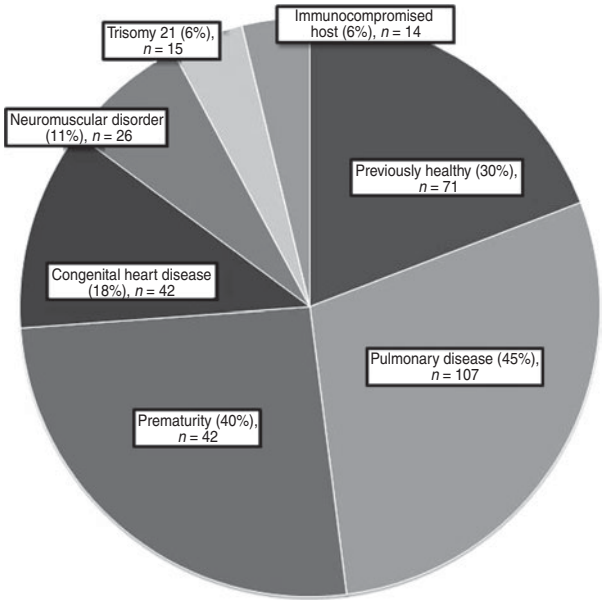

Fig. 2. Traditional risk factors in children hospitalized with human metapneumovirus infection. Pulmonary diseases included chronic lung disease (CLD) of prematurity (bronchopulmonary dysplasia/respiratory distress syndrome), asthma/reactive airway disease (RAD), and anatomical or congenital lung diseases such as tracheo/laryngomalacia. Presence of wheezing/bronchiolitis *per se* was excluded from this larger category due to concerns of potential over-classification, although asthma/RAD and history of wheezing were also evaluated separately. While not shown in the graph, 47% ($n=111$) had asthma/RAD or a history of wheezing, 21% ($n=51$) had CLD, and 14% ($n=34$) had anatomic/congenital lung disease. Prematurity included those subjects with gestational age <37 weeks. Congenital heart disease was limited to structural lesions. Neuromuscular disorders included hypoxic-ischaemic encephalopathy, cerebral palsy, traumatic brain injury, myelomeningocele, spinal muscular atrophy, or infantile spasms and excluded primary seizure disorders or hydrocephalus with placement of ventriculo-peritoneal shunt. Immunodeficiency included primary immune defects or those secondary to use of immunosuppressive medications at time of illness.

[three positive blood cultures of 122 performed were presumed contaminants with coagulase-negative *Staphylococcus* (CoNS) ($n=2$) or viridans streptococcus ($n=1$)]. True positive urine cultures were identified in two immunocompromised subjects (the first with $>100\,000$ colony-forming units (c.f.u.) *Escherichia coli*, 20000 c.f.u. CoNS and 20000 c.f.u. *Enterococcus* sp., and the second with 80000 c.f.u. *E. coli* and 40000 c.f.u. CoNS).

Chest X-ray was performed in 88% ($n=210$) of children and was abnormal as defined by the presence of airspace disease and/or consolidation in 44% ($n=92$).

Bronchiolitis was the most common discharge diagnosis especially in infants aged <12 months and accounted for 48% ($n=115$) of subjects, followed by pneumonia in 15% ($n=37$) and asthma/RAD in 15% ($n=36$) which were more common in older age groups. These diagnoses were not mutually exclusive, and 28% ($n=68$) of subjects had alternate diagnoses. Children with traditional risk factors were more likely to be diagnosed with asthma/RAD ($P=0{\cdot}004$) compared to previously healthy children. Conversely, previously healthy children were more likely to have a discharge diagnosis of bronchiolitis.

Parameters of disease severity

To define the impact of HMPV infection on disease severity, we compared LOS, requirement and duration of respiratory support, need for ICU care and death, first between children with and without traditional risk factors for severe disease, and then based on different age groups.

In the overall cohort the median LOS was 4 (IQR 3–6) days, 18% ($n=43$) required ICU care and 69% ($n=164$) required respiratory support. Mechanical ventilation was required in 5% ($n=13$) of children (median 7, IQR 6–12 days), non-invasive positive pressure ventilation as maximal respiratory support in 9% ($n=21$) of subjects (median 4, IQR 3–11 days), and oxygen supplementation was required as maximal respiratory support in 55% ($n=130$) (median 3, IQR 2–6 days). Most children had a severity score of 1 ($n=57$, 39%), followed by 0 ($n=93$, 24%), 2 ($n=52$, 21%) and 3 ($n=37$, 16%).

Compared to previously healthy children, those with at least one underlying medical condition considered a traditional risk factor ($n=161$, 68%) had longer LOS ($P<0{\cdot}001$), and required ICU admission more frequently ($P=0{\cdot}037$). They also required non-invasive respiratory support for longer duration [positive pressure ventilation ($P=0{\cdot}017$) and oxygen supplementation ($P<0{\cdot}001$)] (Table 1).

To assess whether disease severity was different in children aged 0–15 years, study subjects were grouped into five categories based on age (0–$<$6 months, 6–$<$12 months, 12–$<$24 months, 24–$<$60 months, 5–15 years) and risk factors compared between them. The prevalence of prematurity, CLD, CHD and trisomy 21 was similar across the five age groups, while neuromuscular disorders and immunodeficiency were more prevalent in older children ($P=0{\cdot}001$). Overall, the presence of an underlying medical

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condition was more common in older children. While LOS was significantly longer in children aged >6 months, other parameters of disease severity such as need for ICU care or respiratory support was comparable between age groups (Table 2).

Six percent of subjects ($n=15$; median age 22, IQR 2–9 months) were readmitted to the hospital within 1 week after discharge. Of those, 80% ($n=12$) had underlying traditional risk factors, and 60% ($n=9$) were readmitted for respiratory concerns, 20% ($n=3$) for fever, and 20% ($n=3$) for unrelated reasons. Two children with HMPV infection died during their hospitalization. The first was an 11-month-old male with a history of end stage renal disease, hypoxic-ischaemic encephalopathy, and seizure disorder. He presented after cardiac arrest at home and family withdrew support due to multi-organ system dysfunction and neurological devastation. The cause of his cardiac arrest was reported as respiratory failure secondary to HMPV infection. The second child was a previously healthy 5-month-old female also admitted after cardiac arrest at home. She presented with 1 day of congestion and difficulty breathing. The only pathogen identified was HMPV. She met criteria for brain death and support was withdrawn. Autopsy was not performed for either patient.

Independent risk factors associated with severe disease

To determine which factors were associated with increased disease severity adjusted for other covariates, we performed multivariable logistic regression analyses and analysed simultaneously demographic characteristics, comorbidities, clinical/radiological and medical interventions (Table 3). To further explore the role of age in disease severity, we built a separate multivariable logistic regression model and analysed solely demographic characteristics adjusted for several underlying medical conditions (Table 4).

In the first model that included 22 covariates, several parameters were associated with outcomes of care (LOS, ICU care, respiratory support) adjusted for age, gender and several other covariables. The severity score was not included as an outcome in this first analysis, because of the limited sample size and inability to include all the variables in the multivariable logistic regression model.

Underlying medical conditions

Only CHD was identified as predictor of worse disease defined by longer LOS, adjusted for age, gender and several other comorbidities. On the other hand children with immunodeficiency were less likely to require any kind of respiratory support (Table 3).

Clinical and radiological characteristics

Multivariate analyses identified the presence of diarrhoea to be associated with less severe disease, while duration of fever was associated with significantly longer LOS and need for ICU care, and the presence of retractions on physical examination with increased need for respiratory support (Table 3).

Medical interventions

Use of albuterol was associated with increased need for respiratory support, while steroids were associated with three outcomes of care (increased LOS, need for ICU care, respiratory support). Collection of blood cultures was also associated with the need for ICU care (Table 3).

Next we solely analysed the effect of age and gender adjusted for several comorbidities in a multivariable fashion. Of all age groups, only infants aged 6–12 months had a significant increased risk for ICU care adjusted for all other comorbidities. In addition, multivariate analysis identified several traditional risk factors associated with disease severity. Specifically, pulmonary disease defined as CLD of prematurity, asthma/RAD and anatomical/congenital lung disease was associated with increased LOS, need for ICU care, respiratory support and higher clinical severity scores. CHD and neuromuscular disorders significantly increased the odds of a longer hospital stay, while trisomy 21 was associated with a greater severity score. On the other hand children with immunodeficiency were less likely to require any kind of respiratory support (Table 4).

DISCUSSION

This is one of the largest studies to have examined the morbidity associated with HMPV infection in hospitalized children of all ages. We found that only one third of children hospitalized with HMPV infection were previously healthy during the study period. While the presence of underlying pulmonary disease was independently associated with increased disease severity in all outcomes of care, CHD, neuromuscular disorders, or trisomy 21 were risk factors associated with specific outcomes (longer LOS and increased severity score) adjusted for age and gender. We also found that the presence of symptoms outside the

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Table 2. *Clinical differences in children with human metapneumovirus infection according to age groups*

	Age 0–<6 months ($n=53$)	Age 6–<12 months ($n=46$)	Age 12–<24 months ($n=65$)	Age 24–<60 months ($n=51$)	Age 5–15 years ($n=23$)	*P* value
Demographic characteristics, *n* (%)						
Traditional risk factor (any)*†	19 (36%)	27 (59%)	44 (68%)	47 (92%)	21 (91%)	**<0·001**
Prematurity†	15 (28%)	21 (46%)	21 (32%)	17 (33%)	9 (39%)	0·462
Chronic lung disease†	8 (15%)	12 (26%)	14 (22%)	11 (22%)	6 (26%)	0·753
Other pulmonary diseases*†	4 (8%)	4 (9%)	21 (32%)	19 (37%)	8 (35%)	**<0·001**
Congenital heart disease*†	6 (11%)	11 (24%)	11 (17%)	11 (22%)	3 (13%)	0·411
Neuromuscular disorders*†	1 (2%)	3 (7%)	4 (6%)	9 (18%)	9 (39%)	**<0·001**
Immunocompromised*†	0 (0%)	1 (2%)	2 (3%)	7 (14%)	4 (17%)	**0·001**
Trisomy 21†	2 (4%)	3 (7%)	8 (12%)	2 (4%)	0 (0%)	0·143
Gender*†						
Male	34 (64%)	18 (39%)	35 (54%)	32 (63%)	8 (35%)	**0·010**
Female	19 (36%)	28 (61%)	30 (46%)	19 (37%)	15 (65%)	
Race*†						
White	33 (62%)	18 (39%)	31 (48%)	38 (75%)	14 (61%)	**0·036**
Black	12 (23%)	18 (39%)	18 (28%)	8 (16%)	5 (22%)	
Other	8 (15%)	10 (22%)	16 (25%)	5 (10%)	4 (15%)	
Disease severity, *n* (%) or median (IQR)						
LOS, days, median (IQR)*‡	3 (2–5)	5 (3–8)	4 (3–5)	5 (3–6)	5 (3–7)	**0·034**
Maximum temperature (°C)*‡, median (IQR)	38 (37·7–38·3)§	38 (37·7–38·9)	38 (37·7–39·2)	39 (37·9–39·4)§	38 (37·7–39·1)	**0·012**
Need for ICU, *n* (%)†	9 (17%)	12 (26%)	10 (15%)	9 (18%)	3 (13%)	0·651
Any type of respiratory support†, *n* (%)	32 (60%)	35 (76%)	43 (66%)	37 (73%)	18 (78%)	0·374
(*a*) MV as maximal support						
Need for MV, *n* (%)†	3 (6%)	4 (9%)	2 (3%)	2 (4%)	2 (9%)	0·706
Length of MV, days, median (IQR)‡	8 (6–13)	10 (7–15)	33 (20–46)	6 (6–6)	8 (5·75–9·25)	0·478
(*b*) PPV as maximal support						
Need for PPV, *n* (%)†	3 (6%)	6 (13%)	5 (8%)	6 (12%)	1 (4%)	0·531
Length of PPV, days, median (IQR)‡	4 (4–7)	3 (2·75–7·5)	3 (2–7)	8 (3–18·75)	7 (5–9)	0·604
(*c*) Supplemental O_2 as maximal support						
Need for O_2, *n* (%)†	26 (49%)	25 (54%)	36 (55%)	29 (57%)	15 (65%)	0·741
Length of O_2, days, median (IQR)‡	3 (2–5)	5 (2–7)	3 (2–4)	4 (2–6)	3 (1·25–5)	0·137

ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; MV, mechanical ventilation; O_2, oxygen; Other pulmonary diseases, includes asthma/reactive airway disease and anatomical/congenital lung diseases; PPV, positive pressure ventilation.

* Statistically significant if $P<0·05$.

† χ^2 test.

‡ Kruskal–Wallis ANOVA on ranks.

§ Significantly different pairwise comparisons by Dunn's test.

Table 3. *Odds ratios for demographic characteristics, comorbidities, and clinical factors associated with disease severity in children with human metapneumovirus disease*

	LOS		ICU care		Respiratory support	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographic characteristics						
Gender*	0·79 (0·36–1·74)	0·570	1·12 (0·39–3·22)	0·829	0·82 (0·37–1·82)	0·630
Age†						
0–5 months	1·07 (0·21–5·51)	0·928	2·58 (0·26–24·98)	0·411	0·29 (0·04–1·82)	0·187
6– <12 months	2·21 (0·48–9·81)	0·314	7·20 (0·92–56·36)	0·060	0·40 (0·06–2·63)	0·346
12– <24 months	0·41 (0·09–1·76)	0·235	1·08 (0·13–9·10)	0·938	0·25 (0·04–1·52)	0·132
24- <60 months	1·12 (0·28–4·36)	0·868	1·93 (0·24–15·39)	0·534	0·61 (0·10–3·56)	0·590
5–15 years	—	—	—	—	—	—
Underlying medical conditions						
Prematurity	2·07 (0·93–4·60)	0·073	0·49 (0·17–1·42)	0·193	0·57 (0·24–1·36)	0·208
Congenital heart disease	**2·69 (1·01–7·17)**	**0·047**	1·62 (0·51–5·10)	0·406	0·81 (0·27–2·38)	0·704
Pulmonary disease	2·31 (0·90–5·92)	0·079	1·75 (0·52–5·87)	0·361	1·28 (0·45–3·60)	0·639
Immunodeficiency	3·18 (0·45–22·54)	0·245	0·33 (0·01–6·33)	0·469	**0·04 (0·006–0·37)**	**0·003**
Neuromuscular disorders	3·06 (0·89–10·46)	0·074	0·89 (0·16–4·83)	0·900	1·12 (0·26–4·69)	0·876
Trisomy 21	1·36 (0·31–5·87)	0·673	1·03 (0·20–5·22)	0·970	3·99 (0·57–27·72)	0·161
Asthma/RAD or history of wheezing	0·82 (0·32–2·06)	0·672	0·86 (0·28–2·60)	0·794	0·82 (0·32–2·09)	0·679
Clinical/radiological characteristics						
Coryza	0·35 (0·12–0·98)	0·046	0·63 (0·21–1·85)	0·403	0·98 (0·32–2·92)	0·972
Diarrhoea	0·61 (0·23–1·61)	0·322	**0·02 (0·001–0·72)**	**0·030**	0·79 (0·30–2·08)	0·644
Otitis	0·37 (0·13–1·07)	0·068	0·36 (0·08–1·66)	0·191	0·48 (0·19–1·23)	0·127
Fever (days)	**1·98 (1·34–2·92)**	**<0·001**	**1·68 (1·21–2·32)**	**0·001**	1·28 (0·89–1·86)	0·178
Retractions	1·33 (0·56–3·16)	0·509	2·99 (0·95–9·38)	0·059	**2·45 (1·02–5·85)**	**0·043**
Abnormal chest X-ray	1·83 (0·81–4·12)	0·143	0·63 (0·23–1·73)	0·377	1·52 (0·66–3·53)	0·321
Medical interventions						
Albuterol	1·71 (0·46–6·36)	0·419	1·43 (0·25–8·13)	0·685	**3·88 (1·31–11·51)**	**0·014**
Steroids	**4·16 (1·57–10·99)**	**0·004**	**5·86 (1·51–22·68)**	**0·010**	**3·34 (1·30–8·53)**	**0·011**
Blood cultures	1·92 (0·84–4·58)	0·114	**9·14 (2·86–29·14)**	**<0·001**	1·91 (0·73–5·00)	0·186

ICU, Intensive care unit; LOS, length of hospital stay; OR, odds ratio; CI, confidence interval; RAD, reactive airway disease.

Bold values indicate statistically significant if $P < 0{\cdot}05$.

Prematurity defined as <37 weeks of gestational age. Pulmonary diseases were defined as chronic lung diseases of prematurity, asthma/RAD, and other pulmonary diagnoses such as tracheo/laryngomalacia. Respiratory support includes mechanical ventilation, non-invasive positive pressure ventilation, and oxygen supplementation.

* Female used as reference.

† Age 5–15 years used as reference.

lower respiratory tract (namely diarrhoea) was associated with less severe disease, and that duration of fever and use of steroids were the most consistent independent variables associated with increased disease severity in two or more outcomes of care.

In agreement with previous studies, where the need for ICU care was required in 15–25% of cases, and mechanical ventilation in 8–17% of children with HMPV infection, we found that 18% of children had a HMPV infection severe enough to require ICU care and respiratory support, including the need of positive pressure or mechanical ventilation, which was required in 8% and 5%, respectively [7, 8, 19–23]. The percentage of children requiring oxygen supplementation (55%) was at a higher range than that previously reported (30–54%) [5, 8–10, 20, 22, 24, 25]. In our study, corticosteroids (51%) and bronchodilators (79%) were much more commonly used than in previous reports (17–25% for corticosteroids, 30–48% for bronchodilators), which may be related to the high number of children with underlying pulmonary disease [10, 22, 24]. Similarly to RSV infection, the most frequent discharge diagnoses were bronchiolitis, asthma/RAD, and pneumonia [2–10].

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Table 4. *Odds ratios for gender, age and several comorbidities associated with disease severity in children with human metapneumovirus disease*

	LOS		ICU care		Respiratory support		Severity score	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographic characteristics								
Gender*	0·84 (0·45–1·54)	0·574	0·78 (0·38–1·59)	0·498	0·81 (0·43–1·54)	0·537	0·54 (0·16–1·80)	0·318
Age†								
0–<6 months	0·96 (0·26–3·51)	0·950	3·27 (0·62–17·25)	0·161	0·32 (0·06–1·51)	0·150	0·34 (0·02–4·22)	0·401
6–<12 months	2·06 (0·31–6·95)	0·241	**4·78 (1·01–22·57)**	**0·048**	0·62 (0·13–2·94)	0·554	1·57 (0·14–17·80)	0·711
12–<24 months	0·61 (0·19–1·97)	0·414	1·74 (0·37–8·08)	0·474	0·27 (0·06–1·21)	0·088	0·16 (0·01–2·05)	0·161
24–<60 months	1·49 (0·47–4·65)	0·493	1·91 (0·42–8·60)	0·395	0·58 (0·13–2·62)	0·487	0·89 (0·08–9·74)	0·924
5–15 years	—	—	—	—	—	—	—	—
Underlying medical conditions								
Prematurity	1·50 (0·79–2·83)	0·207	0·59 (0·26–1·32)	0·203	0·67 (0·33–1·35)	0·266	0·48 (0·13–1·71)	0·263
Congenital heart disease	**2·20 (1·01–4·80)**	**0·046**	1·50 (0·64–3·55)	0·347	0·86 (0·36–2·05)	0·745	**5·98 (1·47–24·36)**	**0·012**
Pulmonary disease	**3·43 (1·66–7·07)**	**<0·001**	**3·37 (1·41–8·03)**	**0·006**	**3·42 (1·54–7·59)**	**0·002**	**14·28 (3·39–60·67)**	**<0·001**
Immunodeficiency	2·58 (0·68–9·71)	0·159	1·44 (0·25–8·25)	0·678	**0·09 (0·02–0·43)**	**0·002**	0·23 (0·02–2·49)	0·230
Neuromuscular disorders	**4·22 (1·50–11·84)**	**0·006**	2·37 (0·80–6·98)	0·116	1·04 (0·32–3·31)	0·946	5·51 (0·73–41·21)	0·096
Trisomy 21	2·06 (0·61–6·93)	0·242	1·93 (0·52–7·18)	0·322	5·17 (0·93–28·50)	0·059	**39·75 (2·42–652·94)**	**0·009**
Asthma/RAD or history of wheezing	0·75 (0·37–1·50)	0·422	0·85 (0·38–1·90)	0·708	1·39 (0·69–2·81)	0·348	0·27 (0·06–1·23	0·092

ICU, Intensive care unit; LOS, length of hospital stay; OR, odds ratio; CI, confidence interval; RAD, reactive airway disease.
Bold values indicate statistically significant if $P < 0{\cdot}05$.
Prematurity defined as < 37 weeks of gestational age. Pulmonary diseases were defined as chronic lung diseases of prematurity, asthma/reactive airway disease, and other pulmonary diagnoses such as tracheo/laryngomalacia. Respiratory support includes mechanical ventilation, non-invasive positive pressure ventilation, and oxygen supplementation.

* Female used as reference.

† Age 5–15 years used as reference.

Studies of RSV infection have repeatedly shown that the majority of hospitalized children with RSV disease have no underlying medical conditions and that the hospital course is more severe in younger children [4, 13]. Although RSV and HMPV are closely related, we found that for HMPV specifically in our study most hospitalized children had in fact at least one underlying medical condition that was independently associated with disease severity.

Different studies have found that prematurity, CHD, pulmonary diseases, age <2 years, elderly, or immunocompromised states are associated with increased HMPV severity [2, 3, 7–9, 11, 23, 26]. We also found that pulmonary disease, CHD, neuromuscular disorders, and trisomy 21 increased the risk for severe disease. Conversely, we did not find that prematurity, immunodeficiency, or age <6 months or >12 months were significantly associated with disease severity, which may still be due to residual confounding. Although the reasons why immunodeficiency was found to be associated with decreased need for respiratory support are unclear, it could be explained in part by the fact that in our study children with immunodeficiency were often hospitalized for fever ($n=12$, 86%) rather than for respiratory symptoms.

A relatively low occurrence of bacterial co-infections was found in our study, with no immunocompetent host having a concurrent blood or urinary tract infection. This is in agreement with data from other studies of children with HMPV and other respiratory viral infections such as RSV [7, 13]. On the other hand, severity of HMPV illness has been associated with the presence of viral co-detection, specifically HMPV with RSV [9, 27]. We did not find such association in our study, which is probably related to the different diagnostic methods used as DFA has a lower sensitivity for respiratory virus detection in general and for HMPV in particular compared to PCR [15, 16]. In addition, it could also be related to the wider age range of subjects included in our study. Last, HMPV was associated with the death of two individuals, one of whom had no documented risk factors. Previously reported deaths in children associated with HMPV included children with risk factors and have occasionally had documented secondary bacterial infections [7, 19, 21, 26, 28–30]. There has also been a previously reported death due to encephalitis that possibly was associated with HMPV infection [31, 32]. To our knowledge, our case represents the first otherwise healthy child whose death was presumed to be respiratory failure associated with HMPV infection, although causality cannot be proven as no autopsy was performed.

Limitations to the present study are inherent to its retrospective nature, which accounts in part for possible selection, confounding and confirmation biases, among others. In particular, testing was performed at the discretion of the attending physician, and children with underlying medical conditions were possibly more likely to be hospitalized and thus tested for respiratory viruses than previously healthy children. In addition the data derived from the study come from a single centre, which could limit the generalizability of the results. Nevertheless, the study was conducted over three respiratory seasons and a multivariable analysis performed to control for other factors that may have influenced the results. Last, the fact that non-molecular techniques (DFA) were used for the diagnosis of HMPV infection may have underestimated the impact of HMPV infection. PCR is a more sensitive test and would have probably led to the identification of a greater number of subjects who could have been included in the study as well as possible viral co-infections. On the other hand, DFA was the only viral test used across the study years allowing us to have comparable data.

In summary, we showed that HMPV caused significant morbidity in this large cohort of hospitalized children up to age 15 years. Specifically, we found that the factors independently associated with enhanced disease severity included: (*a*) presence of underlying medical conditions such as pulmonary disease, CHD, neuromuscular disorders and trisomy 21 and (*b*) presence of other clinical and medical variables during hospitalization such as retractions, longer duration of fever and the use of steroids. Future prospective studies are needed to better define the impact and the long-term effects of HMPV in the different age groups and with different underlying medical conditions, as well as to ascertain the role of steroids in this disease. This information could be used to guide the development of targeted prophylaxis strategies including vaccines.

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DECLARATION OF INTEREST

None.

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